

A. INGREDIENT NAME:

IODOFORM

B. Chemical Name:

Tri-iodomethane

C. Common Name:

Compound Iodoform Paint, B.I.P.P. Gauze, Bismuth Sub-nitrate and Iodoform Paste

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specifications)</i>	<i>(Results)</i>
Assay:	99.0-100.5%	99.01%
Not less than 99% of CHI_3		

E. Information about how the ingredient is supplied:

Fine greenish yellow powder, or lustrous crystals, unctuous touch, characteristic. Persistent odor, slightly volatile even at ordinary temperatures, and distils slowly with steam.

F. Information about recognition of the substance in foreign pharmacopeias:

British Pharmacopeia 1954
The National Formulary - Volume VII, 1942

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Corbridge, R. J., Djazaeri, B., and Hellier, W. P. Iodoform Paste. *Clinical Otolaryngology*, 1995; 20(4): 305-307.

Holan, G. and Fuks, A. B. Iodoform-containing paste (KRI). *Pediatric Dentistry*, 1993; 16(6): 403-407.

H. Information about dosage forms used:

Paste
Paint
Gauze

I. Information about strength:

10-50% Topically

J. Information about route of administration:

Topically

K. Stability data:

Decomposition at about 120°; decomposition at high temperature with evolution of iodine.

Decomposes violently at 400F

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

50-1127
52738

PRODUCT: IODOFORM POWDER
RELEASE #: N

LOT # :B59901C13

GRADE: PURIFIED
CODE:A925D053

SPECIFICATIONS

RESULT

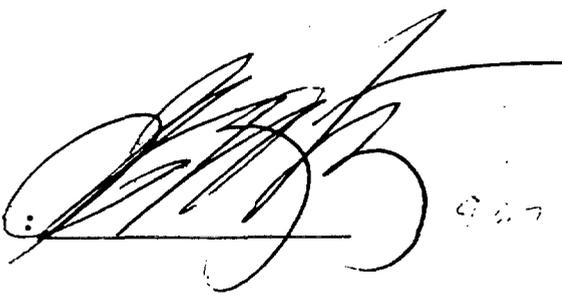
DESCRIPTION	SPECIFICATIONS	RESULT
1. DESCRIPTION	YELLOW POWDER	CONFORMS
2. Melting point	115 deg C min.	120 deg C
3. Moisture	1.0% max.	< 1.0%
4. Residue on ignition	0.2% max.	< 0.2%
5. Assay	99.0 - 100.5%	<u>99.01%</u> D

ATTENTION: TONY HATCHETT

Date :09/02/97

Prepared by : A. HAZARI

10540

Approved by: 

Our Order # 237082 Your PO # 53617

THE ABOVE TEST RESULTS HAVE BEEN OBTAINED BY OUR MANUFACTURER/SUPPLIER AND/OR IN OUR QUALITY CONTROL LABORATORY. THE DATA IS PROVIDED AT THE REQUEST OF AND FOR THE CONVENIENCE OF THE CUSTOMER AND DOES NOT RELIEVE THE CUSTOMER OF ITS RESPONSIBILITY TO VERIFY IT. THIS ANALYSIS IS NOT TO BE CONSTRUED AS A WARRANTY, EXPRESSED OR IMPLIED.



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MATERIAL SAFETY DATA SHEET

**Iodoform, 99+%
97101**

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: Iodoform, 99+%

Triiodomethane
 Company Identification: Acros Organics N.V.
 One Reagent Lane
 Fairlawn, NJ 07410
 For information in North America, call: 800-ACROS-01
 For emergencies in the US, call CHEMTREC: 800-424-9300
 For emergencies in the US, call CHEMTREC: 800-424-9300

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
75-47-8	Iodoform, 99+%		200-874-5

Hazard Symbols: XN
 Risk Phrases: 20/21/22

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: Not available.
 Cancer suspect agent.
 Target Organs: None.

Potential Health Effects

The toxicological properties of this material have not been investigated. Use appropriate procedures to prevent opportunities for direct contact with the skin or eyes and to prevent inhalation.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
 Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids.

Skin:
 Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:

Do NOT induce vomiting. Allow the victim to rinse his mouth and then to drink 2-4 cupfuls of water, and seek medical advice.

Inhalation:

Remove from exposure to fresh air immediately.

Notes to Physician:

Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:

As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. During a fire, irritating and highly toxic gases may be generated by thermal decomposition or combustion.

Extinguishing Media:

Use agent most appropriate to extinguish fire.

Autoignition Temperature: Not available.

Flash Point: 204 deg C (399.20 deg F)

NFPA Rating: Not published.

Explosion Limits, Lower: Not available.

Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:

Clean up spills immediately, observing precautions in the Protective Equipment section. Sweep up, then place into a suitable container for disposal.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:

Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Avoid contact with eyes, skin, and clothing. Avoid ingestion and inhalation.

Storage:

Store in a cool, dry place. Keep container closed when not in use.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:

Use adequate general or local exhaust ventilation to keep airborne concentrations below the permissible exposure limits. Use process enclosure, local exhaust ventilation, or other engineering controls to control airborne levels.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
Iodoform, 99+%	0.6 ppm ; 10 mg/m3	none listed	none listed

OSHA Vacated PELs:

Iodoform, 99+%:

0.6 ppm TWA; 10 mg/m3 TWA

Personal Protective Equipment

Eyes:

Wear safety glasses and chemical goggles if splashing is possible.

Skin:

Wear appropriate protective gloves and clothing to prevent skin exposure.

Clothing:

Wear appropriate protective clothing to minimize contact with skin.

Respirators:

Wear a NIOSH/MSHA-approved (or equivalent) full-facepiece airline respirator in the positive pressure mode with emergency escape provisions.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State: Not available.
 Appearance: Not available.
 Odor: None reported.
 pH: Not available.
 Vapor Pressure: Not available.
 Vapor Density: Not available.
 Evaporation Rate: Not available.
 Viscosity: Not available.
 Boiling Point: @ 760.00mm Hg
 Freezing/Melting Point: 120.00 - 123.00 deg C
 Decomposition Temperature: 204 deg C
 Solubility: freely soluble in benzene and acetone
 Specific Gravity/Density: 4.0080g/cm3
 Molecular Formula: CHI3
 Molecular Weight: 393.72

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:
 Stable under normal temperatures and pressures.
 Conditions to Avoid:
 Incompatible materials, strong oxidants.
 Incompatibilities with Other Materials:
 Strong bases - strong oxidizing agents - magnesium - alkali metals.
 Hazardous Decomposition Products:
 Carbon monoxide, irritating and toxic fumes and gases, carbon dioxide, hydrogen iodide.
 Hazardous Polymerization: Has not been reported.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
 CAS# 75-47-8: PB7000000
 LD50/LC50:
 CAS# 75-47-8: Inhalation, rat: LC50 =165 ppm/7H; Oral, mouse: LD50 = 470 mg/kg; Oral, rabbit: LD50 = 450 mg/kg; Oral, rat: LD50 = 355 mg/kg; Skin, rat: LD50 = 1184 mg/kg.
 Carcinogenicity:
 Iodoform, 99+% -
 Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
 Not available.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
 RCRA D-Series Maximum Concentration of Contaminants: Not listed.
 RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
 RCRA F-Series: Not listed.
 RCRA P-Series: Not listed.
 RCRA U-Series: Not listed.
 Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
 No information available
 IMO
 Not regulated as a hazardous material.
 IATA
 Not regulated as a hazardous material.

RID/ADR

Not regulated as a hazardous material.

Canadian TDG

No information available.

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA

CAS# 75-47-8 is listed on the TSCA inventory.

Health & Safety Reporting List

None of the chemicals are on the Health & Safety Reporting List.

Chemical Test Rules

None of the chemicals in this product are under a Chemical Test Rule.

Section 12b

None of the chemicals are listed under TSCA Section 12b.

TSCA Significant New Use Rule

None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)

None of the chemicals in this material have an RQ.

Section 302 (TPQ)

None of the chemicals in this product have a TPQ.

SARA Codes

CAS # 75-47-8: acute, chronic.

Section 313

No chemicals are reportable under Section 313.

Clean Air Act:

This material does not contain any hazardous air pollutants.

This material does not contain any Class 1 Ozone depleters.

This material does not contain any Class 2 Ozone depleters.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.

None of the chemicals in this product are listed as Priority Pollutants under the CWA.

None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

Iodoform, 99+% can be found on the following state right to know lists: California, New Jersey, Florida, Pennsylvania, Minnesota, Massachusetts.

California No Significant Risk Level:

None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: XN

Risk Phrases:

R 20/21/22 Harmful by inhalation, in contact with skin and if swallowed.

Safety Phrases:

S 24/25 Avoid contact with skin and eyes.

WGK (Water Danger/Protection)

CAS# 75-47-8:

Canada

CAS# 75-47-8 is listed on Canada's DSL/NDSL List.

This product has a WHMIS classification of D1B, D2B.

CAS# 75-47-8 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

CAS# 75-47-8: OEL-AUSTRALIA:TWA 0.6 ppm (10 mg/m³). OEL-BELGIUM:TWA 0.6 ppm (10 mg/m³). OEL-DENMARK:TWA 0.2 ppm (3 mg/m³). OEL-FINLAND:TWA 0.2 ppm (3 mg/m³);STEL 0.6 ppm (1 mg/m³);Skin. OEL-FRANCE:TWA 0.6 ppm (10 mg/m³). OEL-THE NETHERLANDS:TWA 0.2 ppm (3 mg/m³). OEL-SWITZERLAND:TWA 0.6 ppm (10 mg/m³). OEL-UNITED KINGDOM:TWA 0.6 ppm (10 mg/m³);STEL 1 ppm (20 mg/m³). OEL IN BULGARIA, COLOMBIA, JORDAN, KOREA check AC GIH TLV. OEL IN NEW ZEALAND, SINGAPORE, VIETNAM check ACGI TLV

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 2/01/1996 Revision #0 Date: Original.

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

[Back to product information.](#)

QUALITY CONTROL REPORT

CHEMICAL NAME.: IODOFORM PURIFIED _____

MANUFACTURE LOT NO.: B62949P30

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

E YELLOW POWDER OR CRYSTALS; UNCTUOUS TOUCH; CHARACTERISTIC, DISAGREEABLE ODOR.

2) SOLUBILITY.:

VERY SLIGHTLY SOLUBLE IN WATER; 1 GRAM DISSOLVES IN 60ML COLD ALCOHOL, 16ML BOILING ALCOHOL, 10ML CHLOROFORM, 7.5ML ETHER, 80ML IN GLYCEROL; FREELY SOLUBLE IN BENZENE, ACETONE.

K 3) MELTING POINT.:

MELTS AT ABOUT 120 DEGREES; DECOMPOSITION AT HIGH TEMPERATURE WITH EVOLUTION OF IODINE.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

phosphorous acid, H_3PO_3 , added to prevent discoloration on keeping. Wt per ml about 1.1 g. **Incompatible** with alkalis and oxidising agents. Store in well-closed glass-stoppered bottles. Protect from light.

Hydriodic acid has the general properties of iodine in weak combination. It was usually administered as Hydriodic Acid Syrup.

Preparations

Hydriodic Acid Syrup (B.P.C. 1949). Syr. Acid. Hydriod. Dilute hydriodic acid 10 ml, water 5 ml, and syrup to 100 ml. *Dose.* 2 to 4 ml.

4576-k

Iodinated Glycerol. Iodopropylidene Glycerol. An isomeric mixture of iodinated dimers of glycerol, $C_6H_{11}IO_3 = 258.1$. It contains about 50% of organically bound iodine.

CAS — 5634-39-9.

A pale yellow liquid with a pungent bitter after-taste. Soluble in chloroform, ether, and ethyl acetate. Protect from light.

Adverse Effects, Treatment, and Precautions. As for iodine, p.862.

Uses. Iodinated glycerol is used as an expectorant in bronchitis and bronchial asthma in doses of 60 mg four times daily with fluids.

Proprietary Preparations

Organidin (WB Pharmaceuticals, UK; Boehringer Ingelheim, UK). Elixir containing in each 5 ml iodinated glycerol 60 mg and alcohol 1.25 ml (suggested diluent, equal parts of glycerol and water).

Other Proprietary Names

Mucorama Rectal Infantil (Spain).

4577-a

Iodoform (B.P.C. 1954). Formène Tri-iodé.

Iodomethane B
 $CH_3I = 393.7$.

CAS — 75-47-8.

Pharmacopoeias. In Arg., Aust., Belg., Fr., It., Jug., Pol., Port., Rus., Span., and Swiss.

Shining lemon-yellow crystals or powder, somewhat unctuous to the touch, with a characteristic, persistent, penetrating odour and disagreeable taste. Slightly volatile at room temperature. M.p. 115° ; at higher temperatures it decomposes with loss of iodine.

Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 3 of carbon disulphide, 1 in 13 of chloroform, 1 in 8 of ether, 1 in 100 of glycerol, 1 in 35 of olive oil; soluble in other fixed and volatile oils, and in flexible collodion. **Incompatible** with alkalis, oxidising agents, lead, silver, and mercury salts. Store in a cool place in airtight containers. Protect from light.

To cover its odour it may be mixed with coumarin 1 in 50, or with menthol, phenol, or thymol, or with oils of anise, eucalyptus, geranium, peppermint, rosemary, or sassafras, about 1 or 2%.

Adverse Effects. Symptoms of systemic toxicity, as described under Iodine (see p.862), sometimes occur on prolonged or extensive application to wounds. As a precaution not more than 2 g should usually be applied as a wound dressing. Some persons are hypersensitive to iodoform and even small quantities applied locally may cause an erythematous rash.

Severe poisoning, which may be fatal, is characterised by headache, somnolence, delirium, and rapid feeble pulse.

Maximum permissible atmospheric concentration 5 ppm.

Uses. Iodoform has a marked anaesthetic action when applied to mucous membranes. It slowly releases elemental iodine when applied to the tissues and has a mild disinfectant action. It was

formerly used extensively as a wound dressing but is not very effective.

Compound Iodoform Paint has been used as a protective covering and to hold gauze dressings and radium needles in position.

Bismuth Subnitrate and Iodoform Paste (BIPP) has been applied to wounds and abscesses, the area to be treated being cleaned and smeared with the paste. Sterile gauze impregnated with the paste has also been used for packing cavities after oral and otorhinological surgery.

Preparations†

B.I.P.P. Gauze (Roy. Nat. T. N. and E. Hosp.). Sterile ribbon gauze impregnated with a sterile paste consisting of iodoform 40%, bismuth subnitrate 20%, and liquid paraffin 40%.

Bismuth Subnitrate and Iodoform Paste (B.P.C. 1954). Past. Bism. Subnit. et Iodof.; BIPP; Bismuth and Iodoform Paste. Bismuth subnitrate 1, iodoform 2, sterilised liquid paraffin 1, by wt, prepared aseptically. Store in a cool place in sterilised collapsible tubes. Prolonged or extensive application may give rise to iodoform poisoning.

Adverse effects. Open leg ulcers in a Malay child aged 13 months were treated with the paste. They healed but oedema and pain increased. After 9 weeks, X-ray examination showed dense transverse bands of metallic bismuth deposited in metaphyseal growth areas of long bones.—H. N. Krige, *S. Afr. med. J.*, 1963, 37, 1005.

Two reactions to dental dressings with Bismuth Subnitrate and Iodoform Paste occurred in which crystals of bismuth subnitrate were considered to be the cause rather than the iodoform.—W. A. Miller and G. S. Taylor, *Br. dent. J.*, 1968, 124, 420.

Symptoms compatible with iodoform toxicity occurred in 1 patient and raised iodine concentrations in 2 further patients following the packing of cavities with gauze impregnated with Bismuth Subnitrate and Iodoform Paste. In a further patient who received a pack soaked in Compound Iodoform Paint no signs of iodoform toxicity were observed. It was suggested that Bismuth Subnitrate and Iodoform Paste was satisfactory for packing small operative cavities but for large cavities Compound Iodoform Paint pastes were safer.—A. F. F. O'Connor *et al.*, *J. Lar. Otol.* 1977, 91, 903.

Compound Iodoform Paint (B.P.C. 1954). Fig. Iodof. Co.; Iodoform Varnish; Whitehead's Varnish. Prepared from iodoform 10 g, benzoin 10 g, prepared storax 7.5 g, tolu balsam 5 g, and solvent ether to 100 ml.

4578-t

Iodophores

Iodophores are carriers of iodine and are usually complexes of iodine with certain types of surfactants with detergent properties. It is possible for iodine to be taken up in chemical combination by high molecular weight surfactants and water-soluble polymers. The surfactants may be nonionic, cationic, or anionic, but generally the most efficient and stable iodophores are compounds of nonionic surfactants.

Though the iodine in an iodophore is held in loose chemical combination, part of the iodine is available and retains its bactericidal activity. Iodophores may solubilise up to 25% by weight of iodine of which about 80% may be released as available iodine when a concentrated solution is diluted.

Solutions of an iodophore are more stable than solutions of iodine which lose strength by volatilisation and there is no precipitation on dilution of an iodophore solution. The stability of the majority is not affected by changes in pH. As the available iodine is taken up, the colour of the solution changes from amber to pale yellow.

Unlike the hypochlorites, solutions of iodophores can be formulated with acid and the bactericidal action of most of them is enhanced by lowering the pH. Increases in temperature increase the bactericidal action of iodophores, but above 43° they break down with the liberation of iodine.

Stability of solutions. Use-dilutions of an iodophore preparation (Wescodyne) containing 150 ppm available

iodine and 0.05% sodium nitrite lost their typical brown colour after standing for a few days and were found to lose 24% potency in 24 hours or 42% in 48 hours at 35° . Similar dilutions without sodium nitrite were more stable and lost 9.2% potency after 3 weeks at 35° .—R. J. Abrahams and H. J. Derewicz, *Am. J. Hosp. Pharm.*, 1968, 25, 192.

Uses. Solutions of iodophores are employed in pre-operative skin disinfection and for disinfecting blankets and some instruments. Stains of iodophores on skin and natural fabrics may be removed by washing with soap and water. The iodophores described in this section are Povidone-Iodine (see p.867) and Undecoylum Chloride-Iodine (see p.868).

Disinfection of skin. There was no significant difference in the incidence of wound infections when an iodophore and hexachlorophane were used as surgical hand scrubs.—J. J. White and A. Duncan, *Surgery Gynec. Obstet.*, 1972, 135, 890.

The effectiveness of iodophores against both Gram-negative and Gram-positive organisms was an advantage over hexachlorophane, but they did not persist in the skin to provide cumulative, continuing antibacterial activity. Like alcohol, iodophores could cause excessive dryness of the skin with repeated use.—*Med. Lett.*, 1976, 18, 85. Iodophores were active against both Gram-negative and Gram-positive bacteria and did not require repeated application for maximum effectiveness. They were considered to be less bactericidal but less irritant than aqueous or alcoholic solutions of iodine.—*ibid.*, 1977, 19, 83.

Studies involving 95 women in active labour necessitating continuous epidural analgesia indicated that skin disinfection of the catheter site with an iodophore (Prepodyne) was superior to that with a benzalkonium chloride preparation.—E. Abouleish *et al.*, *Anesthesiology*, 1977, 46, 351.

For other reports, see Povidone-Iodine, p.867.

Uses of disinfectants on farms. For a list of disinfectants, including iodophores, and their rate of dilution approved for use in Great Britain in foot-and-mouth disease, swine vesicular disease, fowl pest, and tuberculosis in animals, see *The Diseases of Animals* (Approved Disinfectants) Order 1978 (SI 1978: No. 32), as amended (SI 1978: No. 934; SI 1979: No. 37).

A list of proprietary iodophore preparations approved for the cleansing and disinfecting of milk containers and appliances is contained in Circular FSH 8/78, Ministry of Agriculture, Fisheries and Foods, London, HM Stationery Office, 1978.

Virus disinfection. For the disinfection of materials in contact with lassa fever virus, see *Memorandum on Lassa Fever*, Dept of Health and Social Security, London, HM Stationery Office, 1976.

Recommendations for precautions in medical care of, and in handling materials from, patients with transmissible virus dementia (Creutzfeldt-Jakob disease).—D. C. Gajdusek *et al.*, *New Engl. J. Med.*, 1977, 297, 1253.

For the use of iodophores in the disinfection of fabrics exposed to smallpox virus, see *Disinfectants, General*, p.548.

Proprietary Preparations

Faringets (Winthrop, UK). Lozenges each containing 4 mg of miristalkonium iodine chloride (myristyl benzalkonium iodine chloride; benzyl-dimethyltetradecylammonium chloride-iodine complex; $C_{23}H_{47}ClI_2N = 621.9$). For minor infections of the throat. *Dose.* 1 or 2 lozenges to be sucked slowly every 4 hours; not more than 6 in 24 hours.

Steribath (Stuart, UK). An antiseptic solution containing an iodophore (complexed with a nonoxynol) and providing 4.5% of available iodine; available in 14-ml sachets for addition to the bath.

Vanodine (Evans Vanodine, UK). A bactericidal and fungicidal detergent solution containing available iodine 1.92% w/v (in the form of an iodine-poloxamer complex 18.7%). For the control of foot infections in swimming baths and changing rooms. Dilute 1 vol. in 100 vol. of water for use.

Other Proprietary Names
SeptoDyne (USA).

X 1955

mixture vigorously. After the chloroform has been decolorized allow the mixture to stand for 5 minutes. If the chloroform develops a purple color, titrate further with the iodate solution. Each ml. of 0.05 M potassium iodate is equivalent to 30.55 mg. of iodochlorhydroxyquin (C₁₁H₇ClINO).

Tablets available—Iodochlorhydroxyquin Tablets usually available contain the following amount of iodochlorhydroxyquin: 250 mg. (4 grains).

Packaging and storage—Preserve Iodochlorhydroxyquin Tablets in tight, light-resistant containers.

CATEGORY—Antiprotozoan.

USUAL DOSE OF IODOCHLORHYDROXYQUIN—250 mg. (approximately 4 grains).

Iodoform

IODOFORM

Triiodomethane

CHI₃

Mol. wt. 393.75

Iodoform, previously dried over sulfuric acid for 4 hours, contains not less than 99 per cent of CHI₃.

Description—Iodoform occurs as a fine greenish yellow powder, or lustrous crystals. It has a peculiar, very penetrating, persistent odor. Iodoform is slightly volatile even at ordinary temperatures, and distils slowly with steam.

Solubility—One Gm. of Iodoform dissolves in about 60 ml. of alcohol, in about 80 ml. of glycerin, in about 10 ml. of chloroform, in about 7.5 ml. of ether, and in about 34 ml. of olive oil. One Gm. dissolves in about 16 ml. of boiling alcohol. Iodoform is practically insoluble in water to which, however, it imparts its odor and taste.

Melting point—Iodoform melts to a brown liquid at about 115°, and decomposes at a higher temperature, emitting vapors of iodine, page 691.

Loss on drying—Dry Iodoform over sulfuric acid for 4 hours: it loses not more than 1 per cent of its weight, page 690.

Residue on ignition—Iodoform yields not more than 0.2 per cent of residue on ignition, page 711.

Coloring matter, acids, and alkalis—Shake about 2 Gm. of Iodoform with 5 ml. of water for 1 minute, and filter: the filtrate is colorless and free from bitter taste and is neutral to litmus.

Assay—Dissolve about 200 mg. of Iodoform, previously dried over sulfuric acid for 4 hours and accurately weighed, in 20 ml. of alcohol in a 500-ml. glass-stoppered Erlenmeyer flask. Add 30 ml. of 0.1 N silver nitrate and 10 ml. of nitric acid, stopper the flask, and set it aside overnight. Add 150 ml. of water and 5 ml. of ferric ammonium sulfate T.S., and titrate the excess of silver nitrate with 0.1 N ammonium thiocyanate. Each ml. of 0.1 N silver nitrate is equivalent to 13.12 mg. of CHI₃.

Packaging and storage—Preserve Iodoform in tight, light-resistant containers, and avoid excessive heat.

CATEGORY—Local antibacterial.

IPECAC AN

Dover's Powder

- Ipecac, in very fine powder
 - Powdered Opium
 - Lactose, coarsely powdered
- To make

Triturate the ingredients reduced to a very fine, uniforn

Description—Ipecac and Opium Ihibiting coarse, angular, frequer up to 400 μ in length, very slowly polarizing light with a strong disp of identification are the tissues described in the U. S. Pharmacc

Packaging and storage—Preserve ers.

CATEGORY—Diaphoretic.

USUAL DOSE—300 mg. (ap) One usual metric dose contains

Orizaba Jalap

Ipomea is the dried root c *volvulacæ*).

Ipomea yields not less tha

Unground Ipomea occurs as nearl diameter, and from 1 to 5.5 cm wrinkled, and has a tough, fib rings with protruding lighte crushed has a distinct, somewhe what acid.

Histology—Ipomea shows a corky cells; an outer cortex of sever made up of thick-walled, tange or crystals of calcium oxalate, to yellow resinous latex; rings alternating with bands of pare outside of the wood-wedges. numerous and distributed thro surrounding the bundles are calcium oxalate crystals.

Powdered Ipomea is pale brown up to 35 μ in diameter, mostly

Extract the mixed drugs by percolation, using diluted alcohol as the menstruum. Macerate three hours, and percolate at a moderate rate until 250 cc. of percolate is obtained. To this add sufficient distilled water to make the product measure 1000 cc.; or, to prepare the Infusion in smaller quantities and extemporaneously, add sufficient distilled water to 1 volume of the percolate to make 4 volumes of the Infusion.

NOTE: The percolate or concentrated infusion may be preserved in tight containers, but the Infusion must not be dispensed unless it has been recently prepared.

Storage—Dispense Compound Infusion of Gentian in tight containers.
Alcohol content—From 9 to 11 per cent, by volume, of C_2H_5OH .

AVERAGE DOSE—Metric, 15 cc.; Apothecaries, 4 fluidrachms.

INFUSUM SENNÆ CUM MAGNESII SULFATE

Infusion of Senna with Magnesium Sulfate

Inf. Senn. c. Mag. Sulf.

Compound Infusion of Senna

Senna	60 Gm.
Manna	120 Gm.
Magnesium Sulfate	120 Gm.
Fennel, bruised	20 Gm.
Distilled Water, a sufficient quantity,	
To make	1000 cc.

Pour 800 cc. of boiling distilled water upon the senna, manna, and fennel, contained in a suitable vessel, and allow the mixture to infuse for half an hour, pass the liquid through a strainer and express the marc. Dissolve the magnesium sulfate in the liquid, and add sufficient distilled water through the strainer to make the Infusion measure 1000 cc. Filter if necessary, until the product is clear.

NOTE: This preparation must not be dispensed unless it has been recently prepared.

Storage—Dispense Infusion of Senna with Magnesium Sulfate in tight containers.

AVERAGE DOSE—Metric, 60 cc.; Apothecaries, 2 fluidounces.

IODIFORMUM

Iodoform

Iodof.

Triiodomethane

Iodoform, previously dried over sulfuric acid for 24 hours, contains not less than 99 per cent of CHI_3 (393.78).

Description—Iodoform occurs as a fine lemon-yellow powder, or lustrous crystals. It has a peculiar, very penetrating, persistent odor. Iodoform is slightly volatile even at ordinary temperatures, and distils slowly with the vapor of water.

Solubility—Iodoform is practically insoluble in water to which, however, it imparts its odor and taste. One Gm. of Iodoform dissolves in about 60 cc. of alcohol, in about 80 cc. of glycerin, in about 10 cc. of chloroform, in about 7.5 cc. of ether, and in about 34 cc. of olive oil, at 25° C. One Gm. dissolves in about 16 cc. of boiling alcohol.

Melting point—Iodoform melts to a brown liquid at about 115° C., and decomposes at a higher temperature, emitting vapors of iodine.

Loss on drying—One Gm. of Iodoform dried over sulfuric acid for 24 hours loses not more than 1 per cent of its weight.

Ash—Iodoform yields not more than 0.2 per cent of ash upon ignition.

Coloring matter, acids, and alkalis—Shake about 2 Gm. of Iodoform with 5 cc. of distilled water for one minute, and filter: the filtrate is colorless and free from bitter taste and is neutral to litmus paper.

Assay—Dissolve about 0.2 Gm. of Iodoform, previously dried over sulfuric acid for 24 hours and accurately weighed, in 20 cc. of alcohol in a 500 cc. glass-stoppered Erlenmeyer flask. Add 30 cc. of tenth-normal silver nitrate and 10 cc. of nitric acid, stopper the flask, and set it aside overnight. Add 150 cc. of distilled water and 5 cc. of ferric ammonium sulfate T.S., and titrate the excess of silver nitrate with tenth-normal ammonium thiocyanate. Each cc. of tenth-normal silver nitrate is equivalent to 0.01313 Gm. of CHI_3 .

Storage—Preserve Iodoform in tight containers, protected from light, and avoid excessive heat.

IPOMŒA

Ipomea

Ipom.

Orizaba Jalap

Mexican Scammony

Ipomea is the dried root of *Ipomœa orizabensis* Ledenois (Fam. *Convolvulaceæ*).

Ipomea yields not less than 15 per cent of the total resins of Ipomea and not more than 3 per cent of acid-insoluble ash.

Unground Ipomea—Nearly flat transverse slices, from 2 to 12 cm. in diameter, and from 1 to 5.5 cm. in thickness; externally brown, very deeply wrinkled; fracture tough, fibrous; cut surface showing concentric rings with protruding lighter-colored fibro-vascular bundles.

Histology—A corky layer of several rows of thin-walled, narrow, tubular cells; outer cortex of several layers of thin-walled cells; a broad cortical layer made up of thick-walled, tangentially elongated cells, containing either starch grains or crystals of calcium oxalate, and numerous large cells containing reddish brown to yellow resinous latex; rings or zones of small collateral fibro-vascular bundles, alternating with bands of parenchyma; sieve in semi-cylindrical strands outside of the wood wedges; medullary rays broad; resin cells numerous and distributed throughout the parenchyma; the parenchyma cells surrounding the bundles, more or less collapsed and containing either starch or calcium oxalate crystals.

Powdered Ipomea—Color pale brown to weak yellowish orange; odor distinct, somewhat aromatic; taste sweet, becoming somewhat acrid; starch grains up to 35 microns in diameter, mostly simple, also 2- to 4-compound, and usually with a central cleft; calcium oxalate crystals numerous, mostly in rosette aggregates, occasionally in rhombohedra, from 10 to 45 microns in length; fragments of

Database: Medline <1966 to present>

Set	Search	Results
1	exp hydrocarbons, iodinated/	2722
2	iodoform.tw.	103
3	exp safety/	8472
4	efficacy.tw.	108250
5	2 and 3	0
6	2 and 4	6
7	from 6 keep 3-5	3

<1>

Unique Identifier

96081121

Authors

Corbridge RJ. Djazaeri B. Hellier WP. Hadley J.

Title

A prospective randomized controlled trial comparing the use of merocel nasal tampons and BIPP in the control of acute epistaxis.

Source

Clinical Otolaryngology. 20(4):305-7, 1995 Aug.

Abstract

A prospective study was undertaken to compare the efficacy of Merocel nasal tampons to BIPP (Bismuth Subnitrate and Iodoform Paste) impregnated ribbon gauze in the control of acute epistaxis requiring hospital admission. A total of 50 patients presenting with severe epistaxis was treated with either merocel nasal tampons, or BIPP. The groups did not differ significantly in terms of age, sex distribution, aetiology or severity of the bleed. There was no significant difference in efficacy or patient tolerance of either treatment. It was concluded that Merocel nasal tampons should be considered effective in the first line treatment of severe epistaxis uncontrolled by simple measures. Their ease of insertion makes them suitable for use in the accident and emergency department or in general practice.

<2>

Unique Identifier

94203886

Authors

Holan G. Fuks AB.

Title

A comparison of pulpectomies using ZOE and KRI paste in primary molars: a retrospective study.

Source

Pediatric Dentistry. 15(6):403-7, 1993 Nov-Dec.

Abstract

Maintaining a successfully root-treated primary molar has the advantage of preserving the natural tooth--the best possible space maintainer. The purpose of this study was to compare the success of endodontic treatment of nonvital primary molars using ZOE with that of KRI paste. Of 78 necrotic primary molars, 34 were filled with ZOE and 44 with an iodoform-containing paste (KRI). The canals were prepared with files, rinsed with saline and filled with one of the resorbable pastes, using a spiral Lentulo on a low-speed handpiece. A radiograph was exposed immediately postoperatively to observe whether the root filling was flush, underfilled, or overfilled. The effect of length of fill on the treatment outcome also was evaluated. Teeth were examined periodically clinically and radiographically to assess success of the treatment. Follow-up interval varied from 12 to more than 48 months. Overall success rate for KRI paste was 84% versus 65% for ZOE, which was statistically significant ($P < 0.05$). Overfilling with ZOE led to a failure rate of 59% as opposed to 21% for KRI ($P < 0.02$). Conversely, underfilling led to similar results, with a failure rate of 17% for ZOE and 14% for KRI. These results support the clinical efficacy of root filling with KRI paste as a treatment option for nonvital primary molars.

<3>

Unique Identifier

94087045

Authors

von Schoenberg M. Robinson P. Ryan R.

Title

Nasal packing after routine nasal surgery--is it justified?.

Source

Journal of Laryngology & Otology. 107(10):902-5, 1993 Oct.

Abstract

Ninety-five patients undergoing routine nasal surgery were enrolled into a randomized, prospective trial to investigate the efficacy and morbidity of nasal packing. The patients were randomized to receive a bismuth iodoform paraffin paste (BIPP) pack, a Telfa pack or no pack. Patients for septal surgery were randomized between the

BIPP and Telfa groups only. They were independently randomized to receive or not receive, a silastic nasal splint for the first post-operative week. Post-operative pain levels were analysed using a visual analogue scale. Mean pain scores were increased 50 per cent by the use of nasal packs and pack removal, particularly BIPP which, was a most painful event ($p < 0.001$). Reactionary haemorrhage occurred in only two patients (2.1 per cent), both of whom had packs in situ. Vestibulitis was unique to the patients with a silastic splint, who were packed with BIPP, occurring in 21 per cent of them. Similarly septal perforation was unique to this group. There was no significant difference in the incidence of adhesions between the groups which received packs and those who did not. Routine nasal packing, especially with BIPP, would seem difficult to justify in view of the increased pain levels and increased complications which occur without any demonstrable benefit in the majority of patients. Therefore packing should be reserved for cases where there is concern about persistent haemorrhage. In these cases Telfa would be preferable to BIPP.

A. INGREDIENT NAME:

METRONIDAZOLE BENZOATE

B. Chemical Name:

5-nitro-1*H*-imidazol-1-ylethyl benzoate

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.54% calculated as dried basis

E. Information about how the ingredient is supplied:

White or slightly yellowish, crystalline powder

F. Information about recognition of the substance in foreign pharmacopeias:

The Indian Pharmacopeia Volume I (A-P) 1985

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Stolze, K. Elimination of Elyzol 25% Dentagel matrix from periodontal pockets. *J Clin Periodontol*, 1995; 22(3): 185-187.

H. Information about dosage forms used:

Suspension

I. Information about strength:

400mg- 3 times daily, for 5 - 10 days

J. Information about route of administration:

Topically

K. Stability data:

Melts at about 99-102°
Keep container tightly closed

L. Formulations:

M. Miscellaneous Information:

Milan, 11th December 1997

2 x 25-kg drums

30-1559
55197

Manuf. date : July 1997

~~Expiry date : July 2002~~

ANALYSIS CERTIFICATE No. 3243

Your Ord. No. of the 10th Dec. 1997 Our Ref. No. 2925

MATERIAL	Quantity	Batch
METRONIDAZOLE BENZOATE B.P. micronized	KG. 50.-	0712

Empirical formula

Molecular weight

Aspect micronized powder

Color slig. yellowish

Odor

Taste

Melting point 99 - 102°C

Boiling range

Solubility practically insoluble in water;
freely soluble in Dichloromethone; soluble
in Acetone.

pH (acidity) 0.09 ML

Titer (Assay) 99.54% calculated as dried basis

Specific rotation

Light absorption

Loss on drying 0.1483%

Residue on ignition 0.0398%

Chloride

Sulfate

Heavy metals Less than 20 ppm ✓

Identification : A) Melting 99 - 102°C
B) complies
C) -
D) Related substances pa
E) te

Other requirements, notes Results of test or analysis as per B.P.

The Analyst

12/97

QUALITY CONTROL REPORT

CHEMICAL NAME.:METRONIDAZOLE BENZOATE POWDER

MANUFACTURE LOT NO.:0712

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP___/BP___/MERCK___/NF___/MART.___/CO.SPECS.___.

1)DESCRIPTION.:

WHITE OR SLIGHTLY CREAM TO YELLOWISH,CRYSTALLINE POWDER OR FLAKES.

2) SOLUBILITY.:

VERY SOLUBLE IN CHLOROFORM,ALCOHOL;SOLUBLE IN ETHER,INSOLUBLE IN WATER.

3)MELTING POINT.:

MELTS AT ABOUT 99-102 degree. *K*

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

- A)COMPLIES BY IR SPECTRUM AS PER COMPANY SPECS.
- B)A SOLUTION PH IS 5.8.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

1/4

MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT IDENTIFICATION

Product name : METRONIDAZOLE BENZOATE
 Chemical name : 1-(2-benzoyloxyethyl)-2-methyl-5-nitro imidazole
 Emp. Formula : $C_{13}H_{13}N_3O_4$ - 275.3

2. COMPOSITION / INFORMATION ON INGREDIENTS

Chemical name	CAS N°	EINECS N°	Symbol	%
1-(2-benzoyloxyethyl)-2-methyl-5-nitro imidazole	69198-10-3		Xn	99%

3. HAZARD IDENTIFICATION

Effect(s) of (over)exposure: May cause irritation to respiratory apparatus.

Symptoms of (over)exposure

Inhalation : not available
 Skin : not available
 Eyes : not available
 Ingestion : not available

4. FIRST AID MEASURES

Inhalation:	Effects	May be irritating.
	First aid	Remove victim to fresh air. Keep victim at rest. Consult a doctor.
Skin:	Effects	May be irritating.
	First aid	Remove contaminated clothing. Wash off with plenty of water and soap. Consult a doctor.
Eyes:	Effects	May be irritating.
	First aid	Wash out with plenty of water. Consult a doctor.
Ingestion:	Effects	LD ₅₀ 1.050 mg/Kg
	First aid	Wash out mouth with water. Consult a doctor.

30/04 '98 15:47

NR. TX/RX 4143

P01

Product name: **METRONIDAZOLE BENZOATE**

Page 2 of 4

5. FIRE FIGHTING MEASURES**Extinguishing measures****Suitable** : Water spray, CO₂, foam, dry chemical**Not be used** :**Hazardous thermal decomposition and combustion products** : CO, CO₂, NO_x**Protective equipment** : Self-contained breathing apparatus. Full protective clothing.**6. ACCIDENTAL RELEASE MEASURES****Personal precautions** : Wear suitable protective clothing. When using do not eat, drink or smoke.**Environmental precautions** : Not available.**Cleaning procedures** : Collect spilled material. Clean up affected area with water.**See section 8 and 13****7. HANDLING AND STORAGE****Handling** : Ventilation recommended. When using do not eat, drink or smoke.**Storage** : Keep container tightly closed. K**8. EXPOSURE CONTROLS / PERSONAL PROTECTION****Respiratory protection** : Airlined respirator or dust mask, type P2.**Hand protection** : Rubber gloves.**Eye protection** : Safety goggles or face shield.**Skin protection** : Working clothing.

Product name: METRONIDAZOLE BENZOATE

Page 3 of 4

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	: crystalline powder	Vapour pressure	: Not available
Colour	: white to yellowish-white	Vapour density	: Not available
Odour	: odourless	Flash point	: Not available
Melting point	: 99° - 103°C	Autoignition	: Not available
Boiling point	: Not available	Flammability	: Not flammable
Relative density	: Not available	Explosive properties	: Not available
Bulk density	: Not available	Upper limit	: -
Solubility in water	: 0.5% at 20°C	Lower limit	: -
pH	: Not available	Viscosity	: Not available
Partition coefficient	: Not available	Conductivity	: Not available

10. STABILITY AND REACTIVITY

Conditions to avoid	: -
Materials to avoid	: Oxidizing agents
Hazardous decomposition products	: NOx

11. TOXICOLOGICAL INFORMATION

Acute toxicity	
Oral	: Not available
Dermal	: Not available
Inhalation	: May be irritating
Eye irritation	: May be irritating
Skin irritation	: May be irritating
Other information	: Not available

12. ECOLOGICAL INFORMATION

Mobility	: Not available
Persistence and degradability	: Not available
Bioaccumulative potential	: Not available
Ecotoxicity	: Not available

Product name: **METRONIDAZOLE BENZOATE**

Page 4 of 4

13. DISPOSAL CONSIDERATIONS

Methods of disposal : Combustion in an incinerator for chemical waste.

Danger(s) : Not available

14. TRANSPORT INFORMATION

Special precautions :

Classification

UN Code :

ADR/RID :

IMO :

Packaging group :

ICAO/IATA :

15. REGULATORY INFORMATION

EC Classification

Contains: 1-(2-benzoyloxyethyl)-2-methyl-5-nitro imidazole

Symbol: Xn

Risk phrases: 20/22

Safety phrases: 2

16. OTHER INFORMATION

The information contained in this data sheet is, to the best of our knowledge, true and accurate, but any recommendations or suggestions which may be made are without guarantee, since the conditions of use are beyond our control.

Furthermore, nothing contained herein shall be construed as a recommendation to use any product in conflict with existing patents covering any material or its use.

Issued on January 1998

Storage Store in a well-closed container, protected from light.

Preparation

Methylprednisolone Acetate Injection

Action and use Corticosteroid.

1/95

Metoprolol Tartrate

Identification Test A. Line 4. For '18°' read '-18°'.

Line 6. After 'residue' insert ', Appendix II A'.

12/93

Heavy metals Line 2. For '1 ml' read '10 ml'.

7/94

Add the following statement.

Preparations

Metoprolol Injection

Metoprolol Tartrate Tablets

Metronidazole

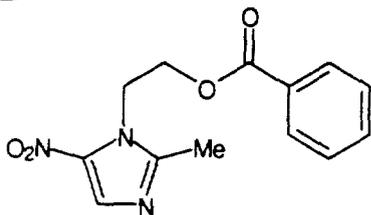
Add a five-pointed star (☆) to the title.

7/94

Preparations Add the following:

Metronidazole Intravenous Infusion

Metronidazole Benzoate ☆



$C_{13}H_{13}N_3O_4$

275.3

13182-89-3

Definition Metronidazole Benzoate contains not less than 98.5% and not more than 101.0% of 2-(2-methyl-5-nitro-1H-imidazol-1-ylethyl benzoate, $C_{13}H_{13}N_3O_4$, calculated with reference to the dried substance.

Characteristics White or slightly yellowish, crystalline powder or flakes; practically insoluble in water; freely soluble in dichloromethane; soluble in acetone; slightly soluble in ethanol (96%); very slightly soluble in ether.

Identification Identification test C may be omitted if identification tests A, B, D and E are carried out. Identification tests B, D and E may be omitted if identification tests A and C are carried out.

A. Melting point, 99° to 102°, Appendix V A, Method I.

B. Dissolve 0.1 g in 1M hydrochloric acid and dilute to 100 ml with the same acid. Dilute 1 ml of the solution to

100 ml with 1M hydrochloric acid. Examined between 220 nm and 350 nm, Appendix II B, the solution shows two absorption maxima, at 232 nm and 275 nm. The specific absorbance at the maximum at 232 nm is 525 to 575.

C. Examine by infrared absorption spectrophotometry, Appendix II A. The absorption maxima in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the spectrum obtained with metronidazole benzoate EPCRS.

D. Examine the chromatograms obtained in the test for Related substances under ultraviolet light (254 nm). The principal spot in the chromatogram obtained with solution (2) is similar in position and size to the principal spot in the chromatogram obtained with solution (3).

E. To about 10 mg add about 10 mg of zinc powder, 1 ml of water and 0.3 ml of hydrochloric acid. Heat on a water bath for 5 minutes and cool. The solution yields the reaction characteristic of primary aromatic amines, Appendix VI.

Appearance of solution Dissolve 1 g in dimethylformamide and dilute to 10 ml with the same solvent. The solution is not more opalescent than reference suspension II, Appendix IV A, and not more intensely coloured than reference solution GY₃, Appendix IV B, Method II.

Acidity Dissolve 2 g in a mixture of 20 ml of dimethylformamide and 20 ml of water, previously neutralised with 0.02M hydrochloric acid VS or 0.02M sodium hydroxide VS using 0.2 ml of methyl red solution. Not more than 0.25 ml of 0.02M sodium hydroxide VS is required to change the colour of the indicator.

Related substances Examine by thin-layer chromatography, Appendix III A, using silica gel HF₂₅₄ as the coating substance. Heat the plate at 110° for 1 hour and allow to cool before use.

Solution (1) Dissolve 0.20 g of the substance being examined in acetone and dilute to 10 ml with the same solvent.

Solution (2) Dilute 1 ml of solution (1) to 10 ml with acetone.

Solution (3) Dissolve 20 mg of metronidazole benzoate EPCRS in acetone and dilute to 10 ml with the same solvent.

Solution (4) Dilute 5 ml of solution (2) to 100 ml with acetone.

Solution (5) Dilute 2 ml of solution (2) to 100 ml with acetone.

Solution (6) Dissolve 10 mg of metronidazole EPCRS in acetone and dilute to 100 ml with the same solvent.

Solution (7) Dissolve 10 mg of 2-methyl-5-nitroimidazole in acetone and dilute to 100 ml with the same solvent.

Solution (8) Dissolve 10 mg of metronidazole EPCRS and 10 mg of 2-methyl-5-nitroimidazole in acetone and dilute to 50 ml with the same solvent.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using ethyl acetate. Allow the plate to dry in air and examine under ultraviolet light (254 nm). In the chromatogram obtained with solution (1) any spot corresponding to metronidazole or 2-methyl-5-nitroimidazole is not more intense than the corresponding spot in the chromatograms obtained with solutions (6) and (7) respectively (0.5%). Any other secondary spot is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%) and at most one such spot is more intense than the spot in the chromatogram

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Ministry of Health & Family Welfare

Pharmacopoeia of India

(The Indian Pharmacopoeia)

Volume—I
(A—P)

Third Edition



PUBLISHED BY THE CONTROLLER OF PUBLICATIONS, DELHI

1985

METRONIDAZOLE

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8.

Assay : Weigh accurately about 0.45 g and dissolve in 10 ml of *glacial acetic acid*, add a few drops of *1-naphthol-benzene solution* and titrate with *0.1N perchloric acid* until a pale-green colour is produced. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.01712 g of $C_6H_9N_3O_3$.

Storage : Store in well-closed light-resistant containers.

Metronidazole Tablets

Category : Anti-amoebic; antitrichomonal; anti-giardial.

Dose : Metronidazole. For trichomoniasis, 200 mg three times daily, for 7 days.

For amoebiasis, 400 mg three times daily, for 8 to 10 days.

For giardiasis, 2 g daily for three successive days for adults, 1 g daily for children and 400 mg daily for infants.

Usual strengths : 200 mg; 400 mg.

Standards : Metronidazole Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Metronidazole, $C_6H_9N_3O_3$. The tablets may be coated.

Identification : (A) Shake a quantity of the powdered tablets equivalent to about 0.2 g of Metronidazole with 4 ml of *N sulphuric acid* and filter. To the filtrate add 10 ml of *picric acid solution* and allow to stand for one hour, the precipitate after washing with cold *water* under suction and drying at 105° melts at about 150°, Appendix 5.11.

(B) Comply with **Identification** test (B) described under Metronidazole, using a quantity of the powdered tablets equivalent to 10 mg of Metronidazole.

2-Methyl-5-nitroimidazole : Comply with the test described under Metronidazole, using as solution (1), a solution prepared in the following manner: Shake a quantity of the powdered tablets equivalent to 0.2 g of Metronidazole with 5 ml of mixture of equal volumes of *chloroform* and *methyl alcohol* for five minutes and filter. The chromatogram obtained with solution (1) may also show spots due to excipients.

Other requirements : Comply with the requirements stated under Tablets.

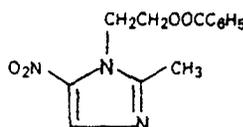
Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.2 g of Metronida-

zole, transfer to a sintered-glass crucible and extract with six quantities, each of 10 ml, of hot *acetone*. Cool, add to the combined extracts 50 ml of *acetic anhydride*, 0.1 ml of a 1 per cent w/v solution of *brilliant green* in *glacial acetic acid* and titrate with *0.1N perchloric acid* to a yellowish-green end-point. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.01712 g of $C_6H_9N_3O_3$.

Storage : Store in well-closed, light-resistant containers.

Metronidazole Benzoate

Benzoyl Metronidazole



$C_{13}H_{13}N_3O_4$

Mol. Wt. 275.27

Category : Anti-amoebic.

Dose : For amoebic dysentery, the equivalent of 400 mg of metronidazole three times, daily, for 5 to 10 days. I

NOTE - 200 mg of Metronidazole Benzoate is approximately equivalent to 125 mg of metronidazole.

Description : White or cream-coloured crystalline powder, odourless; almost tasteless.

Solubility : Sparingly soluble in *water*; soluble in *chloroform*, in *acetone*, and in *alcohol (90 per cent)*.

Standards : Metronidazole Benzoate is 2-(2-methyl-5-nitro-imidazol-1-yl) ethyl benzoate. It contains not less than 98.0 per cent of $C_{13}H_{13}N_3O_4$, calculated with reference to the dried substance.

Identification : (A) The light absorption, in the range 230 to 530 nm of a 1-cm layer of a 0.001 per cent w/v solution in *ethyl alcohol* exhibits a maximum only at 309 nm; *extinction* at 309 nm, about 0.3, Appendix 5.15 A.

(B) It gives the reactions of *benzoates*, Appendix 3.1.

Melting range : Between 100° and 102°, Appendix 5.11.

pH : Between 5.0 and 7.0, determined in a 2.0 per cent w/v suspension, Appendix 5.10.

Free benzoic acid : Not more than 0.2 per cent, determined by the following method: Dissolve 0.50 g in 25 ml of *alcohol* and titrate with *0.1N sodium hydroxide*, using *phenol red solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of

0.1N sodium hydroxide is equivalent to 0.01221 g of $C_7H_6O_2$.

Related substances : Carry out the method for *thin-layer chromatography*, Appendix 5.4.3, using *silica gel HF 254* as the coating substance and a mixture of 8 volumes of *chloroform* and 2 volumes of *acetone* as the mobile phase. Apply separately to the plate 10 μ l of each of three solutions in a mixture of equal volumes of *methyl alcohol* and *chloroform* containing (1) 6.0 per cent w/v of the substance being examined; (2) 0.02 per cent w/v of *2-methyl-5-nitroimidazole R.S.* and; (3) 0.02 per cent w/v of *metronidazole R.S.* After removal of the plate, allow the solvent to evaporate and examine under an ultra-violet lamp having a maximum output at about 254 nm. The spots in the chromatogram obtained with solutions (2) and (3) are more intense than any corresponding spots in the chromatogram obtained with solution (1).

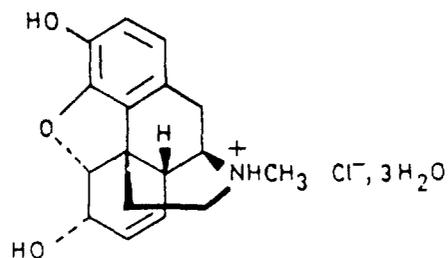
Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying "in vacuo at 60°," Appendix 5.8.

Assay : Weigh accurately about 0.5 g and dissolve in 50 ml of *acetone*. Add 10 ml of *acetic anhydride* and titrate with 0.1N *perchloric acid* using *brilliant green solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of 0.1N *perchloric acid* is equivalent to 0.02753 g of $C_{17}H_{19}NO_3$.

Storage : Store in well-closed, light-resistant containers.

Morphine Hydrochloride



$C_{17}H_{19}NO_3, HCl, 3H_2O$

Mol. Wt. 375.85

Category : Narcotic, analgesic.

Dose : 10 to 20 mg.

Description : Colourless, glistening needles or white crystalline powder; odourless; taste, bitter.

Solubility : Soluble in *water*; sparingly soluble in *alcohol*; practically insoluble in *solvent ether* and in *chloroform*; soluble in *glycerin*.

Standards : Morphine Hydrochloride is the trihydrate of the hydrochloride of 7,8-didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol, which may be obtained from opium. It contains not less than 98.0 per cent and not more than the equivalent of 100.5 per cent of $C_{17}H_{19}NO_3, HCl$, calculated with reference to the dried substance.

Identification : (A) Sprinkle a small quantity in powder form on the surface of a drop of *nitric acid*; an orange-red colour is produced.

(B) To a 2 per cent w/v solution add *potassium ferricyanide solution* containing 1 drop per ml of *ferric chloride test-solution*; an immediate bluish-green colour is produced (distinction from codeine).

(C) Add 5 ml of *sulphuric acid* to 5 mg in a test tube, and add 1 drop of *ferric chloride test solution*, and heat in boiling water for two minutes; a deep blue colour is produced. Add a drop of *nitric acid*; the colour changes to dark red-brown (codeine and ethylmorphine give the same colour reactions, but dihydromorphine and papaverine do not produce this colour change).

(D) Add to about 1 mg of the powdered substance in a porcelain dish 0.5 ml of *sulphuric acid* containing 1 drop of *formaldehyde solution*. A purple colour is formed which turns to violet.

(E) Dissolve about 5 mg in 5 ml of *water*, and add 1 ml of *hydrogen peroxide solution*, 1 ml of *dilute ammonia solution* and 1 drop of a 4 per cent w/v solution of *copper sulphate*. A transient red colour develops.

(F) A solution (1 in 20) gives the reactions of *chlorides*, Appendix 3.1.

Acidity or Alkalinity : Dissolve 0.2 g in 10 ml of freshly boiled and cooled *water* add 1 drop of *methyl red solution*. Not more than either 0.2 ml of 0.02N *sodium hydroxide* or of 0.02N *hydrochloric acid* is required to change the colour of the solution.

Specific optical rotation : Between -112° and -115° , calculated with reference to the dried substance and determined in a 2 per cent w/v solution, Appendix 5.12.

Ammonium salts : Heat 0.2 g with *sodium hydroxide solution* on a water-bath for one minute; no odour of ammonia is perceptible.

Other alkaloids : Not more than 1.5 per cent, calculated with reference to the dried substance, determined by the following method: Transfer 0.5 g to a separator, add 15 ml of *water*, 5 ml of *N sodium hydroxide*, and 10 ml of *chloroform*, shake, allow to separate, and transfer the chloroform solution to another separator. Repeat the extraction with two further quantities, each of 10 ml, of *chloroform*. Wash the mixed chloroform solutions with 10 ml of 0.1N *sodium hydroxide* and then with two successive quantities, each of 5 ml, of *water*, evaporate to dryness on a water-bath, and dry the residue to constant weight at 105° .

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TITLE: Elimination of Elyzol 25% Dentalgel matrix from periodontal pockets.

AUTHOR: Stoltze K

AUTHOR AFFILIATION: Department of Periodontology, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Denmark.

SOURCE: J Clin Periodontol 1995 Mar;22(3):185-7

NLM CIT. ID: 95310528

ABSTRACT: Elyzo 25% Dentalgel (EDG) which is developed for use in the treatment of periodontitis is a suspension of metronidazole benzoate (40%) in a mixture of glyceryl mono-oleate (GMO) and triglyceride (sesame oil). Metronidazole can be detected in the periodontal pockets 24-36 h after application. The aim of the present study was to estimate the period of time that the gel matrix persists on periodontal pockets after 1 application of EDG. 12 patients were included in the study. From each patient, 1 sample was taken before and immediately after, and 1, 2, 3, 4, 5, 6, 8, 12 and 24 h after application. Subgingival scaling followed by absorption of gingival crevicular fluid with filter paper was used for sampling. The sampling unit was 1 tooth. Each sample was assayed for the amount of GMO and oleic acid (a degradation product of GMO) by means of high-performance liquid chromatography (HPLC) with UV detection. To allow determination of the GMO dose applied into the pockets and to estimate the recovery rate of the sampling method, 1 tooth in each patient was selected for sampling as soon as the gel had set, i.e., about 10 min after application. Only in 1 patient was a detectable amount of GMO within the pocket revealed 24 h after application. This amount was approximately 0.5% of the mean GMO dose applied around 1 tooth. GMO was found no longer than 12 h in the remaining patients.

MAIN MESH SUBJECTS: Glycerides/ADMINISTRATION & DOSAGE/ANALYSIS/*PHARMACOKINETICS
Metronidazole/*ANALOGS & DERIVATIVES/ADMINISTRATION & DOSAGE/ ANALYSIS/*PHARMACOKINETICS
Periodontal Pocket/*METABOLISM
Sesame Oil/ADMINISTRATION & DOSAGE/ANALYSIS/*PHARMACOKINETICS

A. INGREDIENT NAME:

PHENINDAMINE TARTRATE

B. Chemical Name:

1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate; 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno-[2,1*c*]pyridine hydrogen tartrate.

C. Common Name:

Thephorin, Dalca, Nolamine, Melodan, Cerose, Carrhist

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Limits)</i>	<i>(Results)</i>
Dry Basis:	98.0% - 101.5%	99.7%

E. Information about how the ingredient is supplied:

A white to cream white crystalline powder. Is odorless or almost odorless.

F. Information about recognition of the substance in foreign pharmacopeias:

Arg., Br., Ind., Int., and Turk.
British Pharmacopeia 1993

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Witek, T. J., Canastrari, D. A., and Miller, R. D. The effects of phenindamine tartrate on sleepiness and psychomotor performance. *J. Allergy Clin Immunol*, 1992;90(6 Pt 1): 953-961.

Sigidinenko, L. V. Various principles of therapeutic tactics in epilepsy patients during pregnancy. *Zh Nevropatol Psikhiatr*, 1984; 84(6): 897-899.

H. Information about dosage forms used:

Tablets
Liquid
Elixir
Capsules

I. Information about strength:

25-50mg

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 162-167° with decomposition.
Solutions were unstable above pH 7 and were most stable at pH 3.5-5. Heating could cause phenindamine to isomerise to an inactive form.

L. Formulations:

M. Miscellaneous Information:

55-2779
30248

CERTIFICATE OF ANALYSIS

Product: **PHENINDAMINE TARTRATE**
Lot No.: **587-65-256**
Date of Analysis: **November 11, 1993**

<u>TESTS</u>	<u>LIMITS</u>	<u>RESULTS</u>
Identification:		
A. Acetic Anhydride and Acetic Acid Test:	A red-violet color must be produced.	Passes Test.
B. Pyridine and Acetic Anhydride Test:	An emerald green color must be produced.	Passes Test.
C. Infrared Spectrum:	Agrees with reference standard.	Passes Test.
D. Ultraviolet:		
1. Spectrum:	Maximum wavelength must be 260 ± 2 nm and minimum at 241 ± 2 nm.	Passes Test.
2. Absorptivities:	Abs. must not differ by more than 3.0%.	1.7%
pH:	3.0 to 4.0	3.5
Loss on Drying:	NMT 1.5%	0.11%
Residue on Ignition:	NMT 0.25%	0.007%
Heavy Metals:	NMT 0.002%	<0.002%
Iron:	NMT 0.005%	<0.005%
Isophenindamine:	NMT 2.0%	1.3%
Assay:		
A. As is Basis:	NLT 96.5%	99.6%
B. Dry Basis:	98.0% to 101.5%	99.7%

0

10/94

QUALITY CONTROL REPORT

CHEMICAL NAME.: PHENINDAMINE TARTRATE

MANUFACTURE LOT NO.:

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

A WHITE TO CREAM WHITE CRYSTALLINE POWDER. IS ODORLESS OR ALMOST ODORLESS.

2) SOLUBILITY.:

SOLUBLE IN 70 PARTS OF WATER; SLIGHTLY SOLUBLE IN ETHANOL (96%); PRACTICALLY INSOLUBLE IN CHLOROFORM AND IN ETHER.

3) MELTING POINT.:

MELTS AT ABOUT 162-167 degree WITH DECOMPOSITION.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

- A) COMPLIES (A) AS PER CO. SPECS.
- B) COMPLIES (B) AS PER CO. SPECS.
- C) COMPLIES (C) AS PER IR SPECTRUM CO. SPECS.

PASSES.: _____

FAILS.: _____

COMMENTS.: ABOVE TEST IS CARRIED OUT BY SUPPLIER CERT. OF ANALYSIS.

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

ALFA CHEM

TEL:(516) 277-7681
TLX: 650 481 1992
FAX:(516) 277-7681

1661 N.SPUR DR. C.ISLIP, NY 11722-4325

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

Page 1 of 7

IDENTIFICATION:

Product Name: Phenindamine tartrate

CAS Registry Number: 569-59-5

RECS Accession Number: NK9460700

Date of Issue: 3/3/92

Chemical Names: 1. 1H-indeno(2,1-c)pyridine, 2,3,4,9-tetrahydro-2-methyl-9-phenyl-, tartrate.
2. 2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1H-indeno(2,1-c)pyridine tartrate.

Synonyms: 1. Phenindamine acid tartrate.
2. Phenindamine tartras.

REMARKS:

Phenindamine tartrate is an antihistamine which may have a stimulant effect. It is toxic if ingested in larger than therapeutic quantities. Wear a NIOSH-approved respirator, goggles, and gloves when handling the material. Use only with adequate ventilation. Wash exposed skin with soap and water. Sweep up spilled material for recovery and flush the swept spill area once with detergent and water. If the spilled material cannot be recovered, incineration is the recommended disposal procedure.

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

Page 2 of 7

HAZARDOUS INGREDIENTS:

<u>Hazardous Components</u>	<u>CAS Number</u>	<u>Percent</u>	<u>OSHA PEL</u>	<u>ACGIH TLV</u>
Phenindamine tartrate	569-59-5	not <98.5	n/a	n/a

PHYSICAL DATA:

Description/odor: White or almost white, almost odorless, voluminous powder.

Melting Range: 160 to 162 degrees C. Boiling Point: n/a

Vapor Density: n/a Vapor Pressure: n/a

Solubility: Soluble in 70 parts of water.

Molecular Weight: 411.45 Specific Gravity: n/a

Molecular Formula: C19H19NC4H6O6 Evaporation Rate:

FIRE AND EXPLOSION DATA:

Flash Point: n/a Flammable Limits: n/a

LEL: n/a UEL: n/a

Extinguishing Media: Water spray, carbon dioxide, or dry chemical.

Special Fire Fighting Instructions:

Isolate hazard and evacuate confined areas. Stay upwind, avoid smoke and fumes. Use water spray to wet containers. If smoke and fumes cannot be avoided, wear a chemical-proof suit with hood and breathing air supply. Fight fire from maximum distance.

Unusual Fire and Explosion Hazards: n/a

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

Page 3 of 7

REACTIVITY DATA:Stability: Stable.Conditions to Avoid: n/aIncompatibility: n/aHazardous Decomposition or Byproducts: When heated to decomposition, toxic fumes such as nitrogen oxides and carbon monoxide are emitted.HEALTH DATA:Toxicity (Reference 2):

Oral LD50	-	rat:	280 mg/kg.
Oral LD50	-	mouse:	255 mg/kg.
Oral LD50	-	rabbit:	577 mg/kg.
Intraperitoneal LD50	-	mouse:	88 mg/kg.
Intravenous LD50	-	mouse:	18 mg/kg.
Subcutaneous LDLo	-	rat:	200 mg/kg.

Saks: Highly toxic by oral administration.CSHA: Toxic material.Routes of Entry: Inhalation, ingestion, and dermal.Acute or Chronic Health Hazards: n/aSigns and Symptoms of Exposure:ACUTE SKIN: Allergic reactions and skin sensitization may occur.INGESTION: Small amounts ingested could lead to nausea, vomiting, diarrhea, anorexia, epigastric pain, blurred vision, tightness of the chest, muscular weakness, headaches, and CNS stimulation. Larger amounts could lead to coma and convulsions.INHALATION: No information available.CHRONIC EXPOSURE: Might impair the power of voluntary motion.Medical Conditions GenerallyAgravated by Exposure:

Acute vesicular and exudative dermatosis, narrow angle glaucoma, hepatic or cardiovascular disorders, focal lesions of the cerebral cortex.

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

Page 4 of 7

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Emergency and First Aid Procedures:

Product on Skin: Immediately wash with water and soap. Remove contaminated clothing while washing proceeds. Contaminated clothing should be washed or dry-cleaned before reuse. Get medical attention if necessary.

Product Inhaled: Remove from exposure, keep warm, and at rest. If breathing is difficult, give oxygen. If not breathing, give artificial respiration. Get medical attention if necessary.

Product Ingested: If conscious, induce vomiting by giving ipecac syrup or two glasses of warm water followed by tickling the back of the throat with a tongue depressor. After vomiting stops, give the patient one or two tablespoons of activated charcoal in a glass of water. Get medical attention immediately.

Product in Eye: Immediately flush the eyes with large amounts of water for 15 minutes. Lift upper and lower lids occasionally. Get medical attention if necessary.

Carcinogenicity: Not listed as a carcinogen by OSHA, ACGIH, NTP, or IARC.

Target Organs: None listed.

Safety Precautions: Avoid breathing the dust.
Avoid contact with eye and skin.
Wash thoroughly after handling.

=====

PROTECTION INFORMATION:

Use with adequate ventilation to prevent dust build up. Wear a NIOSH-approved respirator, gloves, goggles, and other appropriate protective equipment to prevent exposure when handling the product.

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MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

Page 5 of 7

SPILL AND DISPOSAL INFORMATION:

Shovel large quantities of spilled material into drums. Sweep up the spill area and save the swept-up material for recovery. Wash the swept spill area once with detergent and water. If the material cannot be recovered, the preferred method of disposal is incineration in a facility which complies with all federal, state, and local requirements.

STANDARDS AND REGULATIONS:

DOT: Not regulated.

IATA: Not regulated.

IMO: Not regulated.

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

Page 6 of 7

REFERENCES:

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2. Registry of Toxic Effects of Chemical Substances Service, July 1991, update 9107.
3. NIOSH Pocket Guide To Chemical Hazards, U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health, Washington, D.C., June 1990.
4. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Geneva: World Health Organization, International Agency for Research on Cancer, 49 Sheridan Street, Albany, New York.
5. IATA Dangerous Goods Regulations, International Air Transport Association, Montreal, Quebec, Canada. 33rd Edition, 1992.
6. International Maritime Dangerous Goods Code, International Maritime Organization, London, England, 1982.
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10. Handbook of Emergency Toxicology, Sidney Kaye, Fifth Edition, 1988.
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12. American Hospital Formulary Service-Drug Information 89, American Society of Hospital Pharmacists, Bethesda, MD, 1989.

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

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13. AMA Drug Evaluations, 5th, Edition, American Medical Association, W.B. Saunders Company, Philadelphia, PA, 1983.
 14. The Merck Index, 10th Edition, Merck & Co., Inc., Rahway, NJ, 1983.
 15. The Sigma-Aldrich Library of Chemical Safety Data, 1st. Edition, Edited by Robert E. Langa, Sigma-Aldrich Corp., Milwaukee, WI, 1985.
 16. Fourth Annual Report on Carcinogens, U.S. Dept. of Health and Human Services, Research Triangle Park, N.C., National Toxicology Program, 1985.
 17. Handbook of Toxic and Hazardous Chemicals and Carcinogens, 3rd. Edition, Marshall Sittig, Princeton University (retired), 1991.
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ALFA CHEM

6148-y

Methdilazine (U.S.P.), 10-(1-Methylpyrrolidin-3-ylmethyl)phenothiazine.
 $C_{18}H_{20}N_2S=296.4$.

CAS — 1982-37-2.

Pharmacopoeias. In U.S.

A light tan crystalline powder with a characteristic odour. M.p. 83° to 88° with a range of not more than 2°. Methdilazine 7.2 mg is the equivalent of approximately 8 mg of methdilazine hydrochloride. Practically insoluble in water; soluble 1 in 2 of alcohol, 1 in 1 of chloroform, and 1 in 8 of ether; freely soluble in 3M hydrochloric acid. Store in airtight containers. Protect from light.

Methdilazine has actions and uses similar to those of methdilazine hydrochloride. It is given in usual doses of 7.2 mg two to four times daily.

Preparations

Methdilazine Tablets (U.S.P.). Tablets containing methdilazine. Store in airtight containers. Protect from light.

Proprietary Names

Tacaryl (Westwood, USA).

6149-j

Methdilazine Hydrochloride (U.S.P.), 10-(1-Methylpyrrolidin-3-ylmethyl)phenothiazine hydrochloride.

 $C_{18}H_{20}N_2S.HCl=332.9$.

CAS — 1229-35-2.

Pharmacopoeias. In U.S.

A light tan crystalline powder with a slight characteristic odour. It darkens on exposure to light. M.p. 184° to 190°. Soluble 1 in 2 of water and of alcohol, and 1 in 6 of chloroform; practically insoluble in ether; soluble in 0.1 M hydrochloric acid and 0.1 M sodium hydroxide solution. A 1% solution in water has a pH of 4.8 to 6. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions. As for the antihistamines in general, p.1294.

As with all phenothiazine derivatives it should be used cautiously in patients with hepatic diseases.

Uses. Methdilazine hydrochloride is a phenothiazine derivative with the properties and uses of the antihistamines (see p.1295). It is more potent than promethazine and generally causes less sedation. It has a duration of action of 8 to 12 hours. It has serotonergic and anticholinergic properties.

Methdilazine hydrochloride is given for the symptomatic treatment of allergic conditions, particularly to control pruritus. It may also be given for pruritus of non-allergic origin. The usual dose is 8 mg twice daily and may be increased to 4 times daily if necessary. Children may be given 300 µg per kg body-weight daily in 2 divided doses.

Allergy. Ninety-six patients suffering from allergy, of whom 58% had pruritus and 27% hay fever, were studied over 2 weeks in a double-blind study designed to compare methdilazine hydrochloride with promethazine hydrochloride. The dose was usually 8 mg of the former and 20 mg of the latter, twice daily in syrup. Both drugs gave relief to about one-half the patients and there was little difference in efficacy for pruritus, but promethazine was superior to methdilazine in the relief of hay fever. Drowsiness occurred in 32% of the patients when they were taking promethazine, being twice the incidence seen with the other drug, but in spite of this the patients generally preferred it.—Report No. 25 of the General Practitioner Research Group, *Practitioner*, 1962, 138, 803.

Migraine. Methdilazine 4 to 8 mg thrice daily was useful to prevent or reduce the frequency of migraine attacks.—J. M. Sutherland, *Drugs*, 1973, 5, 212.

For a report of the use of methdilazine in the treatment of migraine, see Methysergide Maleate, p.669.

Preparations

Methdilazine Hydrochloride Syrup (U.S.P.). A syrup containing methdilazine hydrochloride, with alcohol 6.5 to 7.5%. pH 3.3 to 4.1. Store in airtight containers. Protect from light.

Methdilazine Hydrochloride Tablets (U.S.P.). Tablets containing methdilazine hydrochloride. Store in airtight containers. Protect from light.

Proprietary Names

Dilosyn (Allen & Hanburys, Austral.; Allen & Hanburys, Canad.); Tacaryl (Mead Johnson, Austral.; Pharmacia, Swed.; Westwood, USA); Tacryl (Pharmacia, Denm.).

Methdilazine hydrochloride was formerly marketed in Great Britain under the proprietary name Dilosyn (Duncan, Flockhart).

6150-q

Metiamide. SKF 92058. 1-Methyl-3-[2-(5-methylimidazol-4-ylmethylthio)ethyl]thiourea.
 $C_9H_{16}N_4S_2=244.4$.

CAS — 34839-70-8.

Adverse Effects. Metiamide may cause agranulocytosis.

Acute reversible neutropenia occurred in 2 patients given metiamide.—J. A. H. Forrest *et al.* (letter), *Lancet*, 1975, 1, 392. Bone-marrow depression due to metiamide was thought to be due to the thiourea present in the metiamide molecule, rather than to H₂-receptor blockade.—*ibid.*, 1975, 2, 802.

A further 4 cases of metiamide-induced agranulocytosis had occurred and trials had stopped.—W. L. Burland *et al.*, *Smith Kline & French* (letter), *Lancet*, 1975, 2, 1085.

Further references: E. J. Feldman and J. I. Isenberg, *New Engl. J. Med.*, 1976, 295, 1178.

Uses. Metiamide is a histamine H₂-receptor antagonist (see p.1294) with actions similar to those of cimetidine (p.1303) but a shorter duration of action. It has been used in doses of 1 g daily in conditions associated with gastric hyperacidity but has been found to cause bone-marrow depression.

References to the action and uses of metiamide: R. W. Brimblecombe *et al.*, *S. Afr. med. J.*, 1974, 48, 2253; D. M. Shepherd *et al.*, *Digestion*, 1974, 11, 307; B. Thjodleifsson and K. G. Wormsley, *Br. med. J.*, 1974, 2, 304; *idem*, *Gut*, 1975, 16, 501; G. I. Barbezat *et al.*, *Gut*, 1975, 16, 186; J. I. Isenberg, *Ann. intern. Med.*, 1976, 84, 212; A. S. MacDonald *et al.* (preliminary communication), *Lancet*, 1976, 1, 68; J. M. Hind and T. J. Sutton, *J. Pharm. Pharmacol.*, 1977, 29, 244; O. R. Griffith *et al.*, *Br. J. Pharmacol.*, 1978, 64, 416P.

Duodenal ulcers. References to the use of metiamide in duodenal ulcers: M. Mainardi *et al.*, *New Engl. J. Med.*, 1974, 291, 373; G. J. Milton-Thompson *et al.*, *Lancet*, 1974, 1, 693; R. E. Pounder *et al.*, *Br. med. J.*, 1975, 2, 307; *Lancet*, 1975, 2, 779; *ibid.*, 802; R. Earlam (letter), *ibid.*, 973; J. H. B. Saunders and K. G. Wormsley, *Lancet*, 1977, 1, 765.

Zollinger-Ellison syndrome. References to the use of metiamide in the Zollinger-Ellison syndrome: M. H. Thompson *et al.* (letter), *Lancet*, 1975, 1, 35; L. G. Halloran *et al.* (letter), *ibid.*, 281; E. R. Smith *et al.*, *Med. J. Aust.*, 1976, 1, 1000; D. M. McCarthy *et al.*, *Ann. intern. Med.*, 1978, 87, 668; J. K. Siepler *et al.*, *Am. J. Hosp. Pharm.*, 1978, 35, 141.

Manufacturers

Smith Kline & French, UK.

6151-p

Oxomemazine. RP 6847; Trimeprazine SS-Dioxide. 10-(3-Dimethylamino-2-methylpropyl)phenothiazine 5,5-dioxide.
 $C_{18}H_{22}N_2O_2S=330.4$.

CAS — 3689-50-7.

A white crystalline powder with a bitter taste. M.p. 155°. Practically insoluble in water; slightly soluble in alcohol; soluble in chloroform and ether.

6152-s

Oxomemazine Hydrochloride. $C_{18}H_{22}N_2O_2S.HCl=366.9$.

CAS — 4784-40-1.

Crystals. M.p. 250°. Oxomemazine hydrochloride 11.1 mg is approximately equivalent to 10 mg of oxomemazine.

Oxomemazine is a phenothiazine derivative with the properties and uses of the antihistamines (see p.1294). It has been given both as the base and as the hydrochloride in doses equivalent to 10 to 40 mg of oxomemazine daily.

Proprietary Names

Doxergan (Specia, Belg.; Specia, Fr.; Specia, Neuchâtel; Specia, Switz.); Imakol (Rhône-Poulenc, Ger.).

6153-w

Phenindamine Tartrate (B.P.), Phenindamine Tartrate; Phenindaminium Tartrate; Phenindamine Acid Tartrate. 1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate;

2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1H-indeno[2,1-c]pyridine hydrogen tartrate,
 $C_{19}H_{19}N.C_4H_6O_6=411.5$.

CAS — 82-88-2 (phenindamine); 569-59-5 (tartrate).

Pharmacopoeias. In Arg., Br., Ind., Int., and Turk.

A white or almost white, almost odourless, voluminous powder with a bitter taste. M.p. 160° to 162°; on further heating it solidifies and melts again at about 168° with decomposition. Soluble 1 in 70 of water and 1 in 300 of alcohol; practically insoluble in chloroform and ether. A 1% solution in water has a pH of 3.4 to 3.9. Store in airtight containers. Protect from light.

Incompatibility. Incompatible with alkalis, sodium metacrylate, phosphates, and oxidising substances. Solutions were unstable above pH 7 and were most stable at pH 3.5 to 5. Heating could cause phenindamine to convert to an inactive form.—*J. Am. Pharm. Assoc. Sci. Pharm. Edn*, 1956, 17, 213.

Adverse Effects, Treatment, and Precautions. As for the antihistamines in general, p.1294.

Unlike most other antihistamines phenindamine tartrate may have a stimulant effect; to avoid the possibility of insomnia it should not be given after 4 p.m.

Allergy. In a modified 'repeated-insult' patch test phenindamine tartrate was found to produce cutaneous sensitisation of the skin.—A. M. Kligman, *J. Invest. Derm.*, 1966, 47, 393.

Extrapyramidal symptoms. For a report of extrapyramidal dyskinesia associated with the use of phenindamine tartrate, see Brompheniramine Maleate, p.1298.

Uses. Phenindamine tartrate has the properties and uses of the antihistamines (see p.1295). It is less potent than promethazine but it does not generally produce drowsiness and may even be mildly stimulating. It has a moderate anticholinergic action.

Phenindamine tartrate is given in doses of 25 to 50 mg up to thrice daily.

Preparations

Phenindamine Tablets (B.P.). Tablets containing phenindamine tartrate. They are sugar-coated.

Thenhorin (Sinclair, UK). Phenindamine tartrate available as tablets of 25 mg. (Also available as a syrup in Austral., S. Afr.).

6154-e
 Phenindamine Maleate
 1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen maleate;
 $C_{19}H_{19}NO_4$
 CAS
 maleate
 Pharma.
 A white
 slightly
 soluble
 in 1
 ether.
 S. S.
 light.
 Adverse
 effects
 general
 Abuse.
 50 mg
 im. O
 marestia
 tion re
 a. al. A
 A report
 who ha
 aminosa
 Med. J.
 Overdos
 major f
 1500 mg
 Med. J.
 Pregnan
 effects
 pregnan
 Treatm
 histam
 Adverse
 effects:
 Boehm
 Overdos
 with ca
 cardiog
 Gamore
 Cooke:
 patient
 (letter)
 Precau
 p.1294
 Absorp
 genera
 On ave
 amine
 repeats
 maleate
 Common
 miramin
 Kabasa
 Uses.
 with th
 (see p.
 has a
 causes
 Phenir
 up to
 prepar
 75 mg
 require
 The d
 daily:
 15 to
 Phenir
 malicy,
 usual
 also be
 Propri
 euterai
 base. I
 Owing
 these
 drug is

phenylthiocarbamate.
 osmolytic agent.
CLIDINE HYDROCHLORIDE. (Parke, 1-(1-phenylcyclohexyl)piperidine hydro-
 .
 rnyl
 analgesic, anesthetic.
ETRAZINE BITARTRATE. Calorie
 0.3/Tab. See: Plegine (Ayerst Lab.)
ZINE. (MacAllister) Amphetamine sulfate.
 oz., 1 pt., 1 gal.
 entral nervous system stimulant.
GERMICIDAL SOLUTION & TINC-
 (Ulmer) Benzalkonium Chloride,
 1%. Bot. 1 qt. & 1 gal.
ZINE SULFATE, N. N. D. 1963. Mono-
 xidase inhibitor, beta-phenylethyl-
 ne sulfate. See: Nardil (Warner-Chilcott)
GAM HCl, N. N. D. 1963. (Wyeth)
 (hazine) N-(2-Dimethylamino-2'-
 thyl)phenothiazine HCl.
 2%, Tube 1.12 oz. Lot., Phenergan 2%,
 mine 15%. Bot. 4 oz.
 25 mg.) Box 12s.
 ntihistaminic.
GAM EXPECTORANT TROCHES.
 Ph. 1.5 mg., Ipecac pow. ext. 2.3
 ol. sulfonate 162 mg./Troche.
 .
 xpectorant.
**GAM EXPECTORANT TROCHES W/
 NE.** (Wyeth) Phenergan 1.5 mg., codeine
 ., Ipecac pow. ext. 2.3 mg., Pot.
 i sulfonate 162 mg./Troche. Jar 36s.
 xpectorant.
GAM HYDROCHLORIDE, N. N. D. 1960.
 . Expectorant: Phenergan HCl 5 mg.,
 ephrine HCl 5 mg., Ipecac fidxt. 0.17
 ol. guaicol sulfonate 44 mg., chloro-
 25 mg., citric acid 60 mg., Sod. citrate
 .75 cc. Bot. 1 pt. Also avail. w/codeine
 ate 1/6 gr./dr. Supp. 25 mg. Box 12s.
 Phenergan HCl 6.25 mg./5 cc. Also
 25 mg./5 cc. Bot. 1 pt. Tab.: Phenergan
 1.5 mg. & 50 mg./Tab. Bot. 100s.
GAM INJECTION. (Wyeth) Promethazine
 vial (25 mg./cc.) 10 cc.; (50 mg./cc.) 10

***PHENERIDINE.** 1-(b-phenyl-b-ethyl)-4-car-
 bethoxy-4-phenylpiperidine.
***PHENETHICILLIN POTASSIUM, N. N. D. 1963.**
 Alpha-phenoxyethyl penicillin pot. Penicillin-152
 pot. See: Alpen, Tabs. (Schering)
 Broxil (Beecham Res.)
 Chemipen, Tab. (Squibb)
 Darcil (Wyeth)
 Dramcillin-s (White)
 Maxipen, Tab. (Roering)
 Ro-Cillin, Tabs. (Rowell)
 Semopen, Tab., Pow. (Massengill)
 Syncillin, Tab. (Bristol)
PHENETRON INJECTABLE. (Lannett)
 Chlorpheniramine maleate 100 mg./cc. Vial 5 cc.
PHENETSAL, N. N. R. 1948.
 See: Salopen, Tab. (Winthrop Labs.)
***PHENFORMIN HCl, N. N. D. 1963.** N'-phen-
 ethylbiguanide HCl.
 See: D. B. I. (U. S. Vitamin)
PHENICHTHOL. (Parke, Davis) Phenol 2%,
 ammonium ichthosulfonate, alum & lead plaster.
 Use: Antiseptic.
***PHENINDAMINE TARTRATE, U. S. P.; Syr. H**
 or Tab., U. S. P. 2-Methyl-9-phenyl-2, 3, 4, 9-
 tetrahydro-1-pyridindene tartrate.
 See: Thephorin, Prep. (Roche)
 W/Aluminum aspirin, chlorpheniramine maleate,
 phenylephrine HCl.
 See: Dalca, Tabs. (Ascher) H
 W/Chlorpropenpyridamine maleate, phenylpro-
 panolamine HCl.
 See: Nolamine, Tab. & Elix. (G. W. Carrick)
 W/Dextromethorphan, chlorpheniramine, maleate,
 phenylephrine HCl, menthol.
 See: Melodan, Symp. (Mayrand)
 W/Dextromethorphan HBr, phenylephrine.
 See: Ceroze, Pediatric (Ives-Cameron)
 W/Phenylephrine hydrochloride, caramiphen
 ethanedisulfonate. See: Dondril (Whitehall Labs.)
 W/Phenylephrine HCl, chloroform, Ipecac fidxt.,
 glycerin, pot. guaicol sulfonate, sod. citrate,
 citric acid. See: Ceroze, Liq. (Ives-Cameron) H
 W/Pyrilamine maleate, chlorpheniramine maleate,
 phenylephrine. See: Carrhist Elixir (Carrtone) H
 W/Sulfadimethoxine, N-acetyl-p-aminophenol,
 caffeine. See: Madricidin, Cap. (Roche) H
***PHENINDIONE, N. N. D. 1963.** (2-Phenylin-
 dane-1, 3-Dione; 2-Phenyl-1, 3-Indandione;
 Phenylindanedion, Dindevan)
 See: Danilone, Tab. (Schieffelin)
 Hedulin, Tab. (Walker)
 Indon, Tab. (Parke, Davis)
PHENIODOL. See: Iodoaliphonic Acid
***PHENIPRAZINE HCl.**
 See: Catron, Tab. (Lakeside)
***PHENIRAMINE.** 1-Phenyl-1-(2-pyridyl)-3-di-
 methylaminopropane. (No pharmaceutical form
 available.)

W/Codeine phosphate.
 See: Antosen, Syr. (Squibb)
 W/Scopolamine HBr.
 See: Nio-Piracene, Tab. (Nion)
***PHENIRAMINE MALEATE, N. F., N. N. D.**
 1963 Tab., N. F.; Ophth. Sol., N. F. 1-Phenyl-
 1-(2-pyridyl)-3-dimethylamino-propane maleate.
 Prophenpyridamine.
 See: Inhibston (Upjohn)
 Trimeton (Schering)
 W/Acetophenetidin, aspirin, phenobarbital,
 hyoscyamine sulfate, phenylephrine HCl.
 See: Phenaphen Plus, Tab. (Robins)
 W/Ammonium chloride, Sod. citrate & chloroform.
 See: Trimetose, Syr. (Schering)
 W/d-Amphetamine sulfate, chloroform, menthol
 & alcohol.
 See: Tussate, Syr. (Pitman-Moore)
 W/Dihydrocodeinone bitartrate, Pot. guaicol
 sulfonate, Sod. citrate, citric acid & chloroform.
 See: Tussar, Liq. (Armour)
 W/Dihydrocodeinone bitartrate, Vit. C, pyrilamine
 maleate pot. citrate.
 See: Citra Forte. (Boyle)
 W/Dihydrocodeinone bitartrate, phenylpropanol-
 amine HCl, pyrilamine maleate, glyceryl guaicol-
 ate, chloroform.
 See: Tussaminic Expectorant, Symp. (Smith-
 Dorsey)
 W/Dihydrocodeinone bitartrate, pyrilamine maleate,
 phenylephrine HCl, pot. guaicol-sulfonate,
 cherry flavor.
 See: Nova-Tussa, Liq. (Drug Specialties-Prane)
 W/Doxylamine succinate, pyrilamine maleate.
 See: Tridecamine, Tab. (National)
 W/Ephedrine sulfate & ammonium chloride.
 See: Extosen, Syr. (Squibb)
 W/Glyceryl guaicolate, desoxyephedrine HCl &
 codeine phosphate.
 See: Robitussin A-C, Syr. (Robins)
 W/Hesperidin, ascorbic acid, thenylpyramine
 fumarate, pyrilamine maleate, salicylamide,
 caffeine. See: Tripac, Cap. (Person & Covey)
 W/Hesperidin, phenylephrine HCl, methapyrilene
 HCl, pyrilamine maleate, vit. C, salicylamide,
 acetophenetidin, caffeine.
 See: Boyle Citra, Caps. (Boyle)
 W/Narcotine, phenylephrine HCl, chloroform,
 menthol. See: Conar, Liq. (Massengill)
 W/Phenylephrine HCl.
 See: Danilone, Tab. (Broemmel)
 W/Phenylephrine HCl.
 See: Phenistan, Tab. (Chicago Pharm.)
 W/Phenylephrine HCl, acetyl-p-aminophenol,
 atropine sulfate.
 See: TPC, Tab. (Tennessee Pharm.)
 W/Phenylephrine HCl, methapyrilene HCl, pyrila-
 mine maleate, aspirin, acetophenetidin,
 caffeine, Vit. C, hesperidin.

See: Darbacin, Cap. (Crestmed)
 W/Phenylephrine HCl, pyrilamine ma-
 ascorbic acid. See: Corizahist,
 W/Phenylephrine HCl, pyrilamine ma-
 methapyrilene HCl.
 See: Citra H. F., Cap. (Boyle)
 W/Phenylephrine HCl & A. P. C.
 W/A. P. C., Cap. (Pitman-Moore)
 See: Novahistine
 W/Phenylephrine HCl, chloroform &
 See: Novahistine, Elixir. (Pitmar)
 W/Phenylpropanolamine HCl, glycer
 See: Darathon, Sol. (Grail)
 W/Phenylpropanolamine HCl, pyrilam
 See: Triaminic, Preps. (Smith-Do
 W/Phenylpropanolamine HCl, pheny
 pyrilamine maleate.
 See: Synergen, Elix. (Lemmon)
 W/Phenylpropanolamine HCl, pheny
 pyrilamine maleate, acetyl-p-amin
 See: Phenagesic (Dalin)
 W/Pyrilamine maleate.
 See: Triaminic, Tab. (Smith-Dors
 W/Pyrilamine maleate, dioxylamine
 See: Tridecamine, Tab. (Merrell)
 W/Pyrilamine maleate & methapyrile
 See: Incorpoist, Tab. (Blue Lin
 Pediahist, Syr. (Columbus)
 Pyma Tamed, Cap. (Testagar)
 W/Pyrilamine maleate, phenylpropa
 See: Trialler, Tab. (Lemor)
 W/Pyrilamine Maleate, phenylpropa
 trisulfapyrimidines.
 See: Trisulfaminic, Prep. (Smith
 W/Pyrilamine Maleate & phenyltolol
 dihydrogen citrate.
 See: Multibist, Cap. & Syr. (Smi
 W/Salicylamide, acetophenetidin, c
 ascorbic acid, hesperidin purific
 See: Coryban, Cap. (Roerig)
 W/Scopolamine hydrobromide, alumi
 gel, ethyl aminobenzoate.
 See: Daptren, Tab. (Davis & Sly
 W/Thenylpyramine HCl, pyrilamine
 phenylpropanolamine.
 See: Histene, Tab. (Paul Maney
 W/Tyrothricin, neomycin, benzocai
 See: Neo-T-Cain, Lozenges (Chi
 W/Vit. C, aspirin & alkalizing bas-
 See: Cahistra, Tab. (Organon)
PHENIRATAN. (Irwin, Neisler) Cl
 tannate 15 mg./Tab. Bot. 100s.
 Use: Antihistamine.
***PHENISONONE HBr.** 3, 4-dihydr
 isopropylaminopropiophenone HBr
 See: Dapanone HBr (Merck, Shar
PHENISTAM. (Chicago Pharm.) P
 10 mg., prophenpyridamine male-
 tab. Bot. 50s, 100s, 1000s.

end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of iodine required. Each ml of 0.05M iodine VS is equivalent to 5.857 mg of $C_8H_{12}N_2 \cdot H_2SO_4$.

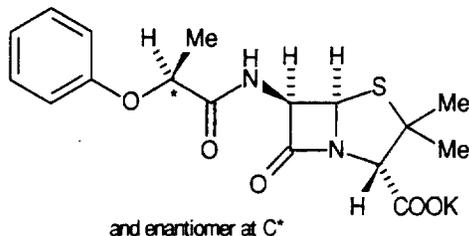
Storage Phenelzine Sulphate should be kept in a well-closed container and protected from light.

Preparation

Phenelzine Tablets

Action and use Monoamine oxidase inhibitor.

Phenethicillin Potassium



$C_{17}H_{19}KN_2O_5S$ 402.5 132-93-4

Definition Phenethicillin Potassium is potassium (6*RS*)-[(2*S*)-2-phenoxypropionamido]penicillanate. It contains not less than 97.0% and not more than 100.5% of $C_{17}H_{19}KN_2O_5S$, calculated with reference to the anhydrous substance.

Characteristics A white or almost white powder.

Freely soluble in *water*; sparingly soluble in *ethanol* (96%); slightly soluble in *absolute ethanol* and in *chloroform*; practically insoluble in *ether*.

Identification A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of phenethicillin potassium.

B. Dissolve 10 mg in 10 ml of *water* and add 0.5 ml of *neutral red solution*. Add sufficient 0.01M *sodium hydroxide* to produce a permanent orange colour and then add 1.0 ml of *penicillinase solution*. The colour changes rapidly to red.

C. Heat 0.5 g with 10 ml of 5M *hydrochloric acid* under a reflux condenser for 4 hours, cool, add a mixture of 7 ml of 5M *sodium hydroxide* and 7 ml of *water* and extract with successive 10-ml quantities of *ether* until complete extraction is effected. Wash the combined ether extracts with *water*, filter through *anhydrous sodium sulphate* and evaporate the filtrate to dryness. The *melting point* of the residue, after recrystallisation from *petroleum spirit* (*boiling range*, 40° to 60°), is about 116°, Appendix V A.

D. Ignite. The residue yields the reactions characteristic of *potassium salts*, Appendix VI.

Acidity or alkalinity pH of a 10% w/v solution, 5.5 to 7.5, Appendix V L.

Specific optical rotation In a 1% w/v solution in a solution containing 0.2% w/v of *dipotassium hydrogen orthophosphate* and 0.8% w/v of *potassium dihydrogen orthophosphate*, +217° to +244°, calculated with reference to the anhydrous substance, Appendix V F.

Iodine-absorbing substances Not more than 3%, calculated with reference to the anhydrous substance, when determined by the following method. Dissolve

0.125 g in sufficient *mixed phosphate buffer pH 7.0* to produce 25 ml. To 10 ml add 10 ml of *mixed phosphate buffer pH 4.0* and 10 ml of 0.01M *iodine VS* and titrate immediately with 0.01M *sodium thiosulphate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of iodine-absorbing substances present. Each ml of 0.01M *sodium thiosulphate VS* is equivalent to 0.425 mg of iodine-absorbing substances.

Water Not more than 1.5% w/w, Appendix IX C. Use 1.5 g.

Assay Dissolve 0.25 g in sufficient *water* to produce 500 ml and dilute 10 ml to 100 ml with *water*. Place two 2-ml aliquots of the resulting solution in separate stoppered tubes. To one tube add 10 ml of *imidazole—mercury reagent*, mix, stopper the tube and immerse in a water bath at 60° for exactly 25 minutes, swirling occasionally. Remove from the water bath and cool rapidly to 20° (solution A). To the second tube add 10 ml of *water* and mix (solution B). Without delay measure the *absorbances* of solutions A and B at the maximum at 325 nm, Appendix II B, using in the reference cell a mixture of 2 ml of *water* and 10 ml of *imidazole—mercury reagent* for solution A and *water* for solution B. Calculate the content of $C_{17}H_{19}KN_2O_5S$ from the difference between the absorbances of solutions A and B, from the difference obtained by repeating the operation using *phenethicillin potassium BPCRS* in place of the substance being examined and from the declared content of $C_{17}H_{19}KN_2O_5S$ in *phenethicillin potassium BPCRS*.

Storage Phenethicillin Potassium should be kept in a well-closed container.

Labelling The label states (1) the date after which the material is not intended to be used; (2) the conditions under which it should be stored.

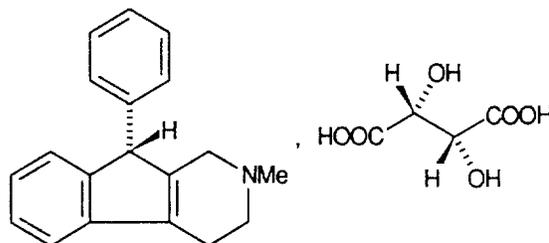
Preparations

Phenethicillin Capsules
Phenethicillin Tablets

1993 BP

Action and use Antibacterial.

Phenindamine Tartrate

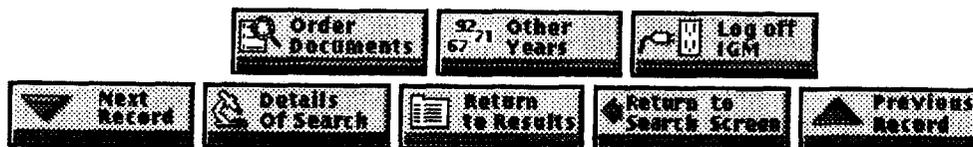


and enantiomer

$C_{19}H_{19}N, C_4H_6O_6$ 411.5 569-59-5

Definition Phenindamine Tartrate is (*RS*)-2,3,4,9-tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine hydrogen (2*R*,3*R*)-tartrate. It contains not less than 98.5% and not more than 101.0% of $C_{19}H_{19}N, C_4H_6O_6$,

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TITLE: The effects of phenindamine tartrate on sleepiness and psychomotor performance.

AUTHOR: Witek TJ Jr; Canestrari DA; Miller RD; Yang JY; Riker DK

AUTHOR AFFILIATION: Regulatory and Clinical Development, Richardson-Vicks USA (A Procter & Gamble Company), Shelton, Conn.

SOURCE: J Allergy Clin Immunol 1992 Dec;90(6 Pt 1):953-61

NLM CIT. ID: 93094481

ABSTRACT: *6* Phenindamine, an H1-receptor antagonist that was developed almost 50 years ago, has been associated with both drowsiness and insomnia. Since its central nervous system profile has not been well characterized, we used a series of psychomotor tests to conduct two studies. In the first, 12 subjects received single oral doses of phenindamine (25 mg), diphenhydramine (50 mg), terfenadine (60 mg), or placebo in a four-way crossover study. Psychomotor tests included choice reaction time (CRT), tracking, and hand steadiness (HS). In the second trial, 15 subjects received single oral doses of phenindamine (25 mg), pseudoephedrine (60 mg), phenindamine and pseudoephedrine, diphenhydramine (50 mg), or placebo in a five-way crossover study. Psychomotor tests included CRT, HS, and a task that divided attention between tracking and reaction time. Introspective drowsiness was measured in both trials with use of a visual analog scale (VAS) and the Stanford Sleepiness Scale (SSS). All assessments were made before and 1, 3, and 5 hours after drug administration. In the first trial, diphenhydramine produced significant impairment relative to placebo ($p < 0.05$) in CRT, tracking, and HS tasks and higher SSS and VAS scores, with peak effect noted at 3 hours. Phenindamine did not significantly differ from placebo or terfenadine. In the second trial, diphenhydramine produced significant impairment relative to placebo ($p < 0.05$) in CRT, divided attention, HS, and VAS, and SSS, also peaking at 3 hours. Stanford Sleepiness Scale scores after phenindamine were greater than placebo at 3 hours ($p < 0.05$) but significantly less than diphenhydramine ($p < 0.05$). (ABSTRACT TRUNCATED AT 250 WORDS) ***

** less drowsiness ^{as} compared to Benadryl*

MAIN MESH SUBJECTS: Histamine H1 Antagonists/*PHARMACOLOGY
Psychomotor Performance/*DRUG EFFECTS
Pyridines/*PHARMACOLOGY
Sleep/*DRUG EFFECTS

ADDITIONAL MESH SUBJECTS: Adolescence
Adult
Diphenhydramine/PHARMACOLOGY
Ephedrine/PHARMACOLOGY
Human
Middle Age
Time Factors

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Histamine H1 Antagonists)
0 (Pyridines)
299-42-3 (Ephedrine)
58-73-1 (Diphenhydramine)
82-88-2 (phenindamine)



TITLE: [Various principles of therapeutic tactics in epilepsy patients during pregnancy]

AUTHOR: Sigidinenko LV

SOURCE: Zh Nevropatol Psikhiatr 1984;84(6):897-9

NLM CIT. ID: 84276611

ABSTRACT: Forty-two epileptics were examined during pregnancy. According to the severity of the paroxysmal symptomatology, the authors identified three clinical groups: the first included patients with a therapeutic remission; the second, those with non-convulsive paroxysms; and the third group comprised patients with convulsive paroxysms. With due regard for impairments identified in the blood content of neurotransmitters, the patients received the multiple modality treatment, which included vitamins of group "B", potassium orotate, antihistamine drugs, the substitution of chloracon for phenobarbital and benzonal for diphenylhydantoin sodium; at the later stage of pregnancy the patients were given phenindamine tartrate. The use of the multiple modality treatment facilitated the cessation of attacks and served as the prevention of epileptic exacerbation in patients during the gestational and post-partal periods.

MAIN MESH SUBJECTS: Anticonvulsants/*ADMINISTRATION & DOSAGE
Epilepsy/BLOOD/*DRUG THERAPY
Neurotransmitters/*BLOOD
Pregnancy Complications/BLOOD/*DRUG THERAPY

ADDITIONAL MESH SUBJECTS: Adult
Drug Therapy, Combination
English Abstract
Epinephrine/BLOOD
Female
Histamine/BLOOD
Human
Norepinephrine/BLOOD
Pregnancy
Serotonin/BLOOD

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Rus

REGISTRY NUMBERS: 0 (Anticonvulsants)
0 (Neurotransmitters)
50-67-9 (Serotonin)
51-41-2 (Norepinephrine)
51-43-4 (Epinephrine)
51-45-6 (Histamine)

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TITLE: The structure of phenindamine base and salts in the solute state.

AUTHOR: Branch SK; Casy AF; Hussain R; Upton C

AUTHOR AFFILIATION: School of Pharmacy and Pharmacology, University of Bath, Bath, UK.

SOURCE: J Pharm Pharmacol 1988 Jan;40(1):83-4

NLM CIT. ID: 88214661

ABSTRACT: High-field NMR (13C and 1H) studies of phenindamine are reported which establish structures of the free base and some of its salts in the solute condition. The base exists as a mixture of two isomers which differ in double bond position (9-9a or 4a-9a) while most salts are 9-9a isomers. The clinically employed tartrate (Thephorin) is exceptional in being a 4a-9a ene. Salts of both double bond type exist in solution as mixtures of protonated epimers of variable epimeric ratio, that of the tartrate in D2O being approximately 1:1.

MAIN MESH SUBJECTS: Pyridines/*ANALYSIS

ADDITIONAL MESH SUBJECTS: Chemistry
Crystallization
Nuclear Magnetic Resonance
Spectrophotometry, Ultraviolet

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Pyridines)
82-88-2 (phenindamine)

A. INGREDIENT NAME:

PHENYLTOLOXAMINE DIHYDROGEN CITRATE

B. Chemical Name:

N, N-Dimethyl-2-(Alpha-Phenyl-O-Toloxyl)Ethylamine, Dihydrogen Citrate
2-(2-Benzylphenoxy)-NN-dimethyl-ethylamine dihydrogen citrate

C. Common Name:

Rinurel, Pholtex, Aust.-Codipront; Fr.- Biocidan: There are various names from different countries. See file.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.9%

E. Information about how the ingredient is supplied:

White crystalline powder, odorless, tasteless, crystals from water or methanol

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Sunshine, A., Zigelboim, I., and De Castro, A. Augmentation of acetaminophen analgesia by the antihistamine phenyltoloxamine. *J Clin Pharmacol*; 1989; 29(7): 660-664.

Falliers, C. J., Redding, M. A., and Katsampes, C.P. Inhibition of cutaneous and mucosa allergy with phenyltoloxamine. *Ann Allergy*, 1978; 41(3): 140-144.

H. Information about dosage forms used:

Expectorant
Suspension
Tablet

I. Information about strength:

25-50mg - 3-4 times daily

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 138-140° centigrade
Stable

L. Formulations:

M. Miscellaneous Information:

30-1462
16618

CERTIFICATE OF ANALYSIS

Product : PHENYLTOLOXAMINE DIHYDROGEN CITRATE USP
Quantity : 5 kgs net
Batch No. : 7083

Appearance : white crystalline powder
Identification (A,B) : conform
Melting point : 141,4 deg. C
Loss on drying : 0,12 %
Residue on ignition : 0,018 %
U.V. : clear solution
G.C. : 99,5 %
Assay : 99,9 %

The above product conforms to the requirements of the USP.

TRANSO-PHARM GmbH
M. Beutner
- M. Beutner -

QUALITY CONTROL REPORT

CHEMICAL NAME: PHENYLTOLOXAMINE DIHYDROGEN CITRATE

MANUFACTURE LOT NO.:

PHYSICAL TEST

SPECIFICATION TEST STANDARD: USP __/NF __/ MERCK*/BP __/COMPANY SPECS. __

1) DESCRIPTION:

E WHITE CRYSTALLINE POWDER; ODORLESS; TASTELESS, CRYSTALS FROM WATER OR METHANOL.

2) SOLUBILITY:

SOLUBLE IN WATER.

3) MELTING POINT:

MELTS AT ABOUT 138-140 degree centigrade *K*

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

----- IDENTIFICATION -----

PRODUCT #: P8404 NAME: PHENYLTOLOXAMINE CITRATE
CAS #: 1176-08-5
MF: C17H21N1O1

SYNONYMS

N,N-DIMETHYL-2-(ALPHA-PHENYL-O-TOLOXY)ETHYLAMINE DIHYDROGEN
CITRATE *

PHENYLTOLOXAMINE DIHYDROGEN CITRATE * PRN *

----- TOXICITY HAZARDS -----

RTECS NO: KR6650000

ETHYLAMINE, N,N-DIMETHYL-2-((ALPHA-PHENYL-O-TOLYL)OXY)-, CITRATE
(1:1)

TOXICITY DATA

ORL-RAT LD50: 1472 MG/KG TXAPA9 1,42,59
IPR-MUS LD50: 246 MG/KG JAPMA8 42,587,53

REVIEWS, STANDARDS, AND REGULATIONS

NOHS 1974: HZD 80480; NIS 3; TNF 517; NOS 9; TNE 4176
NOES 1983: HZD 80480; NIS 2; TNF 41; NOS 8; TNE 1225; TFE 406
EPA TSCA CHEMICAL INVENTORY, JUNE 1990

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES
(RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE
INFORMATION.

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

HARMFUL IF SWALLOWED.

EXPOSURE CAN CAUSE:

NAUSEA, DIZZINESS AND HEADACHE

LIGHT-HEADEDNESS, VOMITING, SEDATION.

THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY
INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS
CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,
CALL A PHYSICIAN.

IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

----- PHYSICAL DATA -----

MELTING PT: 138 TO 140°C

SOLUBILITY: METHANOL-SOLUBLE

APPEARANCE AND ODOR

WHITE CRYSTALLINE POWDER.

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

----- REACTIVITY DATA -----

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

TOXIC FUMES OF:

CARBON MONOXIDE, CARBON DIOXIDE

NITROGEN OXIDES

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

NIOSH/MSHA-APPROVED RESPIRATOR.

MECHANICAL EXHAUST REQUIRED.

COMPATIBLE CHEMICAL-RESISTANT GLOVES.

CHEMICAL SAFETY GOGGLES.

HARMFUL IF SWALLOWED.
WEAR SUITABLE PROTECTIVE CLOTHING.
THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT
PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL
NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM
CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR
ADDITIONAL
TERMS AND CONDITIONS OF SALE

Uses and Administration

Oxatomide, a piperazine derivative, is an antihistamine that has also been reported to have mast-cell stabilising properties.

Oxatomide is used for the symptomatic relief of hypersensitivity reactions including urticaria (see p.431), and rhinitis and conjunctivitis (see p.430).

Oxatomide is given by mouth as the anhydrous substance or as the monohydrate. The dose of anhydrous oxatomide is 30 to 60 mg twice a day; a dose of 30 mg twice daily is recommended for the elderly. Oxatomide should be administered with caution in patients with hepatic impairment but the manufacturer suggests that if treatment is required patients should start with half the usual dose. Children aged 6 to 14 years may be given 15 to 30 mg twice a day.

References.

1. Anonymous. Oxatomide—a new H₁-antihistamine. *Drug Ther Bull* 1983; 21: 35-6.
2. Richards DM, et al. Oxatomide: a review of its pharmacodynamic properties and therapeutic efficacy. *Drugs* 1984; 27: 210-31.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Aust.: Tinset; *Belg.*: Tinset; *Fr.*: Tinset; *Ger.*: Tinset; *Ital.*: Tinset; *Neth.*: Tinset; *S.Afr.*: Tinset; *Spain*: Atoxan; *Cobiona*: Oxleti; *Tanzania*: Tinset; *UK*: Tinset.

Oxomemazine (6151-p)

Oxomemazine (rINN).

RP-6847; Trimeprazine SS-Dioxide. 10-(3-Dimethylamino-2-methylpropyl)phenothiazine 5,5-dioxide.

C₁₈H₂₂N₂O₂S = 330.5.

CAS — 3689-50-7.

Oxomemazine Hydrochloride (6152-s)

Oxomemazine Hydrochloride (rINN).

H₂₂N₂O₂S.HCl = 366.9.

— 4784-40-1.

Pharmacopoeias. In *Fr.*

Oxomemazine hydrochloride 11.1 mg is approximately equivalent to 10 mg of oxomemazine.

Oxomemazine, a phenothiazine derivative, is an antihistamine used for the symptomatic relief of hypersensitivity reactions (see p.430) and in pruritic skin disorders (see p.432). It is also an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (see p.432).

It is given by mouth in doses equivalent to 10 to 40 mg of oxomemazine daily. Oxomemazine may also be administered by the rectal route. Oxomemazine hydrochloride has been used similarly by mouth.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Belg.: Doxergan; *Fr.*: Doxergant; *Neth.*: Doxergan.

Multi-ingredient preparations. *Aust.*: Aplexil; *Belg.*: Rectoplex; *UK*: Toplexil; *Fr.*: Rectoplexil; *Tanzania*: Toplexil; *Switz.*: Toplexil.

Phenindamine Tartrate (6153-w)

Phenindamine Tartrate (BANM, USAN, rINN).

Phenindamine Acid Tartrate; Phenindamine Tartras; Phenindaminium Tartrate. 1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azaflorene hydrogen tartrate; 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1H-indeno[2,1-c]pyridine hydrogen tartrate.

C₁₇H₁₉N.C₄H₆O₆ = 411.5.

CAS — 82-88-2 (phenindamine); 569-59-5 (phenindamine tartrate).

Pharmacopoeias. In *Br.*

White or almost white, odourless or almost odourless, voluminous powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and ether. A 1% solution in water has a pH of 3.4 to 3.9. Protect from light.

The symbol † denotes a preparation no longer actively marketed

Adverse Effects, Treatment, and Precautions

As for antihistamines in general (see p.427).

Unlike most other antihistamines phenindamine tartrate may have a stimulant effect; to avoid the possibility of insomnia patients may be advised to take the last dose of the day before 4 p.m.

Uses and Administration

Phenindamine, a piperidine derivative, is an antihistamine; however it may be mildly stimulating. It is used as the tartrate for the symptomatic relief of hypersensitivity reactions including urticaria (see p.431), and rhinitis (see p.430), and as an ingredient of compound preparations for coughs and the common cold (see p.432).

Phenindamine tartrate is given in doses of 25 to 50 mg up to three times daily. Children over 6 years of age have been given up to 75 mg daily in divided doses.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

BP 1993: Phenindamine Tablets.

Proprietary Preparations

UK: Thephorin; USA: Nolahist.

Multi-ingredient preparations. *Ger.*: Flupromin; *USA*: Nolamine; P-V-Tussin.

Pheniramine (14746-1)

Pheniramine (BAN, rINN).

Propnenpyridamine. NN-Dimethyl-3-phenyl-3,2-pyrrolidylpropylamine.

C₁₆H₂₀N₂ = 240.3.

CAS — 86-21-5.

Pheniramine Aminosalicylate (10013-1)

Pheniramine p-Aminosalicylate; Pheniramine + Aminosalicylate; Pheniramine Para-aminosalicylate. Pheniramine + aminosalicylic acid.

C₁₆H₂₀N₂.C₇H₇NO₃ = 393.5.

CAS — 3269-83-8.

Pheniramine Maleate (6154-e)

Pheniramine Maleate (BANM, USAN, rINN).

Pheniraminium Maleate; Propnenpyridamine Maleate Pheniramine hydrogen maleate.

C₁₆H₂₀N₂.C₄H₄O₄ = 356.4.

CAS — 132-20-7.

Pharmacopoeias. In *Belg.* and *Br.*

A white or almost white crystalline powder, odourless or with a slight odour. M.p. 106° to 109°. Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. A 1% solution in water has a pH of 4.5 to 5.5. Protect from light.

Adverse Effects, Treatment, and Precautions

As for antihistamines in general, p.427.

Abuse. References to the abuse of pheniramine by mouth.

1. Jones IH, et al. Pheniramine as a hallucinogen. *Med J Aust* 1973; 1: 382-6.
2. Csillag ER, Landauer AA. Alleged hallucinogenic effect of a toxic overdose of an antihistamine preparation. *Med J Aust* 1973; 1: 653-4.
3. Buckley NA, et al. Pheniramine—a much abused drug. *Med J Aust* 1994; 160: 188-92.

Pharmacokinetics

The pharmacokinetics of pheniramine and its metabolites, N-desmethylpheniramine and N-didesmethylpheniramine, were investigated in 6 healthy subjects. After oral administration of pheniramine aminosalicylate, peak plasma concentrations of pheniramine aminosalicylate, peak plasma concentrations were reached in 1 to 2.5 hours. The terminal half-life ranged between 8 and 17 hours after intravenous administration (pheniramine maleate) and 16 and 19 hours after oral administration. The total recovery of pheniramine and unchanged drug and metabolites from the urine was 88 to 91% of the intravenous dose and 70 to 83% of the oral dose.

1. Witte PU, et al. Pharmacokinetics of pheniramine (AN-2) and metabolites in healthy subjects after oral and intravenous administration. *Int J Clin Pharmacol Ther Toxicol* 1985; 23: 60-62.

Uses and Administration

Pheniramine, an alkylamine derivative, is an antihistamine with antimuscarinic and central sedative properties.

It is used as the maleate or aminosalicylate for the symptomatic relief of hypersensitivity reactions including urticaria and angioedema (see p.431), rhinitis and conjunctivitis (see p.430), and in pruritic skin disorders (see p.432). It has also been used for its antiemetic properties in the prevention and control of motion sickness (see p.432). Pheniramine maleate is used as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (see p.432).

Pheniramine maleate is given by mouth in a dose of 22.5 to 30 mg two or three times daily, or more commonly, in sustained-release preparations in doses of 75 mg once or twice daily or 150 mg at night. Pheniramine maleate is also used in combination with a decongestant in eye and nasal preparations. In some countries pheniramine maleate has been administered parenterally.

Usual doses of the aminosalicylate are 25 to 50 mg two or three times daily by mouth.

The hydrochloride and the tannate have also been used.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Aust.: Avil; *Austral.*: Aller-Gt; Avil; Avilettes; Fenamine; *Belg.*: Avil; *Eire*: Daneral SA; *Ger.*: Avil; Aviletent; *Ital.*: Inhiston; *S.Afr.*: Avil; *UK*: Daneral SA.

Multi-ingredient preparations. *Aust.*: Neo Citran; *Austral.*: Avil; Avil Decongestant; Triaminic†; *Belg.*: Naphcon-A; Triaminic†; *Canad.*: Ak-Vernacort; Caldormine-DH†; Contac Night-Time Hot Drink†; Diorouge; Dristan; Naphcon-A; Opcon-A; Pulmorph; Pulmorph Pediatric; Robitussin AC; Robitussin with Codeine; Tantacol; Triaminic; Triaminic Expectorant; Triaminic Expectorant DH; Triaminic-DM Expectorant; Triaminic; Triaminic with Codeine†; Triaminic DM; Trisulfaminic; Tussaminic C; Tussaminic DH; *Eire*: Triominic; *Fr.*: Fébrispir; Fervag; Triaminic; Triassuict†; *Ger.*: Cosavil†; Konjunktival Thilo; Potanal†; Triaminic†; *Ital.*: Medramil; Senodin-AN; Tetramil; Triaminic; Triaminic†; Triaminic†; *S.Afr.*: Allertac; Calasthetic; Coff-Up; Degoran; Triami; Triaminic; *Spain*: Regresin Hemorrhoidal†; Rynatan†; Triominic; *Switz.*: Neo Citran; Triaminic†; *UK*: Triominic; *USA*: AK-Con-A; Dristan Nasal Spray; Fiogiesic†; Nafazair A; Naphazole-A; Naphazoline Plus; Naphcon-A; Naphoptic-A; Opcon-A; Poly-Histine; Poly-Histine-D; Rolatuss with Hydrocodone; Ru-Tuss with Hydrocodone; Scot-Tussin Original 5-Action; S-T Forte; Statuss Green; Triaminic Expectorant DH; Triaminic Oral Infant; Tussirex.

Phenyltoloxamine Citrate (6155-1)

Phenyltoloxamine Citrate (BANM, rINN).

C-5581H (phenyltoloxamine); Phenyltoloxamine Citrate; PRN (phenyltoloxamine). 2-(2-Benzylphenoxy)-NN-dimethyl-ethylamine dihydrogen citrate.

C₁₇H₂₁NO.C₆H₈O₇ = 447.5.

CAS — 92-12-6 (phenyltoloxamine); 1176-08-5 (phenyltoloxamine citrate).

Phenyltoloxamine citrate is an ethanolamine derivative with the actions and uses of antihistamines (see p.427). It is usually given by mouth in combination preparations with a decongestant or analgesic. Phenyltoloxamine citrate has been used in nasal preparations. Phenyltoloxamine polistirex has also been administered by mouth.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Multi-ingredient preparations. *Aust.*: Codipront; Codipront cum Expectorans; *Austral.*: Sinutab with Codeine; *Belg.*: Sinutab; *Canad.*: Omni-Tuss; Sinutab SA; Tussionex; *Fr.*: Bioicidan; Né-tux; Rinurel; Rinutan; *Ger.*: Codipront; Codipront cum Expectorans†; ergo sanol special; Naldecolt; *Ital.*: Codipront; *S.Afr.*: Adco-Sinal Co; Decon; Pholtex; Sinustop; Sinustop with Codeine; Sinutab; Sinutab with Codeine; Suncodin; *Spain*: Codipront; *Switz.*: Codipront; Codipront cum Expectorans; Ergosanol special; *UK*: Pholtex; Rinurel†; Sinutab Nighttime; *USA*: Aceta-Gesic; Biotab†; Comhist LA; Decongestabs; Decongestant; Decongestant SR; Kutrase; Lobac; Magsal; Major-gesic; Medatussin Plus†; Menoplex; Mobigestic; Momentum; Myogestic; Naldec Pediatric†; Naldec; Nalgest; New Decongestant Pediatric; Norel Plus; Par Decon†; Percogestic; Phena-Chlor†; Phenylgesic; Poly-Histine;

Pheniramine Maleate (B.P.). Pheniraminium Prophenpyridamine Maleate. *NN*-Dimethyl-3-(2-pyridyl)propylamine hydrogen

$C_{16}H_{20}N_2 = 356.4$.

86-21-5 (pheniramine); 132-20-7

Prop. In Br.

almost white crystalline powder with amine-like odour. M.p. 106° to 109° . Soluble in 0.3 of water, 1 in 2.5 of alcohol, and in chloroform; very slightly soluble in 1% solution in water has a pH of 4.5 to 5.0 in airtight containers. Protect from

Effects. As for the antihistamines in general, p.1294.

Pheniramine aminosalicilate in doses exceeding 10 mg produced hallucinatory effects followed by exhaustion. Side-effects were cramps, dilated pupils, tachycardia, and incoordination. In 1 patient the effects clouded for several days.— I. H. Jones *J. Aust. J.*, 1973, 1, 382.

Transient toxic psychosis in 2 young men when between 0.5 and 1 g of pheniramine maleate.— E. R. Csillag and A. A. Landauer, *J. Pharm. Med.*, 1973, 1, 653.

Hallucinatory effects lasting for 2 days and were reported in a child who took 750 mg of pheniramine maleate.— I. H. Jones *et al.*, *J. Pharm. Med.*, 1973, 1, 382.

and the neonate. For studies on the adverse effects of pheniramine and other antihistamines during pregnancy see p.1294.

Adverse Effects. As for the antihistamines in general, p.1294.

Studies *in vitro* indicated the pheniramine is adsorbed by activated charcoal.— J. J. *Clin. Toxicol.*, 1978, 12, 523.

A comment that pheniramine is associated with arrhythmias in overdosage and that electrocardiogram monitoring may be necessary.— D. W. *Med. J. Aust.*, 1976, 2, 212. See also J. *ibid.*, 1, 895. The use of tacrine in a pheniramine overdosage.— G. Mendelson *et al.*, *J. Pharm. Sci.*, 1968, 57, 621.

As for the antihistamines in general,

Pharmacokinetics and Fate. As for the antihistamines in general, p.1295.

22.6% of an administered dose of pheniramine is excreted unchanged in the urine. Under a dosage with 37 mg of pheniramine maleate 13% was excreted unchanged, 26.1% as *N*-desdimethylpheniramine, 0.5% as *N*-desdimethylpheniramine, about 49% was unaccounted for.— P. *et al.*, *J. Pharm. Sci.*, 1968, 57, 621.

Pheniramine is an alkylamine derivative with properties and uses of the antihistamines in general. It is less potent than promethazine, shorter duration of action, and generally less sedation.

Pheniramine maleate has been given in doses of 10 mg thrice daily but sustained-release preparations are more commonly used in doses of 10 or twice daily or 150 mg at night if

for children given up to three times daily under 1 year of age 7.5 mg, 1 to 5 years 10 mg, 6 years and over 15 to 22.5 mg. It is also administered as the aminosalicilate ($C_{16}H_{20}N_2 \cdot C_7H_7NO_3 = 393.5$) in doses of 25 to 50 mg thrice daily. It has been given as the tannate.

Preparations

Tablets (Hoechst, UK). Sustained-release tablets containing pheniramine maleate 75 mg. 2 tablets daily.

At the risk of intestinal obstruction, sustained-release preparations such as Daneral-SA, where the matrix is in transit, but the matrix ghost is often

eliminated intact, should not be prescribed in patients with Crohn's disease or other intestinal disease in which strictures may form.— J. L. Shaffer *et al.* (letter), *Lancet*, 1980, 2, 487.

Other Proprietary Names

Acovil, Acoviletas (both Spain); Avil (aminosalicylate and/or maleate) (Austral., Belg., Ger., Neth., S.Afr.); Aviletten (aminosalicylate) (Ger.); Avilettes (aminosalicylate) (Austral.); Fenamine (aminosalicylate and/or maleate) (Austral.); Inhibston (Ital.).

A preparation containing pheniramine tannate was formerly marketed in Great Britain under the proprietary name Rynabond (Fisons).

6155-l

Phenyltoloxamine Citrate. C 5581; Phenyltoloxamine Citrate; PRN. 2-(2-Benzylphenoxy)-*NN*-dimethylethylamine dihydrogen citrate. $C_{17}H_{21}NO_6 \cdot C_6H_8O_7 = 447.5$.

CAS — 92-12-6 (phenyltoloxamine); 1176-08-5 (citrate).

Phenyltoloxamine citrate is an ethanolamine derivative with the properties and uses of the antihistamines (see p.1294). It is a structural isomer of diphenhydramine (see p.1311). It has been given in doses of 25 to 50 mg three or four times daily.

Abuse. Mention of the abuse of a cough mixture containing hydrocodone with phenyltoloxamine.— Y. J. Berry (letter), *New Engl. J. Med.*, 1976, 295, 286.

Proprietary Preparations

Phenyltoloxamine citrate is an ingredient of Rinurel, see under Phenylpropranolamine Hydrochloride, p.26.

Phenyltoloxamine is an ingredient of Pholrex; see under Pholcodine, p.1260.

6156-y

Piprinhydrinate. The diphenylpyraline salt of 8-chlorotheophylline; 4-Benzhydryloxy-1-methylpiperidine salt of 8-chlorotheophylline. $C_{26}H_{30}ClN_2O_3 = 496.0$.

CAS — 606-90-6.

Piprinhydrinate is diphenylpyraline theoclate and has the general properties of diphenylpyraline hydrochloride (see p.1312). It has been given in doses of 3 to 9 mg up to thrice daily.

Proprietary Names

Kolton (Byk Lirandi, Arg.); Kolton (see also under Diphenylpyraline Hydrochloride) (Promonta, Belg.; Promonta, Ger.).

6157-j

Pizotifen Maleate. Pizotyline Maleate; BC-105 (base). 9,10-Dihydro-4-(1-methyl-4-piperidylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene hydrogen maleate. $C_{19}H_{21}NS_2 \cdot C_4H_4O_3 = 429.5$.

CAS — 15574-96-6 (pizotifen).

Pizotifen maleate 145 mg is approximately equivalent to 100 mg of pizotifen.

Adverse Effects, Treatment, and Precautions. As for the antihistamines in general, p.1294. Increased appetite and weight gain may occur.

A review of the actions and uses of pizotifen. Tolerance to alcohol could be lowered by pizotifen. The effects of tranquillizers, sedatives, and some tricyclic antidepressants could be enhanced. It should not be given with monoamine oxidase inhibitors. Because of its structural similarity to tricyclic antidepressants it might antagonise the adrenergic neurone blockade induced by some antihypertensive agents.— T. M. Speight and G. S. Avery, *Drugs*, 1972, 3, 159.

Of 47 patients with severe migraine given pizotifen 1 to 2 mg daily adverse effects were recorded in 22 patients. These reactions included weight increase (15), muscle pain or cramps (3), heavy legs or restless legs (3), fluid retention (3), drowsiness (2), more frequent milder headaches (2), facial flushing (1), reduced libido (1),

exacerbation of epilepsy (1), and dreaming (2). Adverse effects necessitating withdrawal from the study occurred in 11 patients. Advantageous effects were mood elevation in 3 and increased alertness in 6.— K. M. S. Peet, *Curr. med. Res. Opinion*, 1977, 5, 192.

Uses. Pizotifen maleate has the properties of the antihistamines (see p.1295). It also has pronounced antiserotonin, antitryptamine, and weak anticholinergic properties.

Pizotifen maleate is used for the prophylaxis of migranous headache. The usual dose is the equivalent of 500 µg of pizotifen thrice daily; some patients may be controlled on 500 µg daily; up to 6 mg daily has been given. It has been recommended that treatment should commence with 500 µg daily increased gradually over the following 5 days.

Reviews and comments on the action and uses of pizotifen.— T. M. Speight and G. S. Avery, *Drugs*, 1972, 3, 159; M. Anthony and J. W. Lance, *ibid.*, 153; *Drug & Ther. Bull.*, 1976, 14, 29.

The use of pizotifen in 3 patients to prevent or reduce the side-effects following calcitonin injections.— A. J. Crisp (letter), *Lancet*, 1981, 1, 775.

Appetite stimulation. In a double-blind study in 40 patients with tuberculosis the mean weekly weight gain in those given pizotifen 500 µg thrice daily for 4 weeks was 890 g compared with 230 g for those given placebo.— A. Tsougranis, *Curr. ther. Res.*, 1972, 14, 372.

Carcinoid syndrome. Pizotifen was found to stop diarrhoea and facial flushing in a patient with malignant carcinoid syndrome, the excision of whose primary tumour was followed by regression of metastatic lesions. Chlorpromazine, methysergide, and cyproheptadine were ineffective.— S. C. Loong *et al.*, *Med. J. Aust.*, 1968, 2, 845.

Carotodynia. A favourable report of the use of pizotifen in the treatment of 4 patients with carotodynia, a form of vascular neck and face pain.— T. J. Murray, *Can. med. Ass. J.*, 1979, 120, 441.

Cluster headache. Patients with cluster headache who did not respond to ergotamine might be relieved by methysergide 3 to 6 mg daily or by pizotifen 1.5 to 3 mg daily for the duration of the bout.— *Br. med. J.*, 1975, 4, 425.

Further references.— K. Ekblom, *Acta neurol. scand.*, 1969, 45, 601.

Cushing's disease. Administration of pizotifen 500 µg thrice daily for 2 to 7 months had a beneficial effect in 4 of 5 women with Cushing's disease, without serious side-effects. On stopping pizotifen one woman remained in remission for 10 months before relapsing, another relapsed 2 months after stopping, and 2 were still in remission 3 and 6 months respectively after withdrawal of pizotifen. One patient's weight increased by about 4 kg after 7 months of therapy. In patients being prepared for surgery or in those in whom other forms of therapy have failed, pizotifen may have a place.— A. Kasperlik-Zaluska *et al.* (letter), *Lancet*, 1980, 1, 490.

Depression. A double-blind study involving 20 patients with minor to moderate depression indicated that pizotifen possessed certain antidepressant properties.— J. E. Standal, *Acta psychiat. scand.*, 1977, 56, 276.

Further references.— W. V. Krumholz *et al.*, *Curr. ther. Res.*, 1968, 10, 342.

Migraine. Of 26 patients suffering from severe attacks of migraine (classical migraine in 25) treated for 8 weeks in a double-blind crossover trial with placebo or pizotifen in doses increased up to 1 mg thrice daily (in addition to any existing medication), 9 obtained complete relief or a reduction of at least one-half in the number of their attacks. Ten patients noted increased appetite, 6 a change of mood, and 5 experienced depression when active treatment ceased. Other side-effects were tiredness (5), facial flushing (1), and increased vomiting (1).— R. C. Hughes and J. B. Foster, *Curr. ther. Res.*, 1971, 13, 63. See also J. B. Foster, *ibid.*, 1976, 19, 66.

Further references.— F. Sicuteri *et al.*, *Int. Archs Allergy appl. Immun.*, 1967, 31, 78; J. W. Lance and M. Anthony, *Med. J. Aust.*, 1968, 1, 54; O. Sjaastad and P. Stensrud, *Acta neurol. scand.*, 1969, 45, 594; J. W. Lance *et al.*, *Br. med. J.*, 1970, 2, 327; J. Schaefer, *Headache*, 1970, 10, 67; B. Anselmi, *Schweiz. med. Wschr.*, 1972, 102, 487; A. J. Krakowski and R. Engisch, *Psychosomatics*, 1973, 14, 302; J. D. Carroll and W. P. MacLay, *Curr. med. Res. Opinion*, 1975, 3, 68; E. R. Lawrence *et al.*, *Headache*, 1977, 17, 109; K. W. G. Heathfield *et al.*, *Practitioner*, 1977, 218, 428; K.

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TITLE:



Augmentation of acetaminophen analgesia by the antihistamine phenyltoloxamine.

AUTHOR:

Sunshine A; Zigelboim I; De Castro A; Sorrentino JV; Smith DS; Bartizek RD; Olson NZ

AUTHOR AFFILIATION:

New York University Medical Center, New York.

SOURCE:

J Clin Pharmacol 1989 Jul;29(7):660-4

NLM CIT. ID:

89341003

ABSTRACT:

G

A double-blind, placebo-controlled, parallel-group study was performed to compare the analgesic activity of the combination of 650 mg acetaminophen plus 60 mg phenyltoloxamine citrate with that of 650 mg acetaminophen alone. Two hundred female inpatients who had severe pain associated with a recent episiotomy procedure were randomly assigned to receive a single dose of one of the two active treatments or a placebo. Analgesia was assessed over a 6-hour period. Treatments were compared on the basis of standard subjective scales for pain intensity and relief, a number of derived variables based on these data and two global measures. For essentially all measures, the two active treatments were significantly superior to the placebo control. The combination was significantly superior to acetaminophen alone for all analgesic measures including SPID, TOTAL, and global ratings. The results of this study demonstrate that 60 mg phenyltoloxamine produces significant augmentation of the analgesic activity of 650 mg acetaminophen in postepisiotomy pain.

MAIN MESH SUBJECTS:

Acetaminophen/ADMINISTRATION & DOSAGE/*THERAPEUTIC USE
 Benzhydryl Compounds/ADMINISTRATION & DOSAGE/*THERAPEUTIC USE
 Histamine H1 Antagonists/*THERAPEUTIC USE
 Pain, Postoperative/*DRUG THERAPY

ADDITIONAL MESH SUBJECTS: Adolescence
Adult
Comparative Study
Double-Blind Method
Drug Synergism
Drug Therapy, Combination
Female
Human
Pregnancy
Random Allocation
Support, Non-U.S. Gov't
Time Factors

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Benzhydryl Compounds)
0 (Histamine H1 Antagonists)
103-90-2 (Acetaminophen)
92-12-6 (phenyltoloxamine)

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Citations 1 to 1 of 1 from MEDLINE 1975-79

TITLE: * Inhibition of cutaneous and mucosal allergy with phenyltoloxamine.
AUTHOR: Falliers CJ; Redding MA; Katsampes CP
SOURCE: Ann Allergy 1978 Sep;41(3):140-4
NLM CIT. ID: 78255039 (abstract present)

*(antihistaminic activity)
+ Safety info*



TITLE: [Clinical comparison of butamirate citrate with a codeine-based antitussive agent]

AUTHOR: Germouty J; Weibel MA

AUTHOR AFFILIATION: Centre hospitalier et universitaire, Hopital du Cluzeau, Limoges, France.

SOURCE: Rev Med Suisse Romande 1990 Nov;110(11):983-6

NLM CIT. ID: 91095848

MAIN MESH SUBJECTS: Antitussive Agents/*THERAPEUTIC USE
Benzhydryl Compounds/*ADMINISTRATION & DOSAGE
Codeine/*ADMINISTRATION & DOSAGE
Cough/*DRUG THERAPY
Phenylbutyrates/*THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS: Adult
Aged
Comparative Study
Drug Combinations
Female
Histamine H1 Antagonists/THERAPEUTIC USE
Human
Male
Middle Age

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Augmentation of Acetaminophen Analgesia by the Antihistamine Phenyltoloxamine

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A double-blind, placebo-controlled, parallel-group study was performed to compare the analgesic activity of the combination of 650 mg acetaminophen plus 60 mg phenyltoloxamine citrate with that of 650 mg acetaminophen alone. Two hundred female inpatients who had severe pain associated with a recent episiotomy procedure were randomly assigned to receive a single dose of one of the two active treatments or a placebo. Analgesia was assessed over a 6-hour period. Treatments were compared on the basis of standard subjective scales for pain intensity and relief, a number of derived variables based on these data and two global measures.

For essentially all measures, the two active treatments were significantly superior to the placebo control. The combination was significantly superior to acetaminophen alone for all analgesic measures including SPID, TOTAL, and global ratings. The results of this study demonstrate that 60 mg phenyltoloxamine produces significant augmentation of the analgesic activity of 650 mg acetaminophen in postepisiotomy pain.

Antihistaminics, in addition to their traditional uses, are becoming recognized for their analgesic or analgesic adjuvant effects. Animal data indicate that certain antihistamines show analgesic activity and others do not.¹ Many mechanisms have been proposed. It may well be that more than one mechanism of action exists for the antihistamines. Evidence in the literature suggests that histamines play a role in both inflammatory and vascular pain, which may explain why some antihistaminic drugs exert analgesic effects alone or in combination.² In clinical studies antihistamines such as diphenhydramine,³ hydroxyzine,⁴ orphenadrine,⁵ and pyril-

amine⁶ have been reported to produce analgesia when tested alone. Analgesic adjuvant effects of several antihistamines demonstrating the analgesic superiority of the combination over each drug alone have also been reported: orphenadrine + acetaminophen,⁷ hydroxyzine + morphine,⁸ meperidine + hydroxyzine⁹ and phenyltoloxamine + acetaminophen.^{10,11}

Antihistaminics may act as analgesics via substance P, prostaglandin, bradykinin or cyclic nucleotides. Substance P is a potent histamine liberator and the vasodilation induced by substance P in the rat hind paw has been shown to be inhibited to about 50% by antihistaminics.¹ The release of bradykinin and prostaglandin, two agents important in the induction of inflammatory pain, is partially mediated by histamine.² Another possible pathway for antihistamine analgesia may be related to the activation of cyclic nucleotides which have recently been shown to act as CNS regulators of analgesia.¹

Phenyltoloxamine is an ethanolamine-type H₁ histamine antagonist. The results with phenyltoloxamine as an analgesic have been equivocal. In clinical studies involving tension headache and musculoskeletal pain associated with anxiety phenyltoloxamine was shown to have analgesic-adjuvant effects

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TABLE I

Distribution of Selected Patient Characteristics

Characteristic	Placebo	Acetaminophen 650 mg	Acetaminophen 650 mg/ Phenyltoloxamine 60 mg
Total Patients	50	75	75
Mean Weight (lb)	134.4	131.4	131.9
Mean Height (in)	61.9	61.8	61.7
Mean Age (yr)	25.7	25.8	25.0
Ambulatory Status			
Semi	0	1	2
Fully	50	74	73
Days Postpartum			
<1	35	55	53
1	13	17	22
2	2	2	0
>2	0	1	0

when combined with acetaminophen.^{10,11} However, in postsurgical dental pain, phenyltoloxamine did not appear to augment the analgesic effect of acetaminophen.^{12,13} This clinical trial was undertaken to determine the relative analgesic efficacy of orally administered acetaminophen alone compared with acetaminophen in combination with phenyltoloxamine citrate and placebo in the treatment of patients with severe postepisiotomy pain.

METHODS

Subjects

This study was conducted in Caracas, Venezuela at the Hospital Maternidad Concepcion Palacios and used a double-blind, parallel groups, single-dose design. The protocol was approved by the hospital's Institutional Review Board. The study subjects were selected from a population of multiparous postpartum inpatients with severe postepisiotomy pain who could tolerate oral medication. Patients who were 18 years or older, able to communicate meaningfully with the nurse-observer and who gave written informed consent to participate in the study were considered. Patients with known allergic sensitivities to any of the test medications were excluded from the study, as were patients with active peptic ulcer disease, gastrointestinal disease, or other complicating illness. Patients with diabetes not controlled by established therapy, and those with a history of drug abuse or alcoholism were also excluded. In addition, patients were not eligible if they had taken any anti-inflammatory, tranquilizing, psychotropic or analgesic medication within four hours of the test medication that could confound quantitating postpartum analgesia.

Medications

All medications were identical in appearance. Patients were randomly assigned to receive either placebo, acetaminophen 650 mg, or the combination of acetaminophen 650 mg plus phenyltoloxamine citrate 60 mg as a single two-tablet dose which was administered double-blind. The randomly-assigned study medication was consumed with an adequate amount of water (approximately 4 fluid ounces). Whenever possible, the patient was asked to either sit up or lie on her right side for at least one hour after medication was administered in order to promote gastric emptying. Treatments were randomized in blocks of eight so that, in each group of eight, the two active treatments were represented three times and the placebo twice. The three treatment groups, two of which consisted of 75 subjects plus the placebo group consisting of 50 subjects provided a total of 200 subjects. No medication that might confound the efficacy and/or adverse effect liability of the study analgesics were permitted concomitantly or during the four hours prior to the administration of the test medication.

Evaluation

When the patient's postepisiotomy pain was severe, study medication was administered by the nurse-observer. The same nurse-observer interviewed the patient at the time medication was administered, and at each of seven follow-up evaluations (0.5, 1, 2, 3, 4, 5 and 6 hr) after taking the study medication. All interviews were conducted in Spanish, the native language of the patients. If the patient was asleep at a scheduled interview time, she was awakened. At each evaluation, the patient was asked to

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TABLE II

Mean Values for Measures of Analgesic Efficacy

Efficacy	Placebo (n = 50)	Acetaminophen 650 mg (n = 75)	Acetaminophen 650 mg/ Phenyltoloxamine 60 mg (n = 75)
Baseline Pain	3.0	3.0	3.0
Pain Relief			
1/2 hr.	0.76	1.27 ^P	1.60 ^{P,A}
1 hr.	0.74	1.60 ^P	2.16 ^{P,A}
2 hr.	0.52	1.72 ^P	2.47 ^{P,A}
3 hr.	0.26	1.37 ^P	2.61 ^{P,A}
4 hr.	0.14	1.09 ^P	2.60 ^{P,A}
5 hr.	0.18	0.89 ^P	2.37 ^{P,A}
6 hr.	0.36	0.77 ^P	1.52 ^{P,A}
Pain Intensity Difference (PID)			
1/2 hr.	0.42	0.67 ^P	0.85 ^{P,A}
1 hr.	0.42	0.91 ^P	1.24 ^{P,A}
2 hr.	0.34	1.00 ^P	1.51 ^{P,A}
3 hr.	0.20	0.83 ^P	1.68 ^{P,A}
4 hr.	0.10	0.68 ^P	1.67 ^{P,A}
5 hr.	0.16	0.56 ^P	1.51 ^{P,A}
6 hr.	0.28	0.57 ^P	0.91 ^{P,A}
SPID ¹	1.50	4.43 ^P	8.31 ^{P,A}
TOTAL ²	2.21	7.29 ^P	13.45 ^{P,A}
Overall Improvement ³	4.46	5.07 ^P	5.73 ^{P,A}
Global Rating of Study Drug ⁴	0.50	1.49 ^P	2.17 ^{P,A}

^P = Significantly better than placebo, LSD, $P < 0.05$.

^A = Significantly better than acetaminophen 650 mg, LSD, $P < 0.05$.

¹ SPID = Weighted sum of pain intensity difference scores.

² TOTAL = Weighted sum of pain relief scores.

³ Based on a rating scale of 1 = very much worse to 7 = very much better; the higher the value the better the patient's evaluation of overall improvement.

⁴ Based on a rating scale of 0 = no help to 3 = excellent; the greater the value the better the patient's overall impression of the study drug.

assess the intensity of her pain which was scored as: none (0), slight (1), moderate (2), or severe (3). The patient was also asked to estimate her degree of pain relief with the analgesic as: no relief (0), 25% relief (1), 50% relief (2), 75% relief (3), or 100% relief (4). If at 2 hours or later a patient requested an additional analgesic because of inadequate relief from the test medication, she was given a conventional analgesic and was included in the efficacy evaluation. In the event a patient re-medicated, a severe pain intensity score and a zero pain relief score were assumed for all subsequent observations. If a patient was re-medicated before the second hour, she was excluded from the efficacy analysis.

In addition, at the last interview, or prior to re-medication, the patient was asked to assess her overall improvement and her overall rating of the test medication. These were respectively quantified on a seven-point scale: very much worse (1); much worse (2); a little worse (3); no change (4); a little better (5); much better (6); very much better (7), and on a four-point scale: poor (0); fair (1); good (2); and

excellent (3). Adverse reactions were noted if they were observed or volunteered.

Statistical Evaluation

Several measures of analgesia were derived from the interview data. The pain intensity difference (PID) score was calculated for each observation by subtracting the present pain intensity from the initial pain intensity. The sum of the pain intensity differences (SPID) is the sum of the PID scores weighted by the length of the time interval between observations and is an estimate of the area under the time-effect curve of the treatment. The weighted sum of pain intensity differences was determined by multiplying each PID by the fraction of an hour elapsed since the previous observation and adding the product for all seven observations. The variable TOTAL is the sum of the relief values also weighted by the length of the time interval between observations. The TOTAL value was similarly determined by multiplying each relief score by the fraction of an hour elapsed since

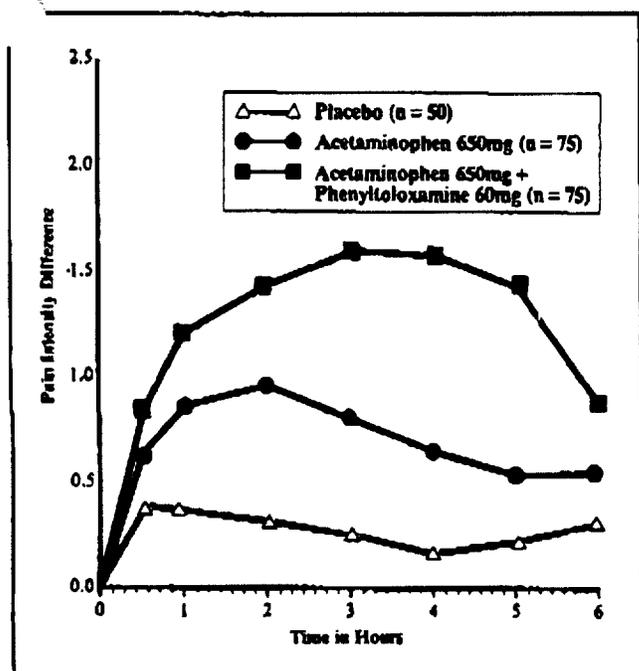


Figure 1. Time-effect curve: mean PID. Scores are calculated by subtracting the pain intensity score from the pain intensity at 0 hour. Patient responses were scored on a four-point scale as 0 = no pain, 1 = slight pain, 2 = moderate pain, and 3 = severe pain.

the previous observation and adding the product for all seven observations.

To study the differences among test treatments, a bioassay computer program performed an analysis of variance (ANOVA) for medication, calculated as a one-way layout on each of the study variables and derived measures.¹⁴ When the ANOVA was significant at the 0.05 level, pairwise contrasts between the treatments were carried out using Fisher's protected least significant difference test (LSD).¹⁵ Since the ANOVA assumption of homogeneity of variances was violated for some efficacy variables, the analysis was confirmed by performing the Kruskal-Wallis test and nonparametric pairwise comparisons. The results from both analysis procedures were in agreement and for simplicity only the ANOVA results are reported here.

RESULTS

Two hundred patients were enrolled in the study and all are included in the efficacy analysis. The distribution of some of the background variables of the study population are given in Table I. There were no significant differences among the three treatment groups in either age, height, weight, amniotomy status or number of days postpartum.

The mean scores for the hourly and summary measures of analgesia, and significant treatment differences are displayed in Table II. The time-effect curves for pain intensity difference (PID) and pain relief are shown in Figures 1 and 2, respectively.

Time Effect Curves

Placebo was clearly the least effective treatment and the combination of acetaminophen plus phenyltoloxamine was the most effective treatment. Acetaminophen alone was midway in effectiveness between the combination and placebo. Acetaminophen alone reached mean peak effect at hour 2 and then decreased in activity. The combination reached mean peak effect at hour 3 and had a sustained effect through hour 5 after which its effect decreased (Figures 1 and 2).

Differences Between Active Treatments and Placebo

Placebo was clearly the least effective treatment. Significant pairwise differences between placebo and each of the two active treatments were seen for

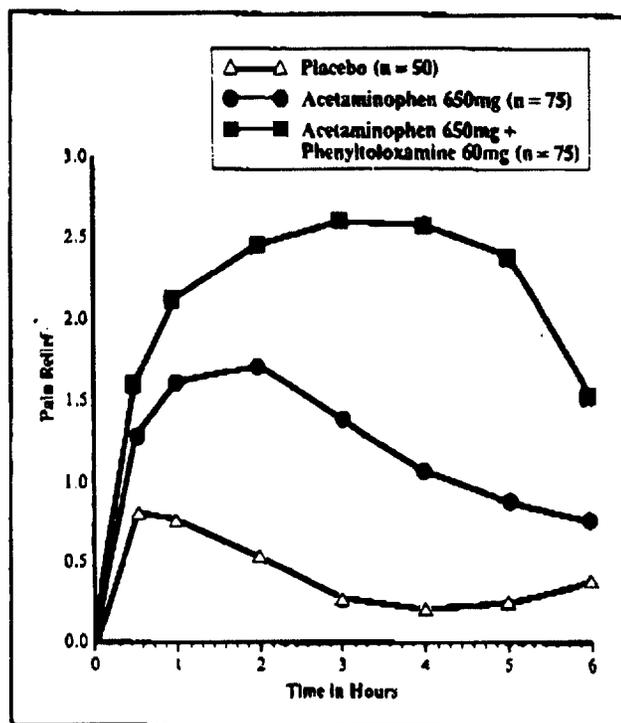


Figure 2. Time-effect curve: Mean pain relief. Mean pain relief is plotted as a percentage of the initial pain that was relieved. Patient responses were scored on a five-point scale as: 0 = no relief, 1 = a little (25%) relief, 2 = some relief (50%), 3 = a lot of relief (75%), and 4 = complete relief (100%).

all of the hourly measures, the summary measures (SPID, TOTAL), and the two global measures.

Differences Between Active Treatments

The combination of acetaminophen plus phenyltoloxamine was found to be significantly more effective than acetaminophen alone for practically all measures including the hourly measures, the summary measures (SPID, TOTAL), and the two global measures.

Adverse Reactions

During the course of this single-dose study two patients reported adverse effects. Both patients had received the combination as the treatment. The reported complaints consisted of dizziness, sleepiness, and sweating and none were considered of serious nature. It is not unusual for patients in this pain model to report or volunteer few or no adverse reactions. The extremely low incidence of adverse effects has been documented in this patient population in previous publications.¹⁶

Remedication

If at any time following the second hour evaluation, a patient obtained inadequate pain relief and requested remedication, a conventional analgesic was given. Only ten patients required remedication because of inadequate pain relief. These differences were significant at the 0.001 level based on the chi square test. None remedicated before the second hour evaluation. Of the ten patients who remedicated, eight had received placebo and two had received acetaminophen. None of the patients who had received the combination required rescue medication.

DISCUSSION

This study indicates that the combination of acetaminophen 650 mg plus phenyltoloxamine 60 mg results in more analgesia than is produced by acetaminophen alone. Compared to acetaminophen alone, the combination produced significantly more analgesia for all time points from 1/2 hr through 6 hours as well as for the summary measures SPID and TOTAL. For the global evaluations, the combination was rated as a significantly more effective medication and as providing a greater degree of overall improvement. In our experience, global measures often do not distinguish between active treatments. How-

ever, in this study, the global evaluations revealed the combination to be significantly more efficacious than acetaminophen alone. We speculate that the contribution of the antihistamine may have contributed to the patient's sense of overall improvement. The results of this study demonstrate that the addition of 60 mg phenyltoloxamine produces a significant enhancement of the analgesic activity of 650 mg acetaminophen in postpartum pain resulting from an episiotomy.

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Within one hour following the oral administration of phenyltoloxamine citrate, a Class I (ethanolamine-type) H₁ antihistaminic, a significant suppression of reagin-mediated skin reactivity was observed and this was correlated with a concomitant reduction in allergic nasal manifestations.

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INHIBITION OF CUTANEOUS AND MUCOSAL ALLERGY WITH PHENYLTOLOXAMINE

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ORAL ANTIHISTAMINIC PREPARATIONS are commonly administered for the symptomatic treatment of upper respiratory allergy and, more specifically, for the relief of clear rhinorrhea, nasal pruritus, edema ("congestion") and impaired nasal ventilatory flow characteristic of allergic rhinitis. One of the *in vivo* manifestations of the anti-allergic effect of oral antihistamines is their capacity to inhibit the wheal-and-flare skin reactions induced by the epicutaneous or intracutaneous application of allergenic extracts on the skin of subjects with reagin-mediated hypersensitivity.^{2,3} Several studies have documented the therapeutic efficacy of selected antihistamines^{4,6} and some investigators have also measured the reduction in the size of the immediate skin reactions following the ingestion of standard doses of antihistamines and certain other drugs.^{4,5} The present study was undertaken in order to evaluate, in a controlled manner, the dose-related and time-dependent effects of phenyltoloxamine citrate (Figure 1), a Class I, ethanolamine-type H₁ antihistaminic compound⁷ on (a) the existing upper respiratory allergic symptoms and (b) the magnitude and duration of immediate skin reactions to known inhalant allergens.

Materials and Methods

The subjects of this investigation were 10 properly informed and consenting adults (six females and four

males) with a confirmed diagnosis of intermittent, seasonal allergic rhinitis (Table I). The age range was 18-38 years for the six females (average 26) and 30-39 for the four males (average 34 years). They all had histories of allergic rhinitis for at least three years, either strictly seasonal (three patients) or perennial — intermittent or continuous — with seasonal exacerbations (seven patients). All participants had shown strongly positive skin reactions with the automatic triple puncture (Sterneedle), as well as with the intradermal techniques, to pollen allergens concordant with their clinical symptomatology (Table I). This reagin-mediated skin reactivity was again confirmed, for the purposes of this study, by the intradermal injection of two selected antigenic extracts per subject in a 1:1,000 aqueous solution. Standard methodology was employed and the

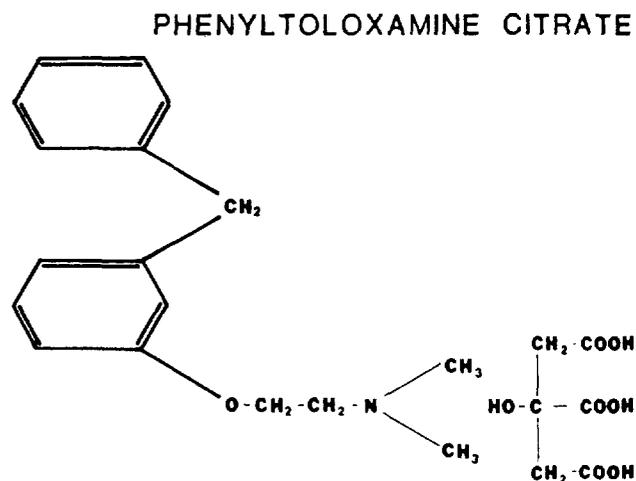


Figure 1. Phenyltoloxamine citrate, a Type 1, H₁ antihistaminic.

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INHIBITION WITH PHENYLTOLOXAMINE—FALLIERS ET AL

Reactions were applied alternatively on the external aspect of the right or left upper arm. Clinical symptomatology was determined by means of standard physical examination procedures, with the patient at rest in the examining room, and scored on a 0-3 scale of increasing severity (Table II) for the cardinal symptoms of (a) nasal obstruction, (b) nasal discharge, (c) nasal and/or ophthalmic pruritus and (d) sneezing, before the ingestion of the study tablets and at one and two hours post-treatment.

Three treatments were administered on three different days, at least 24 hours apart and at the same time of

the day for each subject. Due to scheduling constraints, the timing was not the same for all subjects but in this experiment the known circadian variability in skin test reactions¹ was considered to be relatively unimportant for comparative purposes. All three treatments consisted of the administration of two tablets orally, in a controlled, double-blind fashion and in a randomized sequence. On one of the three treatment days the patient received two 22 mg. tablets of phenyltoloxamine citrate; on a different day the treatment consisted of one tablet of phenyltoloxamine citrate 22 mg. and another identical placebo tablet and on the remaining treatment day —

Table I. Clinical and Demographic Data on 10 Patients with Allergic Rhinitis.

No.	Initials	Age	Sex	Diagnostic Pattern	Allergens tested intracutaneously
1	SM	22	F	Seasonal/Perennial	Elm, June Grass
2	SS	20	F	" "	Cottonwood, Common Sage
3	BMcK	39	M	" "	Prairie Sage, Russian Thistle
4	NB	20	F	" "	June and Rye Grass
5	JK	18	F	" "	Red Top and Timothy Grass
6	DM	35	M	" "	Timothy Grass, Giant Ragweed
7	AV	38	F	" "	Lamb's Quarters, Western Waterhemp
8	MS	33	F	" "	Rye Grass, Russian Thistle
9	JM	30	M	" "	June Grass, Russian Thistle
10	EJ	32	M	" "	Oak, Common Sage

Table II. Data Form and Scoring Method for Clinical and Skin Test Changes Following Treatment.

Clinical Evaluation				
	Baseline (No Rx)	1 hr. \bar{p} Rx	2 hrs. \bar{p} Rx	
Nasal obstruction	0-1-2-3	0-1-2-3	0-1-2-3	
Rhinorrhea (clear)	0-1-2-3	0-1-2-3	0-1-2-3	
Nasal/ophth. pruritus	0-1-2-3	0-1-2-3	0-1-2-3	
Sneezing (ptarmismus)	0-1-2-3	0-1-2-3	0-1-2-3	
Headache-frontal	0-1-2-3	0-1-2-3	0-1-2-3	
Other	0-1-2-3	0-1-2-3	0-1-2-3	
Nasal Microsc. Smear Eosinophilia (pre-Rx)	None + ++	+++ +++++		
Allergy Skin Tests				
Allergen	Baseline (No Rx)	1 hr. \bar{p} Rx	2 hrs. \bar{p} Rx	
	wheal size	wheal size	wheal size	
(a) _____	___x___mm	___x___mm	___x___mm	
	erythema	erythema	erythema	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	
	itching	itching	itching	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	
	wheal size	wheal size	wheal size	
(b) _____	___x___mm	___x___mm	___x___mm	
	erythema	erythema	erythema	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	
	itching	itching	itching	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	

Comments:

Legend: 0=None, 1=Mild, 2=Moderate, 3=Marked or Severe

which could happen to be the first, second or last session — the patient received two placebo tablets and no phenyltoloxamine. Nasal smears were taken from each individual for eosinophil counts before the study and the results were graded on a 0-4+ scale (Table II). The skin test results were assessed visually and then the two perpendicular diameters of the wheal were measured before, one hour and two hours after the administration of the test tablets. The two diameters were multiplied to give an approximation (in arbitrarily "squared" numbers) of the area of the wheal and erythema, in square millimeters. Erythema and pruritus were scored on a 0-3+ scale. Adverse reactions, subjective and objective, were explored, with particular attention to the possible development of somnolence, mucosal dryness, vertigo, irritability, gastric distress and other localized or systemic side effects.

Results

The mean baseline clinical scores were quite close for the three treatment days, being 5.2 for the day when 44 mg. phenyltoloxamine was given, 4.8 when 22 mg. phenyltoloxamine was given with one additional placebo tablet and 5.0 for the day when two placebo tablets were administered (Table III). At one and two hours after treatment two tablets of phenyltoloxamine and one tablet of phenyltoloxamine showed a significant difference ($p=0.01$) from placebo, in the direction of improvement. The larger dose of phenyltoloxamine differed significantly from the lower dose but less than when compared to placebo ($p=0.05$) one hour after administration of treatment. At two hours after medication 44 mg. of phenyltoloxamine citrate was significantly different from 22 mg. at the $p=0.01$ level. In terms of percentage over baseline the improvement after 44 mg. phenyltoloxamine citrate was 67.3%, after 22 mg. phenyltoloxamine 47.9% and after only placebo was ingested there was a 16.0% improvement in nasal allergic symptomatology after two hours. Of course it must be recognized that these percentage changes are relative to the grading system employed. In fact, one could not easily define a change from a score of 2 to a score of 1 as a 50% improvement or a shift from 1

to 2 as 100% aggravation, nor a change from 2 to 1 as "infinite" (!) improvement. Also, under the conditions of the experiment the possible effect of other factors such as physiologic circadian periodicity, the relatively clean environment in the laboratory or other influences could not be excluded.

The size of the urticarial wheals induced by the intradermal injection of the allergenic extracts was found to be remarkably consistent prior to the administration of treatment. Mean baseline wheal sizes were 484 mm² on the day phenyltoloxamine 44 mg. was given; it was 492 mm² when the dose was phenyltoloxamine 22 mg. and 484 mm² when the randomized schedule provided for the administration of placebo. One and two hours after the administration of the two active phenyltoloxamine doses a significant decrease in the wheal size was noted, greater than that following placebo at the $p=0.01$ level. The 44 mg. dose of phenyltoloxamine reduced the size of the wheal significantly more than the 22 mg. dose at the $p=0.05$ level, which was somewhat less than the difference of either drug from placebo (Table IV). Thus it was observed that 44 mg. phenyltoloxamine provided 88.6% and 97.1% protection, respectively, one and two hours after treatment; 22 mg. phenyltoloxamine provided 70.7% and 75.2% protection and placebo reduced the wheal size by 7.6% and 4.4% at one and two hours after administration, respectively.

It was thus noted that the antihistaminic inhibition of the wheal, caused by the intradermal injection of two selected allergens among demonstrably sensitive individuals, correlated well with the clinical improvement induced by two doses of phenyltoloxamine citrate, in comparison to changes observed after the administration of identical-appearing placebo tablets (Figure 2). The higher dose of phenyltoloxamine, 44 mg., or two tablets, was found to be more effective than the lower dose of 22 mg. (one tablet) both in terms of symptomatic relief and in the prevention of whealing after intradermal application of allergens. Noteworthy is the fact that, under the conditions of this experiment,

Table III. Effect of Medication on Clinical Symptom Scores, 10 Ss with Allergic Rhinitis.

Treatment	No. Tabs.	Baseline Score	1 Hour After Rx	Difference	Percentage Improvement	2 Hours After Rx	Difference	Percentage Improvement
I. Phenyltoloxamine	2	5.2	2.2	3.0	57.7	1.7	3.5	67.3
II. Phenyltoloxamine Placebo	1	4.8	2.7	2.1	43.8	2.5	2.3	47.9
III. Placebo	2	5.0	4.5	0.05	10.0	4.2	0.8	16.0

Table IV. Mean Wheal Area (sq. mm.) Following ID Tests (two/Ss) performed on 10 Ss Before and After Medication.

Treatment	No. Tabs.	Baseline Score	1 Hour After Rx	Difference	Percent Protection	Two Hours After Rx	Difference	Percent Protection
I. Phenyltoloxamine	2	484	55	429	88.6	14	470	97.1
II. Phenyltoloxamine Placebo	1	492	144	348	70.7	122	370	75.2
III. Placebo	2	484	447	37	7.6	463	21	4.4

no patient showed any adverse effect which might diminish the clinical usefulness of phenyltoloxamine, especially in higher doses.

After it was ascertained that the skin reactions began to subside and that the patients were not experiencing any systemic adverse effects from the medication given, they were allowed to return home. They were all specifically requested to report any delayed reactions noted but none did, either spontaneously or after questioning at a subsequent visit.

Discussion

The capacity of histamine to produce respiratory mucosal changes and urticarial skin reactions typical of allergy has been recognized for several decades.^{9,10,11} Inhibition of histamine-induced wheals has been used as a means to test the potency of antihistaminic drugs: the intradermal injection of 10-30 mcg. histamine phosphate resulted in 200-260 mm² wheals, which were found to be reduced by 50% or more by certain antihistaminic compounds.⁹ In a double-blind, placebo-controlled comparative study four common antihistaminics were found to suppress or reduce the size of skin test reactions to high concentrations of selected "major" and "minor" allergens,¹² with peak effects noted between one and two hours after ingestion of the drugs. Likewise, another study of five representative drugs — including hydroxyzine — found 30-63% wheal diminution, with an average duration of this effect from 1.89 to 4.31 hours.¹³

Spontaneous variability of the immediate skin reactions to standard allergens of verified potency is not common, provided that uniform and meticulously controlled techniques are applied.¹⁴ Circadian variability in skin reactivity around the 24-hour biological cycle, although measurable,⁸ is several times smaller than that associated with the biological potency of the allergens employed and with the medication administered prior to the testing; therefore, it can be considered negligible for a study placing primary emphasis on medication and/or allergenic exposure. Non-immediate or delayed skin responses, occurring six to 12, or 24 to 48 hours after the intradermal application of the allergens, have been described and have been attributed either to immunoglobulin E antibodies¹⁵ or to Type III and Type IV immune reactions.¹⁶ Such reactions have generally been assumed to be extremely infrequent and in some cases they have been only noted following the suppression of the immediate wheal-and-erythema reactions by antihistamines.¹⁷ When this was noted it has been hypothesized that the immediate "flush" reaction does indeed serve a useful teleologic purpose and that only its suppression allows a delayed-type reaction to become manifest. It is considered noteworthy that in the present study no "late" or delayed skin reactions were observed among the 10 patients tested, either when they received oral antihistaminic medication or when only placebo was given.

The inhibition of classical Type I wheal-and-flare skin

reactions by phenyltoloxamine is of more than casual pharmacologic interest. Indeed, it can be considered as being comparable in its therapeutic implications to the experimental demonstration of a protective antihistaminic effect against the histamine-induced increase in pulmonary vascular permeability and pulmonary edema, demonstrated in certain selected animal species.¹⁸ The clinical improvement in the nasal symptoms of the patients in the study can be viewed as evidence of this therapeutic antihistaminic effect.

Summary

A dose-and-time-related-effect of oral phenyltoloxamine citrate, a Class I, H₁ antihistamine compound, has been demonstrated against allergen-induced wheal-and-erythema skin reactions among 10 adults with a diagnosis of allergic rhinitis and seasonal pollinosis. Clinical improvement in the existing symptoms of rhinorrhea, nasal obstruction, pruritus and sneezing, showed a significant correlation with the inhibition of reagin-mediated skin reactivity caused by phenyltoloxamine. No adverse side effects were observed. It can be concluded that oral phenyltoloxamine citrate possesses antihistaminic properties and a range of safety which make it a useful agent for the symptomatic management of upper respiratory allergy.

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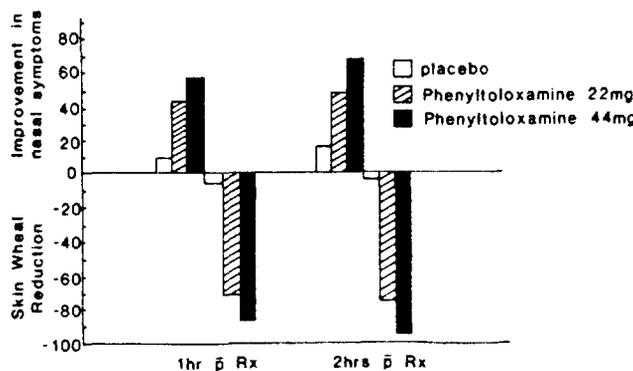


Figure 2. Comparative changes (percentage of baseline) in nasal symptoms and in skin whealing responses after oral phenyltoloxamine and after placebo.

- phenyltoloxamine (Bristamin). *J Am Pharmaceut Assoc* 42: 587, 1953.
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“For better or worse, there are few occupations of a more satisfying character than the practice of medicine, if a man can but once get *orientirt* and bring to it the philosophy of honest work, the philosophy that insists that we are here, not to get all we can out of life about us, but to see how much we can add to it. The discontent and grumblings which one hears have their source in the man more often than in his environment.”

Sir William Osler
*On the Educational Value of the
Medical Society*

Within one hour following the oral administration of phenyltoloxamine citrate, a Class I (ethanolamine-type) H₁ antihistaminic, a significant suppression of reagin-mediated skin reactivity was observed and this was correlated with a concomitant reduction in allergic nasal manifestations.

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INHIBITION OF CUTANEOUS AND MUCOSAL ALLERGY WITH PHENYLTOLOXAMINE

NOTICE
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COPYRIGHT LAW (TITLE 17, U.S. CODE)

CONSTANTINE J. FALLIERS, M.D., F.A.C.A.,
MARIE A. REDDING, M.A., and CHRIS P. KATSAMPES, M.D.

ORAL ANTIHISTAMINIC PREPARATIONS are commonly administered for the symptomatic treatment of upper respiratory allergy and, more specifically, for the relief of clear rhinorrhea, nasal pruritus, edema ("congestion") and impaired nasal ventilatory flow characteristic of allergic rhinitis. One of the *in vivo* manifestations of the anti-allergic effect of oral antihistamines is their capacity to inhibit the wheal-and-flare skin reactions induced by the epicutaneous or intracutaneous application of allergenic extracts on the skin of subjects with reagin-mediated hypersensitivity.^{2,3} Several studies have documented the therapeutic efficacy of selected antihistamines^{4,6} and some investigators have also measured the reduction in the size of the immediate skin reactions following the ingestion of standard doses of antihistamines and certain other drugs.^{4,5} The present study was undertaken in order to evaluate, in a controlled manner, the dose-related and time-dependent effects of phenyltoloxamine citrate (Figure 1), a Class I, ethanolamine-type H₁ antihistaminic compound⁷ on (a) the existing upper respiratory allergic symptoms and (b) the magnitude and duration of immediate skin reactions to known inhalant allergens.

Materials and Methods

The subjects of this investigation were 10 properly informed and consenting adults (six females and four

males) with a confirmed diagnosis of intermittent, seasonal allergic rhinitis (Table I). The age range was 18-38 years for the six females (average 26) and 30-39 for the four males (average 34 years). They all had histories of allergic rhinitis for at least three years, either strictly seasonal (three patients) or perennial — intermittent or continuous — with seasonal exacerbations (seven patients). All participants had shown strongly positive skin reactions with the automatic triple puncture (Sterneedle), as well as with the intradermal techniques, to pollen allergens concordant with their clinical symptomatology (Table I). This reagin-mediated skin reactivity was again confirmed, for the purposes of this study, by the intradermal injection of two selected antigenic extracts per subject in a 1:1,000 aqueous solution. Standard methodology was employed and the

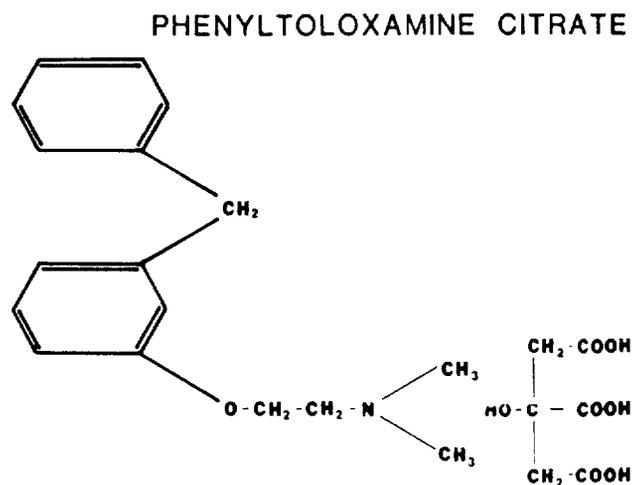


Figure 1. Phenyltoloxamine citrate, a Type 1, H₁ antihistaminic

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Marie A. Redding is Clinical Research Assistant, Allergy and Asthma Clinic, P.C., Denver, Colorado.

Doctor Katsampes is Consultant, Clinical Investigation, Warner, Chilcott Laboratories, Morris Plains, New Jersey, and Clinical Professor of Pediatrics (retired), College of Physicians and Surgeons, Columbia University, New York, New York.

INHIBITION WITH PHENYLTOLOXAMINE—FALLIERS ET AL

injections were applied alternatively on the external aspect of the right or left upper arm. Clinical symptomatology was determined by means of standard physical examination procedures, with the patient at rest in the examining room, and scored on a 0-3 scale of increasing severity (Table II) for the cardinal symptoms of (a) nasal obstruction, (b) nasal discharge, (c) nasal and/or ophthalmic pruritus and (d) sneezing, before the ingestion of the study tablets and at one and two hours post-treatment.

Three treatments were administered on three different days, at least 24 hours apart and at the same time of

the day for each subject. Due to scheduling constraints, the timing was not the same for all subjects but in this experiment the known circadian variability in skin test reactions⁸ was considered to be relatively unimportant for comparative purposes. All three treatments consisted of the administration of two tablets orally, in a controlled, double-blind fashion and in a randomized sequence. On one of the three treatment days the patient received two 22 mg. tablets of phenyltoloxamine citrate; on a different day the treatment consisted of one tablet of phenyltoloxamine citrate 22 mg. and another identical placebo tablet and on the remaining treatment day —

Table I. Clinical and Demographic Data on 10 Patients with Allergic Rhinitis.

No.	Initials	Age	Sex	Diagnostic Pattern	Allergens tested intracutaneously
1	SM	22	F	Seasonal/Perennial	Elm, June Grass
2	SS	20	F	" "	Cottonwood, Common Sage
3	BMcK	39	M	" "	Prairie Sage, Russian Thistle
4	NB	20	F	" "	June and Rye Grass
5	JK	18	F	" "	Red Top and Timothy Grass
6	DM	35	M	" "	Timothy Grass, Giant Ragweed
7	AV	38	F	" "	Lamb's Quarters, Western Waterhemp
8	MS	33	F	" "	Rye Grass, Russian Thistle
9	JM	30	M	" "	June Grass, Russian Thistle
10	EJ	32	M	" "	Oak, Common Sage

Table II. Data Form and Scoring Method for Clinical and Skin Test Changes Following Treatment.

Clinical Evaluation				
	Baseline (No Rx)	1 hr. \bar{p} Rx	2 hrs. \bar{p} Rx	
Nasal obstruction	0-1-2-3	0-1-2-3	0-1-2-3	
Rhinorrhea (clear)	0-1-2-3	0-1-2-3	0-1-2-3	
Nasal/ophth. pruritus	0-1-2-3	0-1-2-3	0-1-2-3	
Sneezing (ptarmismus)	0-1-2-3	0-1-2-3	0-1-2-3	
Headache-frontal	0-1-2-3	0-1-2-3	0-1-2-3	
Other	0-1-2-3	0-1-2-3	0-1-2-3	
Nasal Microsc. Smear Eosinophilia (pre-Rx)	None + ++	+++ +++++		
Allergy Skin Tests				
Allergen	Baseline (No Rx)	1 hr. \bar{p} Rx	2 hrs. \bar{p} Rx	
	wheel size	wheel size	wheel size	
(a) _____	___x___ mm	___x___ mm	___x___ mm	
	erythema	erythema	erythema	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	
	itching	itching	itching	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	
	wheel size	wheel size	wheel size	
(b) _____	___x___ mm	___x___ mm	___x___ mm	
	erythema	erythema	erythema	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	
	itching	itching	itching	
	0-1-2-3+	0-1-2-3+	0-1-2-3+	
Comments:				
Legend: 0=None, 1=Mild, 2=Moderate, 3=Marked or Severe				

which could happen to be the first, second or last session — the patient received two placebo tablets and no phenyltoloxamine. Nasal smears were taken from each individual for eosinophil counts before the study and the results were graded on a 0-4+ scale (Table II). The skin test results were assessed visually and then the two perpendicular diameters of the wheal were measured before, one hour and two hours after the administration of the test tablets. The two diameters were multiplied to give an approximation (in arbitrarily "squared" numbers) of the area of the wheal and erythema, in square millimeters. Erythema and pruritus were scored on a 0-3+ scale. Adverse reactions, subjective and objective, were explored, with particular attention to the possible development of somnolence, mucosal dryness, vertigo, irritability, gastric distress and other localized or systemic side effects.

Results

The mean baseline clinical scores were quite close for the three treatment days, being 5.2 for the day when 44 mg. phenyltoloxamine was given, 4.8 when 22 mg. phenyltoloxamine was given with one additional placebo tablet and 5.0 for the day when two placebo tablets were administered (Table III). At one and two hours after treatment two tablets of phenyltoloxamine and one tablet of phenyltoloxamine showed a significant difference ($p=0.01$) from placebo, in the direction of improvement. The larger dose of phenyltoloxamine differed significantly from the lower dose but less than when compared to placebo ($p=0.05$) one hour after administration of treatment. At two hours after medication 44 mg. of phenyltoloxamine citrate was significantly different from 22 mg. at the $p=0.01$ level. In terms of percentage over baseline the improvement after 44 mg. phenyltoloxamine citrate was 67.3%, after 22 mg. phenyltoloxamine 47.9% and after only placebo was ingested there was a 16.0% improvement in nasal allergic symptomatology after two hours. Of course it must be recognized that these percentage changes are relative to the grading system employed. In fact, one could not easily define a change from a score of 2 to a score of 1 as a 50% improvement or a shift from 1

to 2 as 100% aggravation, nor a change from 1 to 0 as "infinite" (!) improvement. Also, under the conditions of the experiment the possible effect of other factors, such as physiologic circadian periodicity, the relatively clean environment in the laboratory or other influences could not be excluded.

The size of the urticarial wheals induced by the intradermal injection of the allergenic extracts was found to be remarkably consistent prior to the administration of treatment. Mean baseline wheal sizes were 484 mm² on the day phenyltoloxamine 44 mg. was given; it was 492 mm² when the dose was phenyltoloxamine 22 mg. and 484 mm² when the randomized schedule provided for the administration of placebo. One and two hours after the administration of the two active phenyltoloxamine doses a significant decrease in the wheal size was noted, greater than that following placebo at the $p=0.01$ level. The 44 mg. dose of phenyltoloxamine reduced the size of the wheal significantly more than the 22 mg. dose at the $p=0.05$ level, which was somewhat less than the difference of either drug from placebo (Table IV). Thus it was observed that 44 mg. phenyltoloxamine provided 88.6% and 97.1% protection, respectively, one and two hours after treatment; 22 mg. phenyltoloxamine provided 70.7% and 75.2% protection and placebo reduced the wheal size by 7.6% and 4.4% at one and two hours after administration, respectively.

It was thus noted that the antihistaminic inhibitor of the wheal, caused by the intradermal injection of two selected allergens among demonstrably sensitive individuals, correlated well with the clinical improvement induced by two doses of phenyltoloxamine citrate, in comparison to changes observed after the administration of identical-appearing placebo tablets (Figure 2). The higher dose of phenyltoloxamine, 44 mg., or two tablets, was found to be more effective than the lower dose of 22 mg. (one tablet) both in terms of symptomatic relief and in the prevention of whealing after intradermal application of allergens. Noteworthy is the fact that, under the conditions of this experiment

Table III. Effect of Medication on Clinical Symptom Scores, 10 Ss with Allergic Rhinitis.

Treatment	No. Tabs.	Baseline Score	1 Hour After Rx	Difference	Percentage Improvement	2 Hours After Rx	Difference	Percentage Improvement
I. Phenyltoloxamine	2	5.2	2.2	3.0	57.7	1.7	3.5	67.3
II. Phenyltoloxamine	1	4.8	2.7	2.1	43.8	2.5	2.3	47.9
Placebo	1							
III. Placebo	2	5.0	4.5	0.05	10.0	4.2	0.8	16.0

Table IV. Mean Wheal Area (sq. mm.) Following ID Tests (two/Ss) performed on 10 Ss Before and After Medication.

Treatment	No. Tabs.	Baseline Score	1 Hour After Rx	Difference	Percent Protection	Two Hours After Rx	Difference	Percent Protection
I. Phenyltoloxamine	2	484	55	429	88.6	14	470	97.1
II. Phenyltoloxamine	1							
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The capacity of histamine to produce respiratory mucosal changes and urticarial skin reactions typical of allergy has been recognized for several decades.^{9,10,11} Inhibition of histamine-induced wheals has been used as a means to test the potency of antihistaminic drugs: the intradermal injection of 10-30 mcg. histamine phosphate resulted in 200-260 mm² wheals, which were found to be reduced by 50% or more by certain antihistaminic compounds.⁹ In a double-blind, placebo-controlled comparative study four common antihistaminics were found to suppress or reduce the size of skin test reactions to high concentrations of selected "major" and "minor" allergens,¹² with peak effects noted between one and two hours after ingestion of the drugs. Likewise, another study of five representative drugs — including hydroxyzine — found 30-63% wheal diminution, with an average duration of this effect from 1.89 to 4.31 hours.¹³ Spontaneous variability of the immediate skin reactions to standard allergens of verified potency is not common, provided that uniform and meticulously controlled techniques are applied.¹⁴ Circadian variability in skin reactivity around the 24-hour biological cycle, although measurable,⁵ is several times smaller than that associated with the biological potency of the allergens employed and with the medication administered prior to the testing; therefore, it can be considered negligible for a study placing primary emphasis on medication and/or allergenic exposure. Non-immediate or delayed skin responses, occurring six to 12, or 24 to 48 hours after the intradermal application of the allergens, have been described and have been attributed either to immunoglobulin E antibodies¹⁵ or to Type III and Type IV immune reactions.¹⁶ Such reactions have generally been assumed to be extremely infrequent and in some cases they have been only noted following the suppression of the immediate wheal-and-erythema reactions by antihistamines.¹⁷ When this was noted it has been hypothesized that the immediate "flush" reaction does indeed serve a useful teleologic purpose and that only its suppression allows a delayed-type reaction to become manifest. It is considered noteworthy that in the present study no "late" or delayed skin reactions were observed among the 10 patients tested, either when they received oral antihistaminic medication or when only placebo was given.

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Summary

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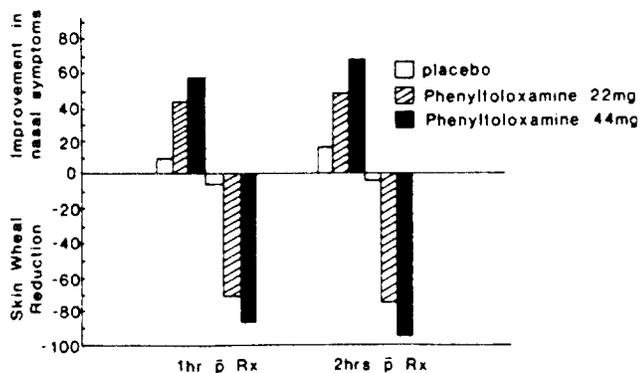


Figure 2. Comparative changes (percentage of baseline) in nasal symptoms and in skin whealing responses after oral phenyltoloxamine and after placebo.

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Sir William Osler
*On the Educational Value of the
Medical Society*

A. INGREDIENT NAME:

PENTYLENE TETRAZOLE

B. Chemical Name:

1,5-Pentamethylenetetrazole, 6,7,8,9-Tetrahydro-5H-tetrazoloazepine

C. Common Name:

Leptazol Injection Giazol, Angioton, Angiotonin, Cardiazol, Cardiazole, Cardifortan, Cardiol, Cardiotonicum, Cardosal, Cordosan, Cenalene-M, Cenazol, Centrazole, Cerebro-Nicin, Coranormal, Coranormol, Corasol, Coratoline, Corazol, Corazole, Corazole (Analeptic) Corisan, Corsedrol, Cortis, Corvasol, Corvis, Coryvet.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Minimum)</i>	<i>(Result)</i>
Assay	98%	99.80%

E. Information about how the ingredient is supplied:

White crystals, slightly pungent and bitter, very stable, not easily attacked by other substances.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Cz., Hung., It., Arg., Belg., Br., Eur., Fr., Ger., Hung., Ind., Int., It., Jug., Mex., Neth., Nord., Pol., Port., Rus., Span., Swiss., and Turk.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Jun, H. W. Absorption and Fate. *J. Pharm. Sci.*, 1975;64:1843.

Khazi, I. A., Mahajanshetti, C. S., and Gadad A. K. Pentylene tetrazole induced convulsions. *Arzneimittelforschung*, 1996;46(10):949-952.

Erol, D. D., Calis, U., and Demirdamar, R. Pentylene tetrazole-induced seizures in mice. *J. Pharm. Sci.* 1995; 84(4):462-465

H. Information about dosage forms used:

Orally
Injection

I. Information about strength:

100-200mg

J. Information about route of administration:

Given by mouth

K. Stability data:

Melts at about 57-60°

L. Formulations:

Leptazol is a sterile solution of pentetrazol 10% and sodium phosphate 0.25% in water for injections, adjusted to pH 7.8 with dilute hydrochloric acid or potassium hydroxide solution.

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1103
#53751

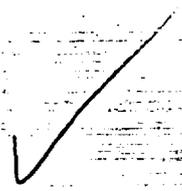
Page 1

Date: 10/15/97

PRODUCT: PENTYLENETETRAZOLE - *A*

CATALOG NO: PE104 **
LOT NO: MJ0251

DESCRIPTION	LIMIT		RESULT
	MIN.	MAX.	
ASSAY	98 %	-	99.80 % <i>D</i>
MELTING RANGE	59 - 61 C		59 - 61 C



APPROVED BY: *Lilian D. Casabar*
LILIAN D. CASABAR

10/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: PENTYLENETETRAZOLE _____

MANUFACTURE LOT NO.: MJ0251

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO.SPECS. ___.

1) DESCRIPTION.:

E WHITE CRYSTALS, SLIGHTLY PUNGENT AND BITTER; VERY STABLE, NOT EASILY ATTACKED BY OTHER SUBSTANCES.

2) SOLUBILITY.:

FREELY SOLUBLE IN WATER AND IN MOST ORGANIC SOLVENTS. SLIGHTLY SOLUBLE IN ALCOHOL.

3) MELTING POINT.:

K MELTS AT ABOUT 57-60 DEGREES.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

----- IDENTIFICATION -----

PRODUCT #: P720-7 NAME: 1,5-PENTAMETHYLENETETRAZOLE, 98%

CAS #: 54-95-5

MF: C6H10N4

SYNONYMS

ANGIAZOL * ANGIOTON * ANGIOTONIN * CARDIAZOL * CARDIAZOLE *
CARDIFORTAN * CARDIOL * CARDIOTONICUM * CARDOSAL * CARDOSAN *

CENALENE-M * CENAZOL * CENTRAZOLE * CEREBRO-NICIN * CORANORMAL *

CORANORMOL * CORASOL * CORATOLINE * CORAZOL * CORAZOLE *

CORAZOLE

(ANALEPTIC) * CORISAN * CORSEDROL * CORTIS * CORVASOL * CORVIS *
CORYVET * ALPHA,BETA-CYCLOPENTAMETHYLENETETRAZOLE *

DEAMOCARD *

DELZOL-W * DIOVASCOLE * DEUMACARD * GEWAZOL * KARDIAZOL *

KORAZOL *

KORAZOLE * LPAZOL * LEPTAZOL * LEPTAZOLE * METRAZOL * METRAZOLE *

NAURANZOL * NAURAZOL * NEDCARDOL * NEOCARDOL * NEURAZOL * NOVO
CORA-

VINCO * OPTICOR * PEMETESAN * PENETRASOL * PENETRATSOL * PENETIAZOL
*

PENTACARD * PENTACOR * PENTAMETHAZOL * PENTAMETHAZOLUM *

PENTAMETHYLENETETRAZAL * PENTAMETHYLENETETRAZOL *

PENTAMETHYLENETETRAZOLE * PENTAMETHYLENE-1,5-TETRAZOLE * 1,5-

PENTAMETHYLENETETRAZOLE * PENTAMETILENTETRAZOLO (ITALIAN) *
PENTAZOL *

PENTAZOLUM * PENTEMESAN * PENTETRAZOL * PENTETRAZOLE *

PENTRAZOL *

PENTROLONE * PENTROZOL * PENTYLENETETRAZOL * PENTYLENETETRAZOLE

*

PETAZOL * PETEZOL * PETRAZOLE * PHRENAZOL * PHRENAZONE * PMT * PTZ *

STELLACARDIOL * STILLCARDIOL * TETRACOR * 6,7,8,9-TETRAHYDRO-5-
AZEPOTETRAZOLE * 6,7,8,9-TETRAHYDRO-5H-TETRAZOLOAZEPINE * 7,8,9,10-

TETRAZABICYCLO(5.3.0)-8,10-DECADIENE * 1,2,3,3A-TETRAZACYCLOHEPTA-8A,

2-CYCLOPENTADIENE * TETRASOL * TETRAZOL * TETRAZOLE,
PENTAMETHYLENE- *

5H-TETRAZOLO(1,5-A)AZEPINE, 6,7,8,9-TETRAHYDRO- (8CI,9CI) * TT87 *

VASAZOL * VASOREX * VENTRAZOL * YETRAZOL *

----- TOXICITY HAZARDS -----

RTECS NO: XF8225000

5H-TETRAZOLOAZEPINE, 6,7,8,9-TETRAHYDRO-

TOXICITY DATA

ORL-MAN LDLO:147 MG/KG	85DCAI 2,73,70
IVN-MAN LDLO:29 MG/KG	85DCAI 2,73,70
ORL-RAT LD50:140 MG/KG	JPPMAB 13,244,61
IPR-RAT LD50:62 MG/KG	TXAPA9 18,185,71
SCU-RAT LD50:85 MG/KG	TXAPA9 18,185,71
IVN-RAT LD50:45 MG/KG	AIPTAK 135,9,62
REC-RAT LD50:8 MG/KG	AACRAT 46,395,67
ORL-MUS LD50:88 MG/KG	JPETAB 128,176,60
IPR-MUS LD50:55 MG/KG	AIPTAK 123,419,60
SCU-MUS LD50:70 MG/KG	BCFAAI 111,293,72
IVN-MUS LD50:31400 UG/KG	AIPTAK 103,146,55
PAR-MUS LD50:72 MG/KG	ARZNAD 6,583,56
SCU-RBT LD50:76 MG/KG	JAPMA8 29,2,40
IVN-RBT LD50:30 MG/KG	PHTXA6 21,1,58
SCU-FRG LD50:1600 MG/KG	PLRCAT 1,7,69

REVIEWS, STANDARDS, AND REGULATIONS

NOHS 1974: HZD 84704; NIS 1; TNF 68; NOS 6; TNE 2770

EPA TSCA CHEMICAL INVENTORY, JUNE 1990

TARGET ORGAN DATA

BRAIN AND COVERINGS (RECORDINGS FROM SPECIFIC AREAS OF CNS)

BEHAVIORAL (TREMOR)

BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)

BEHAVIORAL (EXCITEMENT)

BEHAVIORAL (MUSCLE CONTRACTION OR SPASTICITY)

LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES
(RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE
INFORMATION.

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

MAY CAUSE IRRITATION.

EXPOSURE CAN CAUSE:

CNS STIMULATION

CONVULSIONS

TARGET ORGAN(S):

CENTRAL NERVOUS SYSTEM

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH COPIOUS

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR,
CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

SAFETY SHOWER AND EYE BATH.

USE ONLY IN A CHEMICAL FUME HOOD.

DO NOT BREATHE DUST.

AVOID CONTACT WITH EYES, SKIN AND CLOTHING

AVOID PROLONGED OR REPEATED EXPOSURE.

WASH THOROUGHLY AFTER HANDLING.

TOXIC.

KEEP TIGHTLY CLOSED.

STORE IN A COOL DRY PLACE

TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE

POSSIBLE).

WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE
PROTECTION.

TARGET ORGAN(S):

NERVES

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT
PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL
NOT BE

HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM
CONTACT WITH THE

ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR
ADDITIONAL

TERMS AND CONDITIONS OF SALE

Preparations
 Preparations are listed below; details are given in Part 3.
Preparations
 Nikethamide Injection.
Preparations
 Glucose; Coraminet; Spain: Cora; Coraminat; etc.
Parental preparations. Ger.: Antiadiposum X-112; Herzfluid; Hypotonin forte; Poikiloton; Spain: Ignat; Tosidrin; Switz.: Gly-Coramine.

Vomica (538-h)
 Neuz Vómica; Noce Vomica; Noix Vomique; Semen.
 57-57-3 (anhydrous brucine).
 Pharmacopoeias. In Aust., Chin., Cz., Fr., Hung., Jpn. and Swiss.
 It also includes Powdered Nux Vomica.
 Yields *Strychnos pteriana*.
 The seeds of *Strychnos nux-vomica* (Loganiaceae).

Nuxvomica has the actions of strychnine (see p.1547).
 Extracts of *nux vomica* have been used for a variety of disorders including those of digestive debility.
 As containing strychnine, *nux vomica* con-
 tains strychnine which has similar properties.

Nuxvomica (*Nux vom.*) is used in herbal and homeopathic medicine. *Ignatia*, the dried seed of *Ignatia*, is also used in homeopathic medicine where it is known as *Ignatia amara* or *Ignatia*.

Preparations
 Preparations are listed below; details are given in Part 3.
Proprietary Preparations
Ingredient preparations. Belg.: Aperop; Digestobiaset; Solar; Fr.: Climaxol; Creme Rap; Curoveinyl; Digestobiaset; Grez Chlorhydropepsique; Phosma-Hématoporphyrinet; Pink; Quintonine; YSE; YSE Glutamine; Ital.: Amaro; Enteroton Digestivo; Gastro-Pepsin; Lassatina; Pillole; S.Afr.: Peter Pote's; Spain: Alofedina; Switz.: Padma-Lax.

Pemoline (1436-b)
 Pemoline (BAN, USAN, INN).
 NSC-25159; Phenoxazole; Phenylisohydantoin; Phenylisohydantoin, 2-Imino-5-phenyl-4-oxazolidinone.
 $C_{12}H_{17}NO_2 = 176.2$.
 2152-34-3 (pemoline); 68942-31-4 (pemoline hydrochloride); 18968-99-5 (magnesium pemoline).

Adverse Effects, Treatment, and Precautions
 For Dexamphetamine Sulphate, p.1547; however, the effects of over-stimulation and sympathomimetic activity are considered to be less with pemoline. There have been reports of impaired liver function in patients taking pemoline; its use is contraindicated in patients with liver disorders. There have also been rare or isolated reports of chorea, mania, and neutropenia.

Paranoid psychosis was observed in a 13-year-old child taking pemoline 75 to 225 mg daily. The child's compulsive use of the drug, development of paranoid depressive psychosis, and inability to discontinue the drug, suggested a withdrawal syndrome, and it was evident that the patient was dependent on pemoline.

Michael SE, Morse RM. Pemoline abuse. *JAMA* 1974; 231: 76-77.
Effects on growth. Results of a study in 20 hyperkinetic children suggested that growth suppression was a potential effect of prolonged treatment with clinically effective doses of pemoline and that this effect might be dose-related. See under Dexamphetamine Sulphate, p.1548.

Stinson LC, et al. Impaired growth in hyperkinetic children receiving pemoline. *J Pediatr* 1979; 94: 538-41.

Effects on the liver. Of children taking pemoline for 3 months had elevated concentrations of serum aspartate aminotransferase (SGOT) and serum alanine aminotransferase (SGPT); the effect was stated to be transient and self-limiting.

Hepatitis was associated with pemoline in a 10-year-old child. Liver enzyme values fell to normal after withdrawal of pemoline. Lower doses did not increase the enzyme activity, suggesting a toxic threshold. Close attention to hepatic function is advised.

† denotes a preparation no longer actively marketed.

function during the first few weeks of pemoline therapy was considered essential and it was recommended that serum enzymes should be measured at no less than every 2 weeks for the first 6 weeks and then every other month.

1. Anonymous. 'Hyperkinesia' can have many causes, symptoms. *JAMA* 1975; 232: 1204-16.
2. Patterson JF. Hepatitis associated with pemoline. *South Med J* 1984; 77: 938.

Effects on muscle. See under Effects on the Nervous System, p.1555.

Effects on the nervous system. Choreoathetosis and rhabdomyolysis developed in a patient following a marked increase in intake of pemoline. Abnormal movements responded to diazepam.

For a discussion on central stimulants provoking Tourette's syndrome, see Dexamphetamine Sulphate, p.1548.

1. Briscoe JG, et al. Pemoline-induced choreoathetosis and rhabdomyolysis. *Med Toxicol* 1988; 3: 72-6.

Effects on the prostate. Experience in one patient suggested that pemoline might adversely affect the prostate gland or interfere with tests for prostatic acid phosphatase used in the diagnosis of prostatic carcinoma.

1. Lindau W, de Girolami E. Pemoline and the prostate. *Lancet* 1986; i: 738.

Pharmacokinetics

Pemoline is readily absorbed from the gastro-intestinal tract. About 50% is bound to plasma protein. It is partially metabolised in the liver and excreted in the urine as unchanged pemoline and metabolites.

It has been suggested that magnesium hydroxide might increase the absorption of pemoline. Pemoline with magnesium hydroxide is known as magnesium pemoline.

References

1. Vermeulen NPE, et al. Pharmacokinetics of pemoline in plasma, saliva and urine following oral administration. *Br J Clin Pharmacol* 1979; 8: 459-63.
2. Sallee F, et al. Oral pemoline kinetics in hyperactive children. *Clin Pharmacol Ther* 1985; 37: 606-9.
3. Collier CP, et al. Pemoline pharmacokinetics and long term therapy in children with attention deficit disorder and hyperactivity. *Clin Pharmacokinet* 1985; 10: 269-78.

Uses and Administration

Pemoline has similar actions to dexamphetamine (see p.1548) and is used as an alternative to dexamphetamine or methylphenidate in the management of hyperactivity disorders in children (see p.1544). In the UK the initial dose by mouth in such children is 20 mg each morning, increased by 20 mg at weekly intervals to 60 mg. If no improvement occurs the dose can be gradually increased to a maximum of 120 mg each morning. In the USA 37.5 mg is given each morning initially, increased gradually at weekly intervals by 18.75 mg; the usual range is 56.25 to 75 mg daily and the maximum recommended daily dose is 112.5 mg.

Pemoline is also an ingredient of an oral preparation, also containing yohimbine hydrochloride and methyltestosterone, which is given with the intention of managing failure of sexual desire and functioning in males and females.

Pemoline has been given with magnesium hydroxide (magnesium pemoline) in an attempt to increase its absorption.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations
 Canad.: Cylert; Ger.: Senior; Tradon; S.Afr.: Dynalert; Switz.: Stimul; UK: Volial; USA: Cylert.

Multi-ingredient preparations. Ger.: Cephalo-Teknosalt; Ital.: Deadyn; S.Afr.: Lentogestic; Spain: Neurocordin; UK: Proress.

Pentetrazol (1437-v)

Pentetrazol (BAN, INN).
 Corazol; Leptazol; Pentamethazol; 1,5-Pentamethylenetetrazole; Pentazol; Pentetrazolum; Pentylentetrazol. 6,7,8,9-Tetrahydro-5H-tetrazoloazepine.
 $C_6H_{10}N_4 = 138.2$.
 CAS — 54-95-5.

Pharmacopoeias. In Aust., Cz., Hung., and It.

Pentetrazol is a central and respiratory stimulant similar to doxapram hydrochloride (see p.1550). It has been used in respiratory depression but when respiratory stimulants are indicated other agents are generally preferred. It has also been included in multi-ingredient preparations intended for the treatment of respiratory-tract disorders including cough, cardiovascular disorders including hypotension, and for the treatment of pruritus.

Administration has been by mouth and by injection.

Porphyria. Pentetrazol has been associated with acute attacks of porphyria and is considered unsafe in patients with acute porphyria.

1. Moore MR, McColl KEL. *Porphyria: drug lists*. Glasgow: Porphyria Research Unit, University of Glasgow, 1991.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations
 Spain: Cardiorapide.

Multi-ingredient preparations. Fr.: Désintex-Pentazol†; Ger.: Cardaminol†; Jasivita†; Poikiloton†; Sympatocard†; Ital.: Cardiazol-Paracodina; Spain: Cardiorapide Efed; Espectona Compositum; Fluidin Infantil†.

Phenbutrazate Hydrochloride

(1485-y)
 Phenbutrazate Hydrochloride (BANM).
 Fenbutrazate Hydrochloride (rINN); R-381. 2-(3-Methyl-2-phenylmorpholino)ethyl 2-phenylbutyrate hydrochloride.
 $C_{23}H_{29}NO_3.HCl = 403.9$.
 CAS — 4378-36-3 (phenbutrazate); 6474-85-7 (phenbutrazate hydrochloride).

Phenbutrazate hydrochloride was formerly used as an anorectic agent.

Phendimetrazine Tartrate (1486-j)

Phendimetrazine Tartrate (BANM, rINN).
 Phendimetrazine Acid Tartrate; Phendimetrazine Bitartrate. (+)-3,4-Dimethyl-2-phenylmorpholine hydrogen tartrate.
 $C_{12}H_{17}NO.C_4H_8O_6 = 341.4$.
 CAS — 634-03-7 (phendimetrazine); 7635-51-0 (phendimetrazine hydrochloride); 50-58-8 (phendimetrazine tartrate).
 Pharmacopoeias. In US.

A white odourless crystalline powder. Freely soluble in water; sparingly soluble in warm alcohol; practically insoluble in acetone, in chloroform, and in ether. A 2.5% solution in water has a pH of 3 to 4. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Dexamphetamine Sulphate, p.1547.

Pharmacokinetics

Phendimetrazine tartrate is readily absorbed from the gastro-intestinal tract and is excreted in the urine, partly unchanged and partly as metabolites, including phenmetrazine.

Uses and Administration

Phendimetrazine tartrate is a sympathomimetic agent with the actions of dexamphetamine (see p.1548). It is used as an anorectic and is administered by mouth as an adjunct to dietary measures in the short-term treatment of moderate to severe obesity. The use of adjuncts in the management of obesity is discussed on p.1544 where the use of stimulant anorectics such as phendimetrazine is questioned. The usual dose is 35 mg two or three times daily 1 hour before meals, but doses should be individualised and in some cases 17.5 mg twice daily may be adequate; the dose should not exceed 70 mg three times daily. An alternative dose is 105 mg once daily in the morning as a sustained-release preparation. Phendimetrazine hydrochloride is used similarly; it is given by mouth in doses of 15 to 40 mg daily.



1437-v

Pentetrazol (*B.P., Eur. P.*). Leptazol; Pentazol; Pentamethazol; Pentylenetetrazol; Pentetrazolum; Corazol; 1,5-Pentamethylenetetrazole. 6,7,8,9-Tetrahydro-5H-tetrazoloazepine.
 $C_6H_{10}N_4 = 138.2$.

CAS — 54-95-5.

Pharmacopoeias. In *Arg., Aust., Belg., Br., Cz., Eur., Fr., Ger., Hung., Ind., Int., It., Jug., Mex., Neth., Nord., Pol., Port., Rus., Span., Swiss, and Turk.*

Colourless, almost odourless crystals or white crystalline powder with a slightly pungent bitter taste. M.p. 57° to 60°. Soluble 1 in less than 1 of water, of alcohol, and of chloroform, and 1 in less than 4 of ether; soluble in carbon tetrachloride. A 10% solution in water has a pH of 5.5 to 7. A 4.91% solution is iso-osmotic with serum. Solutions are sterilised by autoclaving or by filtration, avoiding contact with metal. Protect from light.

An aqueous solution of pentetrazol iso-osmotic with serum (4.91%) caused 100% haemolysis of erythrocytes cultured in it for 45 minutes.— E. R. Hammarlund and K. Pedersen-Bjergaard, *J. pharm. Sci.*, 1961, 50, 24.

Pentetrazol in a concentration of 1 to 3% inhibited the growth of *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. This substantiated the statement in the *B.P.* 1958 that no bactericide needed to be added to solutions for injection.— R. J. Gilbert and A. D. Russell, *Pharm. J.*, 1963, 1, 111.

Adverse Effects. High dosage produces epileptiform convulsions, and overdosage may result in respiratory depression.

Treatment of Adverse Effects. As for Nikethamide, p.367. If pentetrazol has been ingested the stomach should be emptied by aspiration and lavage.

Precautions. Pentetrazol may provoke seizures in patients with epilepsy or other convulsive disorders.

Absorption and Fate. Pentetrazol is readily absorbed after administration by mouth and by injection. It is rapidly metabolised, chiefly in the liver. About 75% of a parenteral dose has been reported to be excreted in the urine.

Peak plasma concentrations of about 2µg per ml were obtained about 2 hours after a dose of 100 mg of pentetrazol by mouth. The drug was excreted in the urine.— W. R. Ebert *et al.*, *J. pharm. Sci.*, 1970, 59, 1409.

Plasma-pentetrazol concentrations in 3 patients, who were taking the drug regularly, ranged from 1.45 to 3.1 µg per ml when measured 1.25 to 5 hours after a 100-mg dose.— H. W. Jun *et al.*, *J. pharm. Sci.*, 1975, 64, 1843.

Uses. Pentetrazol is a respiratory stimulant with actions and uses similar to those of nikethamide (see p.367). It has been given in usual doses of 100 mg, administered subcutaneously, intramuscularly, or intravenously. Pentetrazol has been employed in the elderly to alleviate the symptoms of senility. For this purpose it has been given by mouth in a dose of 100 to 200 mg twice or thrice daily, usually in conjunction with nicotinic acid, but its value has not been substantiated in trials.

Pentetrazol has been administered intravenously as an aid to the diagnosis of epilepsy.

Preparations

Leptazol Injection (*B.P.C. 1963*). Inj. Leptazol. A sterile solution of pentetrazol 10% and sodium phosphate 0.25% in Water for Injections, adjusted to pH 7.8 with dilute hydrochloric acid or potassium hydroxide solution. The addition of a bactericide is unnecessary. Dose. 0.5 to 1 ml subcutaneously.

Proprietary Names

Cardiazol (*Knoll, Ger.; Medinsa, Spain; Knoll, Switz.*); Cardiorapide (*Rapide, Spain*); Metrazol (*Knoll, USA*).

1438-g

Phenatine. *N*-(α -Methylphenethyl)nicotinamide diphosphate; *N*-(α -Methylphenethyl)pyridine-3-carboxamide diphosphate.
 $C_{15}H_{16}N_2O_2H_3PO_4 = 436.3$.

CAS — 139-68-4 (base); 2964-23-0 (diphosphate).

Pharmacopoeias. In *Rus.*

Odourless colourless crystals or white crystalline powder with a bitter saline taste. Soluble in water and alcohol; practically insoluble in ether. A 5% solution in water has a pH of 1.8 to 2.4.

Uses. Phenatine is claimed to stimulate the central nervous system in a similar way to dexamphetamine without causing vasoconstriction. It is also claimed that it reduces blood pressure. In the USSR it has been employed similarly to dexamphetamine as a central stimulant; it has also been suggested in the treatment of hypertension.

1439-q

Picrotoxin (*B.P. 1963*). Picrotox.; Picrotoxinum; Cocculin.

 $C_{30}H_{34}O_{13} = 602.6$.

CAS — 124-87-8.

Pharmacopoeias. In *Arg., Int., It., Mex., Span., Swiss, and Turk.*

An active principle from the seeds of *Anamirta cocculina* (= *A. paniculata*) (Menispermaceae).

Odourless, colourless, flexible, shining prismatic crystals or white or nearly white microcrystalline powder, with a very bitter taste. M.p. about 199°.

Soluble 1 in 350 of water, 1 in 35 of boiling water, 1 in 16 of alcohol, and 1 in 3 of boiling alcohol; soluble in glacial acetic acid and solutions of acids and alkali hydroxides; slightly soluble in chloroform and ether. A saturated solution in water is neutral to litmus. Solutions are sterilised by autoclaving or by filtration. Protect from light.

The potency of picrotoxin solutions diminished as the pH increased above 7.— P. W. Ramwell and J. E. Shaw, *J. Pharm. Pharmac.*, 1962, 14, 321.

Adverse Effects and Treatment. As for Nikethamide, p.367. As little as 20 mg may cause severe poisoning.

Uses. Picrotoxin is a respiratory stimulant with actions and uses similar to those of nikethamide (p.367). Its duration of effect is brief.

It was formerly given in usual doses of 3 to 6 mg intravenously.

1440-d

Pipradrol Hydrochloride (*B.P.C. 1963*). α -(2-Piperidyl)benzhydrol hydrochloride; $\alpha\alpha$ -Diphenyl- α -(2-piperidyl)methanol hydrochloride.

 $C_{18}H_{21}NO.HCl = 303.8$.

CAS — 467-60-7 (pipradrol); 71-78-3 (hydrochloride).

Odourless, tasteless, small white crystals or white or almost white crystalline powder. M.p. about 290° with decomposition. Soluble 1 in 30 of water, 1 in 35 of alcohol, 1 in 1000 of chloroform, and 1 in 8 of methyl alcohol; practically insoluble in ether. A 1% solution in water has a pH of 5 to 7. Protect from light.

Adverse Effects. Pipradrol hydrochloride may cause nausea, anorexia, aggravation of anxiety, hyperexcitability, and insomnia. Epigastric discomfort, skin rash, dizziness, and hallucinations have been reported.

Precautions. Pipradrol hydrochloride is contra-indicated in endogenous depression, in agitated prepsychotic patients, chorea, paranoia, obsessional disorders, and anxiety states, and in patients for whom ECT is indicated.

Uses. Pipradrol hydrochloride is a stimulant of the central nervous system which was formerly given in usual doses of 2 to 6 mg daily in fatigue and some depressive states.

Proprietary Names

Detaril (*ISOM, Ital.*); Stimolag Fortis (*Lagap, Switz.*).

1441-n

Cropropamide. *NN*-Dimethyl-2-(*N*-crotonamido)butyramide.

 $C_{13}H_{24}N_2O_2 = 240.3$.

CAS — 633-47-6.

1442-h

Crotethamide. 2-(*N*-Ethylcrotonamido)butyramide.

 $C_{12}H_{22}N_2O_2 = 226.3$.

CAS — 6168-76-9.

1443-m

Prethcamide. G 5668. A mixture of cropropamide and crotethamide.

 $C_{12}H_{22}N_2O_2 = 226.3$.

CAS — 8015-51-8.

Prethcamide is soluble in water and ether.

Adverse Effects. Side-effects include paraesthesiae, restlessness, muscle tremors, dyspnoea, and flushing. Gastro-intestinal disturbances have also been reported.

Precautions. Prethcamide should be given with care to patients with epilepsy.

Uses. Prethcamide is a respiratory stimulant which has been given in usual doses of three or four times daily in the treatment of respiratory insufficiency in chronic bronchitis. It has also been given intramuscularly, intravenously, and by inhalation.

Proprietary Preparations

Micoren (*Geigy, UK*). Prethcamide, available in doses of 400 mg. (Also available as Micoren, *Neth., Switz.*)

Other Proprietary Names

Micorene (*Belg.*).

1444-b

Prolintane Hydrochloride. *S*-Propylphenethylpyrrolidine hydrochloride.

 $C_{15}H_{23}N.HCl = 253.8$.

CAS — 493-92-5 (prolintane); 121-31-1 (hydrochloride).

A white odourless powder with a melting point of about 133°. Soluble in water and chloroform; practically insoluble in ether.

Adverse Effects and Precautions. Prolintane hydrochloride causes nausea, and tachycardia have been reported in patients receiving prolintane. It should be given with care in patients taking monoamine oxidase inhibitors, and should not be given to patients with hyperthyroidism or epilepsy.

Uses. Prolintane hydrochloride is a stimulant of the central nervous system which has been given, in fatigue and to improve concentration, usually with vitamin supplements, in doses of 10 mg twice daily, with the second dose given not later than mid-afternoon.

Proprietary Preparations

Villescon (*Boehringer Ingelheim, UK*). Prolintane hydrochloride 5 mg in each 5 ml prolintane hydrochloride solution. Prolintane hydrochloride 1.67 mg, riboflavin 3 mg, pyridoxine hydrochloride 1.36 mg, pyridoxine hydrochloride 5 mg, and alcohol 12.2% w/v (in water) and Tablets each containing prolintane hydrochloride 10 mg, thiamine mono-nitrate 5 mg, pyridoxine hydrochloride 1.5 mg, riboflavin 3 mg, and ascorbic acid 50 mg. For use in patients with loss of appetite and mood. Dose. 10 ml of solution twice daily; children 5 to 12 years, 2.5 ml twice daily.

Other Proprietary Names

Protil (*Fr.*).

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	Return to Search Screen	Previous Record



Diagnostic aid of epilepsy →

TITLE: Facilitation of pentylene tetrazole-kindled seizures by mild thyroid hormone deficiencies.

AUTHOR: Pacheco-Rosado J; Angeles-Lopez L

AUTHOR AFFILIATION: Department of Physiology Mauricio Russek, Escuela Nacional de Ciencias Biologicas, I.P.N., Mexico, D.F.

SOURCE: Proc West Pharmacol Soc 1997;40:75-7

NLM CIT. ID: 98098613

MAIN MESH SUBJECTS: Convulsants/*TOXICITY
Kindling (Neurology)/*PHYSIOLOGY
Pentylene tetrazole/*TOXICITY
Triiodothyronine/BLOOD/*DEFICIENCY

ADDITIONAL MESH SUBJECTS: Animal
Dose-Response Relationship, Drug
Hypothyroidism/BLOOD
Male
Rats
Rats, Wistar
Support, Non-U.S. Gov't
Time Factors

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Convulsants)
54-95-5 (Pentylene tetrazole)
6893-02-3 (Triiodothyronine)



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92 Other
67 71 YearsLog off
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Previous Record



TITLE: Synthesis, anticonvulsant and analgesic activities of some 6-substituted imidazo(2,1-b)-1,3,4-thiadiazole-2-sulfonamides and their 5-bromo derivatives.

AUTHOR: Khazi IA; Mahajanshetti CS; Gadad AK; Tarnalli AD; Sultanpur CM

AUTHOR AFFILIATION: Department of Chemistry, Karnatak University, Dharwad (India).

SOURCE: Arzneimittelforschung 1996 Oct;46(10):949-52

NLM CIT. ID: 97085798

ABSTRACT: A series of 6-substituted imidazo(2,1-b)-1,3,4-thiadiazole-2-sulfonamides (V) were prepared by condensation of 2-amino-1,3,4-thiadiazole-5-sulfonamide (II) with an appropriate 2-bromo-ketone (III). Bromination of V in glacial acetic acid gave the corresponding 5-bromo derivatives (VI). Five selected compounds (15-18 and 28) were evaluated for their anticonvulsant and analgesic activities. Compounds 15-17 showed maximum protection (83%) against pentylene tetrazole induced convulsions and maximum electroshock induced seizures while the standard phenobarbital sodium and phenytoin sodium showed 100% protection, respectively. Compounds 15, 16 and 18 showed superior analgesic activity to acetylsalicylic acid in rat caudal immersion test.

Diagnostic use

MAIN MESH SUBJECTS: Analgesics/*CHEMICAL SYNTHESIS/PHARMACOLOGY/TOXICITY
Anticonvulsants/*CHEMICAL SYNTHESIS/PHARMACOLOGY/TOXICITY
Sulfonamides/*CHEMICAL SYNTHESIS/PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Animal
Convulsants
Dose-Response Relationship, Drug
Electroshock
Female
Indicators and Reagents
Male
Mice
Pain Measurement/DRUG EFFECTS
Pentylentetrazole/ANTAGONISTS & INHIB
Rats
Rats, Wistar
Spectrophotometry, Infrared

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Analgesics)
0 (Anticonvulsants)
0 (Convulsants)
0 (Indicators and Reagents)
0 (Sulfonamides)
54-95-5 (Pentylentetrazole)



Order Documents	52, 67, 71 Other Years	Log off IGM		
Next Record	Details of Search	Return to Results	Return to Search Screen	Previous Record



TITLE: Synthesis and biological activities of some 3,6-disubstituted thiazolo[3,2-b][1,2,4]triazoles.

AUTHOR: Erol DD; Calis U; Demirdamar R; Yulug N; Ertan M

AUTHOR AFFILIATION: Hacettepe University, Faculty of Pharmacy, Pharmaceutical Chemistry Department, Ankara, Turkey.

SOURCE: J Pharm Sci 1995 Apr;84(4):462-5

NLM CIT. ID: 95356086

ABSTRACT: Some new 2,3-dihydro-3-hydroxy-6-phenyl-3-(4-substituted-phenylthiazolo[3,2-b][1,2,4]triazole derivatives were synthesized as antifungal agents. After their structures were confirmed by microanalysis and IR and NMR spectral analysis, their antifungal activities against *Candida albicans*, *Candida parapsilosis*, *Candida stellatoidea*, and *Candida pseudotropicalis* were investigated. Contrary to our expectations, all proved to have poor antifungal activities. Because 2,4-dihydro-3H-1,2,4-triazol-3-ones are a new class of anticonvulsant agents, a series of thiazolo[3,2-b][1,2,4]triazoles was evaluated for anticonvulsant activity and observed as potential anticonvulsant candidates. All compounds examined exhibited activity against both maximal electroshock and pentylene tetrazole-induced seizures in mice.

MAIN MESH SUBJECTS: Anticonvulsants/*CHEMICAL SYNTHESIS/PHARMACOLOGY
Antifungal Agents/*CHEMICAL SYNTHESIS/PHARMACOLOGY
Thiazoles/*CHEMICAL SYNTHESIS/PHARMACOLOGY
Triazoles/*CHEMICAL SYNTHESIS/PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Animal
Candida/DRUG EFFECTS
Convulsions/CHEMICALLY INDUCED/PREVENTION & CONTROL
Electroshock
Male
Mice
Microbial Sensitivity Tests
Pentylentetrazole
Spectrophotometry, Infrared

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Anticonvulsants)
0 (Antifungal Agents)
0 (Thiazoles)
0 (Triazoles)
54-95-5 (Pentylentetrazole)

A. INGREDIENT NAME:

PIRACETAM

B. Chemical Name:

1-Acetamido-2-Pyrrolidinone, Euvicor, Gabacet, Genogris, 2-Ketopyrrolidine-1-Ylacetamide, Nootron, Nootropil, Nootropyl, Normabrain, 2-Oxo-Pyrrolidine-Acetamide, 2-Oxo-Pyrrolidin-1-Ylacetamide, Piracetam, Pirazetam, Pirroxil, Pyracetam, Pyramem, 2-Pyrrolidininnoneacetamide, 2-Pyrrolidoneacetamide, UCB 6215

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.27%

E. Information about how the ingredient is supplied:

White or almost white crystal powder

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Mondadori, C. Nootropics: Preclinical Results in the Light of Clinical Effects; Comparison with Tacrine. *Critical Reviews™ in Neurobiology*, 1996; 10: 357-370.

Tallal, U., Chase, C., and Russell, G. Calculation of the Efficacy of Piracetam in Treating Information Processing, Reading, and Writing Disorders in Dyslexic Children. *International Journal of Psychophysiology*, 1986; 4: 41-52.

Mindus, P., Cronholm, B., and Levander, S. E. Piracetam-induced improvement of mental performance: a controlled study on normally aging individuals. *Acta Psychiat. Scand.*, 1976; 54(2):150-160.

Simeon, J., Waters, B., and Resnick, M. Effects of Piracetam in children with learning disorders. *Psychopharmacol.Bull.*, 1980; 16: 65-66.

Stegink, K. J., The clinical use of Piracetem, a new nootropic drug: the treatment of senile involution. *Arzneim-Forsch*, 1972; 22: 975-977.

Wilsher, C., Atkins, G., and Mansfield, P. Piracetam as an aid to learning in dyslexia, preliminary report. *Psychopharmacology*. 1979; 65: 107-109.

Wilsher, C., Atkins, G., and Mansfield, P. Effects of Piracetam on dyslexic' reading ability. *J. Learn. Disability*. 1985; 18: 19-25.

Mondadori, C., Petschke, F., and Häusler, A. The Effects of Nootropics on Memory: new Aspects for Basic Research. *Pharmacopsychiatry*. 1989; 22: 102-106.

YaI, V., Derzhiruk, L. P., and Mogilevskii, A. Piracetam-induced changes in the functional activity of neurons as a possible mechanism for the effects of nootropic agents. *Neurosci Behav. Physiol.*, 1996; 26(6): 507-515.

Pepeu, G. and Spignoli, G. Nootropic drugs and brain cholinergic mechanisms. *Prog. Neuropsychopharmacol Biol. Psychiatry*. 1989; 13Suppl: S77-78.

Pilch, H. and Muller, W. E. Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice. *Psychopharmacology*. 1988; 94(1): 74-78.

De Deyn, P. P., Reuck, J. D., and Deberdt, W. Treatment of acute ischemic stroke with Piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group. *Stroke*. 1997; 28(12): 2347-2352.

Di Ianni, M., Wilsher, C. R., and Blank, M. S. The effects of Piracetam in children with dyslexia. *J. Clin Psychopharmacol*. 1985; 5(5): 272-278.

Wilsher, C. R., Bennett, D., and Chase, C. H. Piracetam and dyslexia: effects on reading tests. *J. Clin Psychopharmacol*. 1987; 7(4): 230-237.

Reisberg, B., Ferris, S. H., and Gershon, S. An overview of pharmacologic treatment of cognitive decline in the aged. *Am J. Psychiatry*. 1981; 138(5): 593-600.

Bartus, R. T., Dean, R. L., and Sherman, K. A. Profound effects of combining choline and Piracetam on memory enhancement and cholinergic function in aged rats. *Neurobiol Aging*. 1981; 2(2): 105-111.

- Buresova, O. and Bures, J. Piracetam-induced facilitation of interhemispheric transfer of visual information in rats. *Psychopharmacologia*. 1976; 46(1): 93-102.
- Dimond, S. J., Scammell, R. E., and Pryce, I. G. Some effects of Piracetam (UCB 6215, Nootropyl) on chronic schizophrenia. *Psychopharmacology*. 1979; 64(3): 341-348.
- Dimond, S. J. and Brouwers, E. M. Increase in the power of human memory in normal man through the use of drugs. *Psychopharmacology*. 1976; 49(3): 307-309.
- Sara, S. J., David-Remacle, M., and Weyers, M. Piracetam facilitates retrieval but does not impair extinction of bar-pressing in rats. *Psychopharmacology*. 1979; 61(1): 71-75.
- Brandao, F., Paula-Barbosa, M. M., and Cadete-Leite, A. Piracetam impedes neuronal loss withdrawal after chronic alcohol intake. *Alcohol*. 1995; 12(3): 279-288.
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- Song, C., Earley, B., and Leonard, B. E. Effect of chronic treatment with piracetam and tacrine on some changes caused by thymectomy in the rat brain. *Pharmacol Biochem. Behav*. 1997; 56(4): 697-704.

H. Information about dosage forms used:

Patients received either 3.3 g of Piracetam daily or matching placebo syrup. Each dose of test medication was 5 ml. administered before breakfast and again before the evening meal. A 5 ml dose of active medication contained 1.65 g of Piracetam. No dosage adjustments were allowed. The patient's parents were contacted to review dosage instructions and to determine whether any adverse effects had been observed.

I. Information about strength:

1.65 g -3.3 g

J. Information about route of administration:

Orally

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

See File

CERTIFICATE OF ANALYSIS

Coa No: 7777

30-2213
54051

PIRACETAM

Batch No: 96120006

Manufacturing Date: Dec 3, 1996

Testing Result

Appearance	E	White or almost white crystal powder	E
Identification		Positive	
Melting Point		152.5-153.5°C	
Clarity of Solution		Clear	
Heavy Metals		< 20ppm	
Residue on Ignition		0.02%	
Loss on Drying		0.12%	
Assay		99.27%	D ✓

Conclusion: Conforms to China Provincial Standard

Remarks: The above testing result is per manufacturer's information.

10/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: PIRACETAM

MANUFACTURE LOT NO.: 97060036

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

WHITE TO OFF WHITE CRYSTALS FROM ISOPROPANOL OR WHITE TO OFF WHITE CRYSTALLINE POWDER.

2) SOLUBILITY.:

VERY SOLUBLE IN WATER; SOLUBLE IN ALCOHOL, ESPECIALLY IN ISOPROPANOL.

3) MELTING POINT.:

MELTS AT ABOUT 151.5-152.5 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

----- IDENTIFICATION -----

PRODUCT #: P5295 NAME: PIRACETAM

CAS #: 7491-74-9

MF: C6H10N2O2

SYNONYMS

B 1-ACETAMIDO-2-PYRROLIDINONE * EUVIFOR * GABACET * GENOGRIS * 2-KETOPYRROLIDINE-1-YLACETAMIDE * NOOTRON * NOOTROPIL * NOOTROPYL

* NORMABRAIN * 2-OXO-PYRROLIDINE ACETAMIDE * 2-OXO-PYRROLIDIN-1-

YLACETAMIDE * PIRACETAM * PIRAZETAM * PIRROXIL * PYRACETAM * PYRAMEM *

2-PYRROLIDINONEACETAMIDE * 2-PYRROLIDONEACETAMIDE * UCB 6215 *

----- TOXICITY HAZARDS -----

RTECS NO: UX9660500

1-PYRROLIDINEACETAMIDE, 2-OXO-

TOXICITY DATA

IPR-MUS LD50:>10 GM/KG

PCJOAU 23,795,89

SCU-MUS LD50:12 GM/KG

KHFZAN 11(8),132,77

IVN-MUS LD50:10 GM/KG

KHFZAN 11(8),132,77

IVN-CAT LD50:10 GM/KG

RPTOAN 47,205,84

UNR-MAM LD50:>10 GM/KG

RPTOAN 44,22,81

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.

MAY CAUSE IRRITATION.

EXPOSURE CAN CAUSE:

CNS STIMULATION

THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,

CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER
FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING
THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

----- PHYSICAL DATA -----

APPEARANCE AND ODOR

SOLID

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING
TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

----- REACTIVITY DATA -----

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

THERMAL DECOMPOSITION MAY PRODUCE CARBON MONOXIDE, CARBON
DIOXIDE,

AND NITROGEN OXIDES.

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR PROTECTIVE EQUIPMENT.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS
COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN
IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR,
CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.

CAUTION:

AVOID CONTACT AND INHALATION.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT
PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL
NOT BE

HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM
CONTACT WITH THE

ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR
ADDITIONAL

TERMS AND CONDITIONS OF SALE

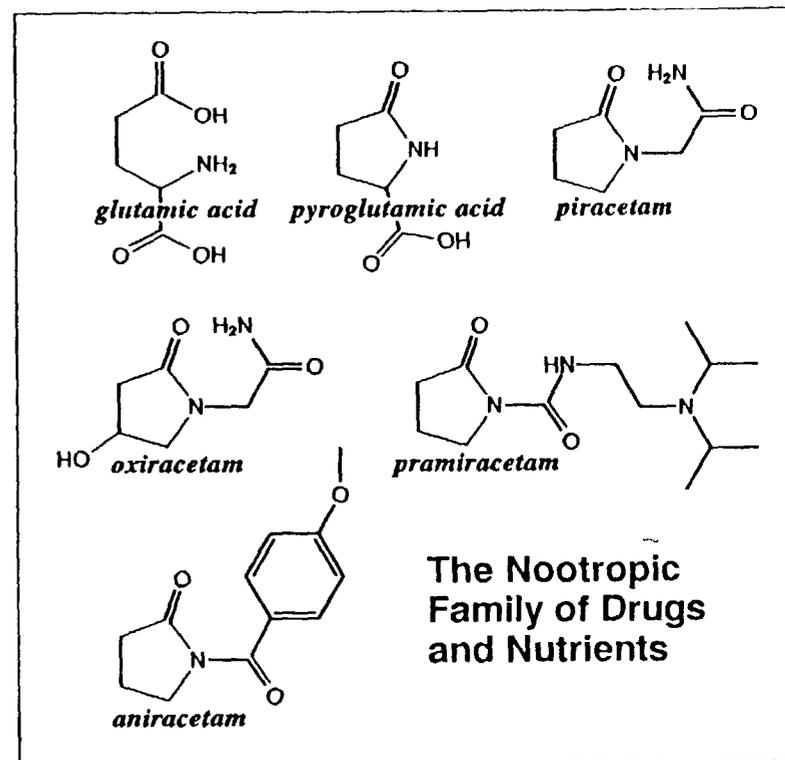
Acetyl-L-Carnitine Update

- patients with Alzheimer's disease. *Arch Neurol* (United States) 49(11): 1137-41, November 1992.
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- Tempesta E, Casella L, Pirrongelli C, Janiri L, Calvani M, Ancona L. L-acetylcarnitine in depressed elderly subjects. A cross-over study vs. placebo. *Drugs Under Experimental Clinical Research* 13(7): 417-23, 1987.
- Tempesta E, Troncon R, Janiri L, Colusso L, Riscica P, Saraceni G, Gesmundo E, Calvani M, Benedetti N and Pola P. Role of acetyl-L-carnitine in the treatment of cognitive deficit in chronic alcoholism. *Int J Clin Pharmacol Res* 10(1-2): 101-7, 1990.
- Vecchi GP, Chiari G, Cipolli C, Cortelloni C, De Vreese L and Neri M. Acetyl-L-carnitine treatment of mental impairment in the elderly: Evidence from a multi-centre study. *Arch Gerontol Geriatr* (Netherlands) 12(Suppl. 2): 159-68, 1991.
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Piracetam Update

This unique substance is probably the most popular smart drug for normal, healthy people. We've received many positive comments about piracetam in the smart-drug fan mail. Some of the most interesting of these piracetam stories (and a couple of mild caveats) are included in the Smart Drug Users chapter of this book.

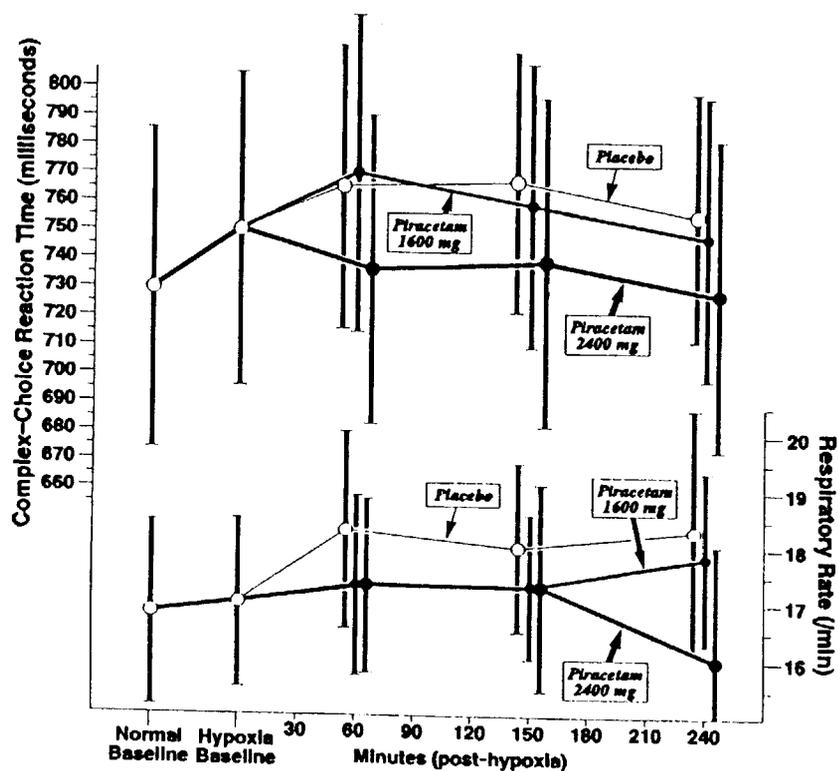
In the three years since *Smart Drugs & Nutrients* was researched and published, over 150 papers have appeared in the world's scientific literature which describe human studies of piracetam. Piracetam is, in fact, a broadly effective enhancer of many



aspects of human performance. The studies presented in this chapter clearly indicate the breadth of piracetam's clinical application. These studies amply illustrate piracetam's benefits for normal, healthy adults, normally aging elderly adults, and people suffering from overt cognitive disorders like senility and Alzheimer's disease.

Piracetam and Weekend Athletes

The ability of piracetam to reduce metabolic stress under low-oxygen conditions was investigated by Schaffler and Klausnitzer in 1988. The researchers induced hypoxia (low oxygen levels) in healthy young men (early 20s to early 30s) by reducing the oxygen content of the laboratory air that they breathed by about half (10.5% instead of 20% oxygen). This resembled "the



oxygen supply at an altitude of about 5300 meters" (17,400 feet). The degree of cognitive impairment due to the low oxygen levels was investigated, and the ability of piracetam (in single doses of 1600 mg or 2400 mg) to prevent this impairment was measured (see opposite figure). Half of the group was given a placebo.

Various tests of reaction time were performed, and in all cases, the piracetam-treated group performed better. Best results were obtained at the higher dose (see opposite figure, upper data points). The increased breathing rate that is usually seen under low oxygen conditions was significantly reduced by a single dose of piracetam (lower data points).

The significance of these results is that normal, healthy people who travel from lower altitudes to higher altitudes for physical activities that require stamina, coordination, concentration, and muscular output are likely to greatly benefit from piracetam. Skiers, take note! Smart-drugged skiers on vacation are probably less likely to injure themselves or someone else, and may be more likely to enjoy their vacation. Piracetam will probably not only make high-altitude sports safer, but is likely to improve performance as well.

Other high-altitude activities likely to be safer with piracetam include mountain bicycling, backpacking, rock climbing, hang gliding, and bungee jumping. And piracetam is likely to improve performance of the sport.

All of these activities involve some risk. Statistically speaking, compared to taking piracetam these sports are absolutely throw-caution-to-the-wind dare-devilish. Recently a bungee jumping trainer forgot to attach his own bungee to the mooring and jumped to his death. Would he have forgotten if he had taken piracetam? The research points to a decrease in the odds of making just this kind of error.

Piracetam for Cigarette Smokers

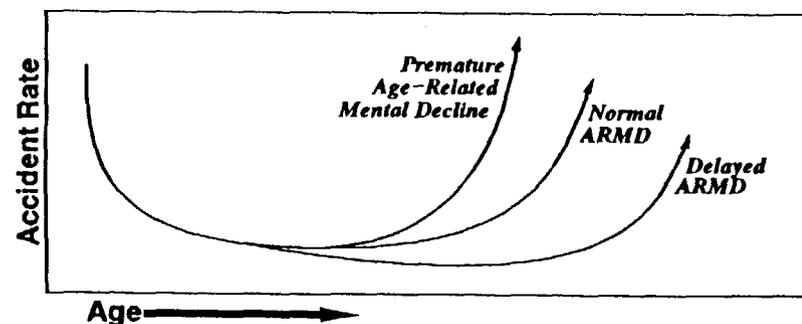
Of even more potential significance is the possibility that other disease conditions resulting from low oxygen levels in the blood

may also be alleviated by piracetam. For example, a two-pack-per-day cigarette smoker at sea level has the oxygen levels of a person at 10,000 feet. Also, many clinical conditions like atherosclerosis (occluded arteries) and many pulmonary diseases (especially emphysema) cause reduced blood and brain oxygenation. Piracetam may greatly relieve the adverse effects of oxygen shortage in these conditions.

Driving Skills in Elderly Motorists

Statistically, middle-aged drivers have the lowest accident rates. The rate of age-related accidents can be represented by a graph with a U-shaped curve (see illustration below) with the highest values in the late teens (learning to drive) and early twenties (learning traffic judgment), the lowest values in middle age (maximum skill, experience and judgment), and higher levels again at advanced ages (impaired vision, hearing, reaction time and/or judgment).

One study of elderly drivers (average age 62.7 years) showed slightly diminished performance in "driving tasks" as compared to middle-aged drivers (average age 40.6 years). This decrement was characterized by significantly diminished performance in sign observance, lane discipline, hesitant driving, technical handling, and "junction alertness" (leading to "twice as many risk situations which required driving-instructor intervention"). No differences in speed or safe-distance behavior were noted between the groups.



Could piracetam alter the shape of the accident curve and alleviate these decrements in older drivers by delaying the onset and slowing the progression of age-related changes?

A recent study conducted at the University of Cologne in Germany was performed to answer this question [Schmidt, 1991]. The researchers examined the driving skills of 101 elderly drivers with "reduced reaction capacity." In a randomized, double-blind, placebo-controlled study, in real-traffic conditions, those patients treated with piracetam exhibited significantly improved performance. Over the six-week test period, piracetam-treated drivers' "sign-observance" scores improved from 77.08% pre-treatment to 84.16% post-treatment.

This study indicates clearly that some of the age-related reductions in driving performance can be improved by piracetam. In only six weeks, the piracetam-treated drivers improved 7.08% on the sign-observance test. Of particular interest is the authors' note that "all of the drivers who scored less than 80% improved when treated with piracetam." This indicates that piracetam is most helpful in those people with the greatest driving impairment.

The number and percentage of elderly drivers in developed countries is increasing, as birth rates drop and life-expectancy increases. The extent to which widespread piracetam use by elderly drivers might diminish the rising costs of accidents caused by elderly drivers is not yet known, but it is certainly worth investigating.

Changes in Attitudes

Only three years ago, smart-drug critics were focusing on the lack of human testing in normal, healthy individuals. They said, "just because piracetam corrects cognitive deficits caused by disease doesn't mean it will correct cognitive deficits caused by aging, or that it will enhance cognitive abilities in healthy

people." However, increasing data now confirm that piracetam does, in fact, improve cognitive performance in normal people.

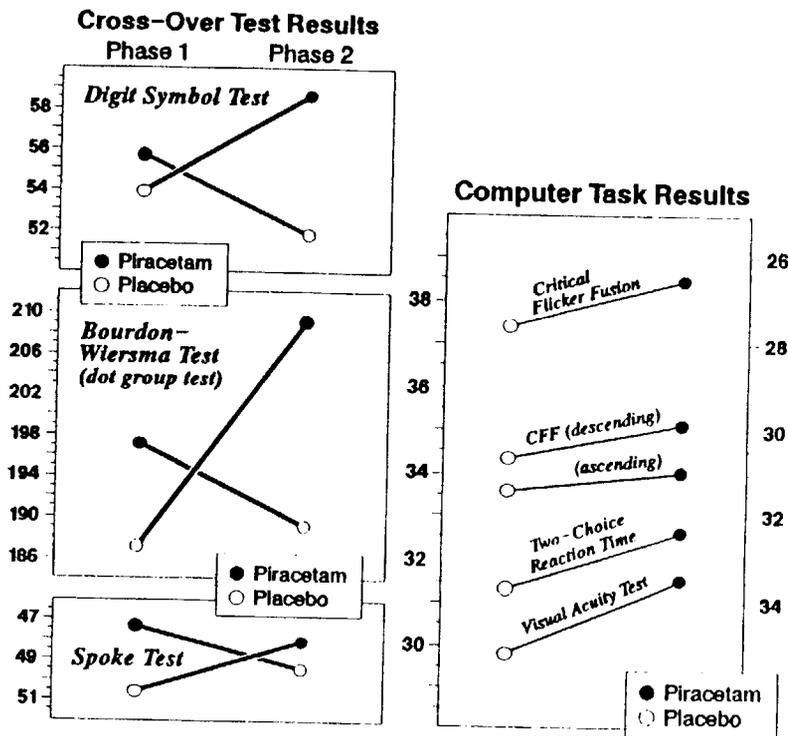
One of the first pioneering studies to investigate this possibility was conducted 17 years ago in Sweden long before the complaints of smart-drug critics [Mindus, 1976]. These researchers selected late-middle-aged test subjects (50 years and older) of above average intelligence (their IQs averaged above 120) and who were otherwise healthy (none had any clinical signs of rapidly deteriorating mental abilities).

All 18 test subjects reported "slight but seemingly permanent reduction for some years in their capacity to retain or recall information" (AAMI). They all had developed compensatory strategies and behaviors to continue in their highly demanding jobs, such as "taking notes" and "working slower." All in all, these subjects were a good cross-section of the more productive and accomplished senior members of the work force.

The researchers employed a double-blind, cross-over study. Half of the test subjects were given placebo for the first four weeks (phase 1), and piracetam (4.8 grams daily) for the second four weeks (phase 2). The other half were given piracetam first, and placebo second.

The subjects then took a number of performance tests, including computer-based tests. In all phases of testing, piracetam scores were higher. In the cross-over phase, all subjects who switched from placebo to piracetam improved in score, and all subjects who switched from piracetam to placebo lowered in score (see the graphs below).

The computer-test results were converted into like-magnitude units to illustrate the similarity of the performance increases from piracetam. It can be seen that all five computerized tests showed identical magnitude gains. This is certainly a striking observation, given the selective effects of some other smart drugs. Piracetam and other nootropic drugs seem to produce positive effects in many aspects of mental function.



Claims that smart drugs have not proven effective on normal, healthy people are clearly wrong. Such allegations are not based on science, but rather on the personal prejudices of the accusers and their unfamiliarity with the scientific literature.

Cognitive Enhancement in Senility

Although some critics may criticize the use of smart drugs to treat AAMI, many acknowledge that smart drugs *are* effective in the treatment of overt senile cognitive impairment. In a recent study of 84 geriatric patients with non-vascular senile cognitive deterioration, piracetam was found to be better than a placebo at enhancing several cognitive abilities, including attention, memory, and behavior [Fioravanti, 1991]. Dosages of 6 grams per day appeared to be more effective than 3 grams

per day. However, once optimum benefits had been obtained on the 6-gram-per-day dose, the 3-gram-per-day dose was adequate to maintain the cognitive gains induced by the higher dose.

Cognitive Performance in Epileptics

Anti-epileptic medicines often exhibit cognitive side effects in the inverted-U dose-response manner. For example, at low doses, many anti-epileptic drugs improve cognition scores. However, at the high doses often necessary to control epileptic seizures, anti-epileptic drugs can cause profound cognitive impairment.

In a new study of the cognitive properties of piracetam in epileptic patients, piracetam was found to significantly improve cognitive test results without interfering with the efficacy of anti-epileptic medications. Patients taking one anti-seizure drug (carbamazepine) appeared to have even greater seizure protection when the carbamazepine was combined with piracetam [Chaudhry, 1992].

New Research Trends

Recent research into the mechanisms of nootropic drugs (drugs in the same class as piracetam) is shedding light on the crucial question, "How does piracetam work?" New findings point to a number of modes of action, including 1) stimulation of glucose metabolism, 2) increased ATP turnover, 3) increased 'internal messenger' (cyclic AMP, or cAMP) levels, 4) enhanced phospholipid levels, 5) increased protein biosynthesis, and 6) increased cholinergic and dopaminergic stimulation. Nootropics also seem to produce resistance to several neurotoxic substances, and stimulate learning through influences on the hippocampus and cortex. Oxygen utilization by the brain appears to be significantly enhanced. [Schaffler, *et al.*, 1988].

The Recognition Piracetam Deserves

It is long past time to recognize and acknowledge that piracetam does indeed enhance cognition in both normal healthy people *and* the cognitively impaired. In 1990, piracetam sales from one brand alone (Nootropil, UCB) topped *one billion dollars* worldwide. According to UCB's annual report, Nootropil sales are still increasing, years after their patent on piracetam has expired, and numerous competitive generic piracetam products have entered the market. After decades of completely safe use, and millions of prescription and over-the-counter sales in many countries, we believe that it's time for the United States to join the rest of the world in approving piracetam for its citizens. Piracetam's absence of any known toxicity makes it an ideal candidate for over-the-counter status.

Precautions

Piracetam may increase the effects of certain drugs, such as amphetamines, psychotropics, and Hydergine, as previously stated. Adverse effects are extremely rare, but include insomnia, psychomotor agitation, nausea, gastrointestinal distress, and headaches. Piracetam has no known toxicity or contraindications.

Dosage

Piracetam is supplied in 400 mg or 800 mg capsules or tablets. The usual dose is 2400 to 4800 mg per day in three divided doses. Some literature recommends a high "attack" dose be taken for the first two days. We have noticed that often when people first take piracetam they do not notice any effect at all until they take a high dose (approximately 4000 to 8000 mg). Thereafter, they may notice that a lower dosage is sufficient. Piracetam takes effect within 30 to 60 minutes.

Piracetam Update

☞ Note that piracetam seems to synergize with other smart drugs. If piracetam is combined with other smart drugs, the dosage of one or more drugs/nutrients may need to be reduced.

Sources

Piracetam is not available in the U.S. but can be easily ordered from most overseas mail-order pharmacies. An up-to-date listing of such overseas sources is maintained by CERi (see the tearout card at the front of this book).

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Vitamin Update

When *Smart Drugs & Nutrients* was written in 1990, vitamins were still considered "fringe science" by many in the medical profession. Nevertheless, we reviewed in that book some of the scientific evidence on the cognitive-performance-enhancing benefits of vitamins.

Since the publication of *Smart Drugs & Nutrients*, there seems to have been a paradigm shift away from the bad old days of physicians warning against vitamins, to a new consensus in the scientific and medical community that vitamins are potent disease fighters and potential aging-retardants.

On April 6, 1992, *Time* magazine published a cover story on vitamins, proclaiming that, "New evidence shows they may help fight cancer, heart disease, and the ravages of aging." A mere ten years ago, such a story would have generated a storm of protest from medical authorities. Today, the ever-mounting evidence for the abilities of nutrients to prevent and treat disease is so overwhelming that only a few die-hard anti-vitamin medical "authorities" remain vocal critics. Vitamins are now mainstream.

As Barbara Walters commented on ABC's *Nightline*, "There was a time when doctors said, 'Eat a balanced diet and you don't have to take vitamins.' Now we are learning that this vitamin or that vitamin might help prevent cancer." At the 1992 *American Aging Association* Conference in San Francisco, one researcher volunteered that nearly everyone in the field of gerontology (the study of aging) is now taking megadoses of vitamins. Ten years ago, only a few were.

Approximately half of all Americans take vitamin supplements and about half of those take daily supplements. Americans spend \$3.3 billion on vitamins and nutrients every year — and that figure is growing.

Nootropics: Preclinical Results in the Light of Clinical Effects; Comparison with Tacrine

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ABSTRACT: This review is meant to serve several purposes. First, it surveys the preclinical and clinical profiles of piracetam-like nootropics. Second, the conditions under which the nootropics are active in preclinical studies are identified and analyzed with a view to finding a common denominator that could explain the observed effects. Third, the clinical profile is examined, on the one hand to assess whether these drugs are in fact active in humans, and on the other to determine how the clinical effects of the nootropics compare with those of tacrine. Lastly, the clinical data are then further scrutinized to assess whether they fulfill the expectations based on the preclinical findings.

KEY WORDS: Nootropics, piracetam, oxiracetam, pramiracetam, aniracetam, tacrine, preclinical, clinical, responders, nonresponders.

INTRODUCTION

The discovery of piracetam¹ shook faith in Paracelsus' famous axiom, "dosis facit venenum." This memory improving substance not only was devoid of other biological activity but also had no toxic effects whatever at doses up to grams per kilogram of body weight. Even today, nearly 30 years after the discovery, the "nootropic" class of substances² newly created to accommodate piracetam still splits pharmacologists into two camps. For some, the absence of toxicity indicates a lack of any pharmacological action, while others see it as pointing to a new therapeutic approach. Depending on the observer's standpoint, either the nonresponders in clinical trials testify to the inefficacy of these agents, or the responders bear out their activity. This controversy has severely hindered genuine scientific progress and has prevented full advantage from being taken of the therapeutic potential of the nootropics.

Piracetam is long since not the sole representative of this class. In the meantime a great many structurally related active compounds have been synthesized, confirming the need to assign the nootropics to a category of their own. The term *nootropic* derives from the Greek words *noos*,

mind, and *tropos*, toward, and thus reflects not a class of chemical structures, but the supposed effect of these compounds on cognitive processes. It is consequently inevitable that a certain tendency exists to attach this label to all memory-enhancing substances (for a comprehensive review, see references 3,4).

The present review is devoted entirely to the piracetam-like preparations and focused on their direct nootropic effects, i.e., the spectrum of effects on the memory of intact animals, rather than on their mechanism of action. The latter aspect was the subject of recent reviews.^{4,5} Since it is impossible to assess the activity of a substance without recourse to reference compounds, both the preclinical and the clinical results are discussed on that basis. Tacrine, the only compound registered for the treatment of Alzheimer's disease, is taken as the sole reference drug for comparisons of the clinical results.

II. PRECLINICAL EFFECTS OF THE NOOTROPICS

Although the first observed effect of piracetam on the central nervous system (CNS) was inhibi-

tion of central nystagmus in the rabbit.¹ further findings made during the past 25 years showed that its main action consists in the improvement of cognitive functions. The earliest studies were concerned with pharmacological modulation of the amnesiogenic effects of a cerebral electroshock. When Giurgea and Mouravieff Lesuisse⁶ demonstrated that piracetam reduced the disrupting influence of an electroshock on the orientation of rats in a water maze, this effect was taken as an indication that piracetam improved memory consolidation. Over the years, this anti-amnesic action of the piracetam-like preparations has often been confirmed. Studies with aniracetam,⁷ oxiracetam,⁸ pramiracetam, and a series of analogues⁹ all showed a distinct protective action against the effect of electroshock on memory.

This rather indirect indication of a nootropic action was supplemented and reinforced by findings showing a direct memory-enhancing effect. A great many results emerged from experiments in avoidance learning. For example, aniracetam and piracetam^{10,11} and oxiracetam¹² were found to exert direct effects on the acquisition and retention performance of rats and mice in both passive and active-avoidance paradigms. Of particular value were the results of investigations in which the preparations were administered immediately after the learning trial ('post-trial'). In such conditions, the animal experiences the learning situation without being under the influence of the drug and is likewise uninfluenced during the retention test. Any demonstrable effect can then be ascribed to a direct action of the substance on memory processes that outlast the learning situation for some time. Several experiments showed that nootropics can improve the memory under such conditions.^{13,14}

The learning situations in which piracetam-like nootropics were active were not limited to experiments involving avoidance behavior. Pramiracetam had positive effects in a place navigation task¹⁵ and was also found to improve the acquisition rate in a 16-arm radial maze,¹⁶ whereby the effect related exclusively to reference memory, not working memory. A slight, but significant, effect of pramiracetam was also demonstrable in a delayed alternation trial.¹⁷ Aniracetam likewise displayed positive effects in a radial maze¹⁸ and a matching-to-sample test.¹⁹ Moreover, it was found

that piracetam and pramiracetam improved performance in an object recognition test.²⁰ Aniracetam²¹ and oxiracetam²² were observed to have positive effects in a social-recognition test in rats.

In sum, from the data so far available it can be concluded that the nootropics exert a distinct memory-enhancing effect in various learning situations and in different animal species. In most experiments the acquisition or storage of the information occurred under the influence of the drug and retention was assessed after an interval of at least one day. Effects on short-term retention have been described (e.g., in a delayed-alternation or delayed matching-to-sample task, and social recognition after short intervals), but these observations have not yet been confirmed.

A. Which Memory Processes Are Facilitated by Nootropics?

The many experimental situations in which nootropics have been asserted to exert a memory-enhancing action raise the question whether there is a common denominator underlying all these effects: such as a similar target process, or whether even the whole spectrum of activity of the nootropics is the same. The available evidence would suggest that their activity spectra are not identical, but at least very similar, inasmuch as all these preparations improve passive avoidance^{23,24} and active avoidance,^{12,25} and all of them improve retention performance, even if administered post-trial.¹³ The results of studies with post-trial administration reveal a high degree of concordance: it has been demonstrated that all four prototype nootropics—oxiracetam, piracetam, pramiracetam, and aniracetam—can enhance memory even if administered up to eight hours after the learning trial. After an interval of 16 hours, an effect was no longer evident.^{13,14} It can be inferred that under these conditions all these drugs affect a process that outlasts the learning situation by more than 8, but less than 16, hours (a hypothesis relative to the process affected is advanced in reference 14). The improvement in retention performance in all these experiments was assessed after 24 or 72 hours, i.e., at a time when the memory content is generally supposed to be

present in a long-term form. It was further shown that the retention performance of mice exposed to a learning situation after receiving a single dose of oxiracetam was distinctly better than that of controls even after one, two, or four months.²⁶ This finding lent additional support not only to the assumption that the substances ultimately improve long-term memory (LTM) storage, but also to the supposition that after intervals of 1 to 120 days memory is based on the same substrate.

Also in accord with the hypothesis that the nootropics improve LTM storage are the responses evoked by pramiracetam¹⁶ and aniracetam¹⁸ in the radial maze, in which solely effects on reference memory were observed. Thus, the only effects remaining to be explained are those noted in the delayed matching-to-sample test¹⁹ and the improvements seen in the social-recognition test after a two-hour interval.²¹ If these effects hold good for all nootropics, they can be taken as an indication that the facilitation of LTM is just one aspect of a whole range of activity; if not, they could indicate differences in the activity spectra of the various nootropics. Many indications of differences have been observed. Comparative studies of pramiracetam and etiracetam, for example, showed that only etiracetam had effects on memory retrieval.²⁷ Moreover, a long list of experiments indicate quantitative and qualitative differences in the biochemical activity spectrum of piracetam-like nootropics^{4,28-30} so that there is hardly cause to expect such drugs to display an identical spectrum of activity.

Thus, the most obvious common feature of the nootropics is their capacity to facilitate LTM storage. This conclusion is consistent with the majority of the available preclinical results. Despite the high degree of similarity in the observed effects, some experimental findings do appear to indicate differences in the activity spectra.

B. Effects of Nootropics Compared with Those of Other Memory Enhancers

Comparative studies have revealed that there are no differences among the LTM effects of the four prototype nootropics—oxiracetam, piracetam, aniracetam, and pramiracetam—the cholinomimetics—tacrine, physostigmine, and arecoline—

the ACE inhibitor captopril, the calcium antagonist nimodipine, and the gamma-aminobutyric acid B (GABAB)-receptor antagonist CGP 36742 in a passive-avoidance paradigm (Figure 1). It was subsequently observed that all these LTM effects were equally steroid sensitive: i.e., experimentally elevated aldosterone or corticosterone levels suppressed the effects of all these memory enhancers to the same extent.^{23,31} The pharmacodynamics of oxiracetam, arecoline, CGP 36742, and captopril were similar: there was an 8-hour drug-sensitive window after the learning trial (Figure 2). Note that the memory-enhancing effects induced by captopril, CGP 36742, and the muscarinic cholinergic agonist arecoline followed almost exactly the same pattern as that of oxiracetam, in that they were not immediately detectable, i.e., not in evidence as soon as the animals showed signs of retention. At least a further 16-20 hours elapsed before it emerged (Figure 3). This surprising concordance in the findings strongly suggests that all four of these drugs affect the same process.

By analogy with the results obtained with oxiracetam, it seems reasonable to assume that the process in question is LTM storage. This conclusion is proposed purely as a possible common denominator and must not be construed as an exhaustive description of the activity spectrum. The totality of the cholinergic effects induced by physostigmine activates the brain quite differently from blockade of the angiotensin-converting enzyme or the effects of piracetam. It is consequently logical that, despite the common effects, differences in the activity spectra are to be expected. Such differences have been observed in experimental studies: only captopril facilitated memory retrieval after a 2-month retention interval; piracetam did not.³² Piracetam and pramiracetam improved performance in an object recognition test,²⁰ whereas physostigmine had no such effect.³³ In contrast to pramiracetam,¹⁶ and aniracetam,¹⁸ physostigmine had no memory-enhancing effect in radial-maze tests.³³ It must, however, be conceded that these results are not derived from comparative studies.

In summary, all memory-enhancing compounds display similarities in their activities and in the intensities and dynamics of their effects in LTM experiments. The effects are steroid sensitive and become detectable only after a lapse of

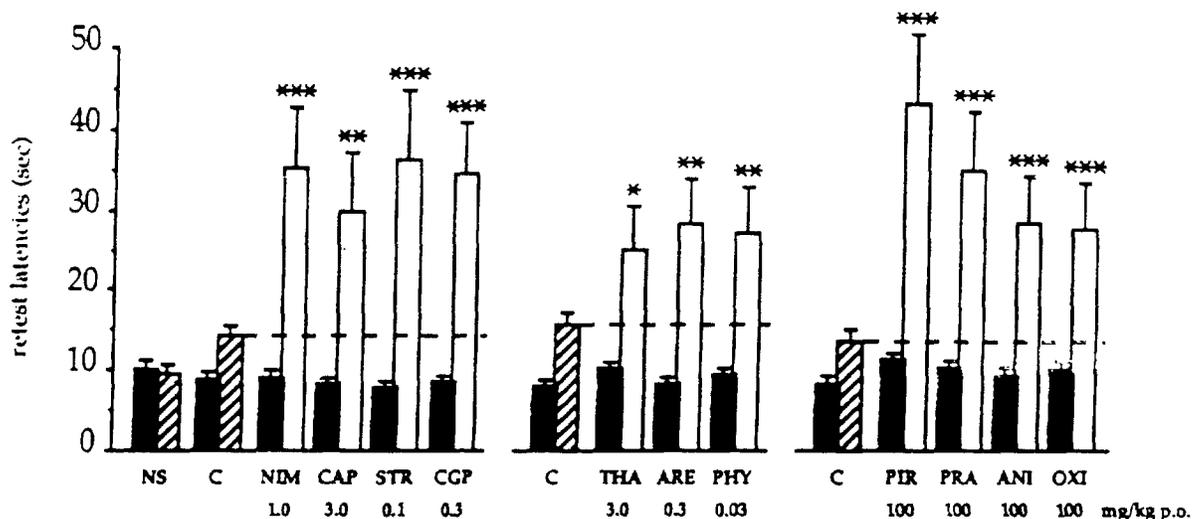


FIGURE 1. The effects of various memory-enhancing substances on the retention performance of mice in a passive-avoidance task. Mice were given footshock for leaving a "safe" small platform in the center of a grid floor. The spontaneous ("baseline") latencies to step onto the grid were measured. Retention (i.e., the retest latencies) was assessed 24 hours later. The histograms represent the step-down latencies in seconds. Solid columns: baseline latencies; blank columns: retest latencies of drug-treated animals; hatched columns: retest latencies of the vehicle-treated controls. NIM: nimodipine; CAP: captopril; STR: strychnine; CGP: CGP 36742 (GABAB antagonist); THA: tacrine; ARE: arecoline; PHY: physostigmine; PIR: piracetam; PRA: pramiracetam; ANI: aniracetam; OXI: oxiracetam. Physostigmine was given orally 30 minutes, all other substances, two hours, before the learning trial. Optimal doses for memory improvement were determined in independent pilot experiments. Prolongation of the retest latencies (in comparison with the no-shock controls [NS] and baseline latencies) indicates learning. Prolongation of the retest latencies in comparison with the retest latencies of the vehicle-treated controls indicates drug-induced memory improvement. $N = 25$ mice/group. * $2p < 0.05$, ** $2p < 0.01$, *** $2p < 0.001$ (Mann-Whitney U-test)

several hours. There are, nevertheless, experimental findings indicating differences in activity spectra, both within and between the various groups of memory enhancers, above all in tests not related to LTM.

III. THE CLINICAL EFFECTS OF THE NOOTROPICS

Any attempt to pinpoint common features in the available clinical data on these compounds quickly runs into certain problems. One major difficulty is due to the heterogeneity of the patient populations. Studies have been carried out in probable cases of Alzheimer's disease,³⁴⁻³⁸ in a mixed population of Alzheimer and multiinfarct dementia patients,³⁹ in multiinfarct patients,⁴³ in patients with psychoorganic syndrome,⁴⁴⁻⁴⁸ in aged volunteers,⁴⁹ in students,⁵⁰ in epileptic patients,⁵¹ in dyslexic schoolchildren,⁵² in patients suffering from effects of exposure to organic solvents,^{53,54}

in victims of head trauma,^{55,56} in patients with Korsakoff's syndrome,⁵⁷ and even in patients with artificial pacemakers.⁵⁸ The numbers of patients in each study ranged from 4⁵⁶ to 289.⁴¹ Durations of treatment also varied greatly: for example, 9 days,⁵⁸ 4 weeks,^{43,45} 3 months,^{39-41,46,47,51} and up to 1 year.³⁴ The study design was variously open,^{59,60} single-blind,^{43,61} double-blind,^{34,39,40} parallel with placebo controls^{36,39,41,42} or active controls,^{62,63} crossover,^{37,54} or enriched;⁵⁵ even comparisons with historical controls were used.⁶⁴

No less heterogeneous was the clinical and psychometric instrumentarium employed to assess the effects. Besides neuropsychological tests and scales, psychophysiological tests were also used. The quality of reporting differed greatly. In some studies, the test used is not simply mentioned but described exactly (e.g., reference 40), whereas in others the sole indication of the nature of the effect observed and the methodology applied was the single word *memory*.⁶³ In evaluating the effects, the psychometric tests were some-

times supplemented by staff-rated scales⁴⁷; sometimes only staff-rated scales were used,⁶⁵ or even just the clinician's global impression was given.⁶⁶ The study design was entirely adapted to demonstrating the existence of an effect of the preparation in patients.

Surprisingly, at first glance, scrutiny of the results of the published clinical studies reveals that the majority (more than 60%) of the reports are positive; i.e., the authors conclude from their findings that the treatment was effective. Villardita et al.,³⁹ for instance, showed that after three months the 30 patients treated with oxiracetam in a double-blind, parallel-design study displayed significant improvements in 9 of the 18 tests used compared with their baseline performance before the beginning of treatment. The 30 placebo-treated patients, on the other hand, showed no improvements, and even performed significantly worse in two of the tests. The positive effects were particularly clear-cut in the Mini Mental State Examination (MMSE), the Auditory Continuous Performance Test (ACPT), Rey's 15 Words Test, the Block

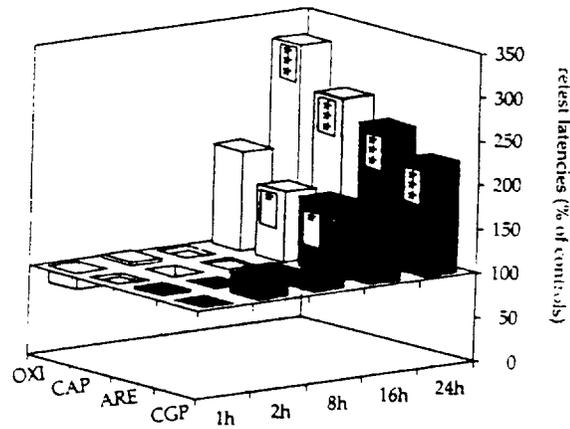


FIGURE 3. The emergence of the memory facilitation effect induced by the nootropic oxiracetam (100 mg/kg), the ACE-inhibitor captopril (3 mg/kg), the muscarinic agonist arecoline (0.3 mg/kg), and the GABA-receptor blocker CGP 36742 (10 mg/kg). The animals were trained in a passive-avoidance situation and treated immediately thereafter. Retention performance was measured at various intervals (1, 2, 8, 16, or 24 hours) after training and treatment. The columns indicate the drug-induced prolongation of the retest latencies (in percent of the vehicle-treated controls). * $2p < 0.05$, ** $2p < 0.01$, *** $2p < 0.001$. Prolonged latencies indicate better memory. All treatments were given intraperitoneally immediately after the learning trial (from Mondadori et al., *Proc. Natl. Acad. Sci.*, 91, 2041, 1994).

Tapping Test (BTT), the Mattis Word Fluency Test, Luria's Alternating Series, and the Instrumental Activities of Daily Living Test (IADL-E).

Senin et al.³⁸ performed a study with aniracetam, using a test battery different from that applied by Villardita. At the end of the 6-month treatment period the authors found significant improvements of performance in all 18 parameters assessed. As in Villardita's study, positive effects were recorded in Rey's 15 Word Test. Note that besides effects on cognitive parameters, these authors also observed distinct effects on behavioral parameters. The 6-month study with aniracetam performed by Parnetti et al.⁹⁷ according to a similar design yielded practically identical results: in 17 of 18 tests, aniracetam improved the patients' performance. In this comparative study the activity spectrum of aniracetam in some tests was distinctly different from that of piracetam. Unlike aniracetam, for instance, piracetam displayed no effects in Rey's 15 Words Test, in the Toulouse Pieron Test, and in the

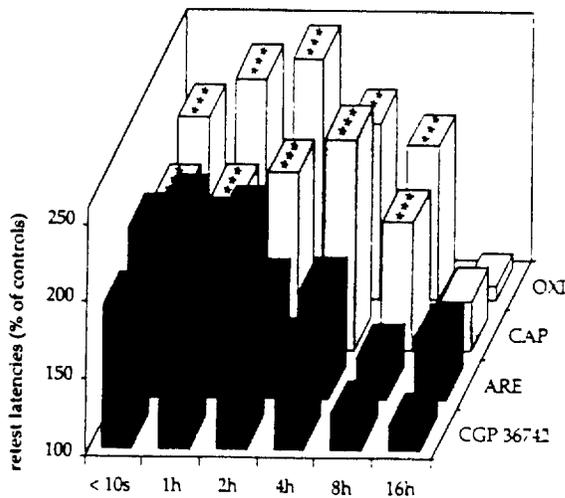


FIGURE 2. The effects of various compounds on memory if administered at various intervals after the learning experience. The animals were exposed to the passive-avoidance situation, and after the indicated intervals (<10 seconds, 1, 2, 4, 8, 16 hours) treated with optimal doses of the memory enhancers. Retest was performed after 72 hours. The columns indicate the prolongation of the retest latencies (in percent of the vehicle-treated matched controls). Prolonged latencies indicate better memory. ARE: arecoline; CAP: captopril; OXI: oxiracetam. * $2p < 0.05$, ** $2p < 0.01$, *** $2p < 0.001$.

Raven Test. According to the Sandoz Clinical Assessment Geriatric (SCAG) Scale, however, the effects were nearly identical. Bottini et al.⁴⁰ observed distinct effects of oxiracetam in five of eight cognitive tests. In particular, there were significant positive effects on verbal fluency, similar to those described by Villardita et al., and the retention of a short story (after a delay of 10 minutes) was also improved. In the 12-month study with piracetam conducted by Croisile et al.,³⁴ indications of a retardant effect of the drug on the progress of mental decline were noted: in the placebo group a significant deterioration was evident at the end of the year in 8 of 14 tests, whereas in the piracetam group negative results were recorded in only one test. In contrast to the findings of Senin et al. and Parnetti et al., direct comparisons of the performance of placebo-treated and piracetam-treated patients yielded scarcely any statistically significant results. The study carried out by Maina et al.⁴¹ in the largest population samples of all (N = 144 + 145), positive (good to very good) effects of oxiracetam were recorded in 90 of 145 patients (global evaluation), whereas, according to the same criteria, only 27 of 144 placebo-treated patients were rated as showing good or very good responses. Only 51 of 144 patients taking oxiracetam as against 107 of 144 receiving placebo were rated as showing no effect or a poor effect. Note that the patients in this study, in contrast to those in the study by Villardita et al., showed positive effects in the IPSC-E (Inventory of Psychic and Somatic Complaints, Elderly). Statistically significant increases in the IPSC-E scores were also recorded in the 6-month study performed by Mangoni et al.,³⁶ while no changes were seen in the placebo-treated controls.

Itil et al.⁴⁶ also reported significant effects of oxiracetam in the IPSC-E, not in Alzheimer patients, but in diagnostically less precisely defined cases of organic brain syndrome (OBS). These effects were more pronounced than the corresponding effects of piracetam. Such changes in the IPSC-E suggest that oxiracetam exerts effects that can be manifest as an improvement in the quality of life of the patients. The results obtained by Saletu et al.⁴⁵ in their study of a similar patient population were far less distinct: apart from an improvement in verbal memory, only the overall

score in the SCAG was significantly better (the IPSC-E was not used). The duration of treatment in this study was only four weeks. More modest still were the clinical effects noted in the study of piracetam performed by Abbuzahab et al.⁴⁸ in OBS patients (geriatric memory): apart from a slight overall improvement, no relevant effects were observed. Much more pronounced positive effects emerged from the investigation by Moglia et al.⁴² In this parallel-design study in 21 + 22 OBS patients, these authors showed that oxiracetam induced an overall improvement in cognitive and behavioral parameters. Particularly notable were the significant improvements seen in the Benton Visual Motor Retention test (as also used by Itil et al.) and in the arithmetical part of the Wechsler Adult Intelligence Scale (WAIS). The conclusion that the general well-being of the patients treated with oxiracetam had improved is consistent with the many global clinical assessments, as exemplified by a 3-month placebo-controlled study in 60 patients with two doses of piracetam carried out by Chouinard et al.⁴⁷ In this study, the results of the monthly evaluations by the nursing staff (Nurses Global Improvement Rating Scale) clearly indicated an improvement in the patients' sense of well-being, whereby particular emphasis was placed on alertness, socialization, and orientation. Another study by Foltyn et al.,⁶⁵ showing aniracetam to have been effective over a duration of four weeks in N = 30 + 30 patients, was based exclusively on staff ratings.

Nootropics were also tested for efficacy in completely different clinical indications. McLean et al.,⁵⁶ for example, examined pramiracetam in four patients with head injuries or anoxia and showed that the drug exerted clear-cut effects on immediate and delayed recall. In patients with pacemakers, in whom the fixed heart rate often leads to diminished cerebral circulation and consequent disturbances of performance during exertion, piracetam was found to induce a slight improvement in psychomotor tests⁵⁸; no cognitive tests were performed, however. In a study in epileptic patients with memory disorders, Aldenkamp et al.⁵¹ observed no effects after 12 weeks, but all parameters measured revealed a trend favoring oxiracetam.

In some investigations, comparative evaluations were made of the effects of nootropics. In

the above-mentioned study by Itil et al.,⁴⁶ oxiracetam was found to have a slightly better effect on cognitive parameters than piracetam, whereas piracetam displayed a slightly better antipsychotic effect than oxiracetam. Although the greater efficacy of oxiracetam in regard to cognitive aspects was confirmed in the studies by Gallai et al.⁶¹ and Ferrero,⁶³ these studies were not carried out under double-blind conditions and are consequently not admissible as valid scientific evidence. The same applies to the study conducted by Falsaperla,⁶² in which the effects of oxiracetam were compared with those of deprenyl in Alzheimer patients. Here, both drugs improved the patients' performance above baseline levels in a whole series of tests, deprenyl emerging as the more effective treatment. Aniracetam was also shown to be slightly more active than piracetam in the study by Parnetti et al.⁶⁷

In contrast to the many positive results reported, a 3-month study in Alzheimer patients performed by Green et al.⁶⁸ and using a broad battery of neuropsychological tests revealed no signs of efficacy of oxiracetam, either on the basis of group analyses or in individual patients. Similarly, a 3-month trial by Hjorth et al.⁵³ with a very extensive test battery gave no indication of any effects of oxiracetam: neither behavioral nor memory parameters showed any signs of improvement. Note that this trial was done in a special group of OBS patients, suffering from toxic encephalopathy following exposure to organic solvents. In full concordance with these results, Somnier et al.⁵⁴ detected no signs of efficacy of aniracetam in such patients. A notable feature of this study was that Somnier employed a crossover design. Other crossover trials have also revealed no positive effects. Lloyd-Evans et al.⁴⁴ were unable to detect any effects of piracetam in a 6-month double-blind trial in OBS patients. The 2 × 4-week crossover study with oxiracetam performed by Molloy et al.³⁷ in Alzheimer patients likewise showed no effects. In none of these crossover trials was the first drug/placebo phase evaluated separately as a parallel study. Negative results further emerged from an enriched-design study by Claus et al.,³⁵ who concluded from their results that pramiracetam is ineffective as a symptomatic treatment for Alzheimer patients. This rating was based on the scores achieved by 10

patients in the Alzheimer's Disease Assessment Scale (ADAS). In patients with alcoholic organic mental disorders also, a study conducted by Fleischhacker et al.⁵⁷ demonstrated no relevant improvement after treatment with piracetam.

Given the existence of studies with positive and others with negative results or overall ratings, one question that arises is what 'positive' or 'negative' means to the individual patients. As regards the positive studies, that question has already been answered, insofar as it was often mentioned that only a limited number of patients responded to the treatment (e.g., reference 41). Unfortunately, in the clinical studies with nootropics, only scant information is given about the frequency of significant therapeutic effects and the quality of such effects in individual patients. The fact that, despite many nonresponders, positive overall ratings were still reported would at least seem to justify the reverse question of how often individual responders were present even in the negative studies. For want of adequate information on responders and nonresponders in most double-blind studies, illustrative data must also be drawn from the results of open trials. In the study performed by Claus et al.,³⁵ the conclusion that piracetam was ineffective was based on the lack of significant effects in the ADAS in 10 patients. In fact, however, there was at least one responder with a reduction of more than four points in the ADAS and significant, drug-related improvements in both the Visual Selective Reminding Task (total and delay) and Logical Memory Immediate Recall. These effects were inevitably submerged in the calculations of the means values and statistical analysis. In the study by Baumel et al.⁴³ also, where the drug effects were rated as very modest, 4 of the 12 patients showed responses. In that the case reports were described as typical, this was a substantial effect from the viewpoint of the quality of life. This outcome is closely similar to the results of the open study in six patients by Dager et al.,⁵⁹ in which there was one definite responder. Irrespective of the extent to which the cited data were attributable to drug effects, they demonstrate the need for analyses of this nature.

It can be concluded that the piracetam-like nootropics can evoke significant effects in Alzheimer patients, becoming manifest on the

one hand in cognitive improvements and on the other in behavioral aspects. The effect appears to become more marked during prolonged treatment. The various nootropics differ in their activity spectra. In general, however, there were only a limited number of responders. The few efforts made to characterize this group of patients (e.g., reference 59) were unsuccessful.

IV. COMPARISON WITH THE CLINICAL EFFECTS OF TACRINE

Any attempt to characterize the clinical effects of the nootropics almost automatically necessitates a comparison with cholinomimetics. In contradistinction to the nootropics, cholinergic substances are used in Alzheimer patients, not because of their memory-enhancing effects in animals, but because of the existence of a cholinergic deficit in these patients.⁶⁹ In this respect, the patient population studied is homogeneous and, unlike the very mixed populations treated with nootropics, includes only (probable) Alzheimer patients. The group sizes are similar to those in the nootropic studies. The methodology used is more nearly uniform but different from that adopted for nootropics. The following section is confined to tetrahydroaminoacridine (THA, tacrine, Cognex®), a cholinesterase inhibitor and the only substance so far registered for the treatment of Alzheimer's disease.

The first study by Summers et al.⁷⁰ was conducted in three phases. In the first phase, the tolerability and efficacy of incremental doses of THA were assessed in 23 patients. THA was always administered in combination with lecithin. In a second double-blind, crossover phase, 15 of these patients were treated with the best or highest dose of THA, or with placebo, for three weeks, after which the treatments were switched. Only the 12 patients showing a clear-cut response to THA in the second phase went on to receive long-term treatment over periods ranging from 3 to 26 months (enriched design). The final assessment revealed distinct positive results (global assessment, orientation, Alzheimer deficit scale, names learning test), whereby only patients classed as Stages 3-4, but not Stages 5-6, on the Reisberg scale responded.

Most of the subsequent studies initially failed to confirm Summers' results. A crossover study conducted by Davies et al.,⁷¹ for example, in which 10 patients were treated for up to four months, showed hardly any notable effects of the combined treatment with THA and lecithin. Only in 1 of 10 tests were positive results recorded. The same results were obtained by Chatterlier et al.⁷² In this crossover study with 67 patients, tacrine (combined with lecithin) was administered orally for four weeks. Apart from a slight improvement in the Physician's Score, THA was ineffective. Neither in behavioral scales (Stockton) nor in cognitive scales (MMSE) were any effects demonstrable. Similarly, in a crossover trial done by Gauthier et al.⁷³ over two 8-week treatment periods, the response to THA was limited to an improvement in the MMSE. Despite this improvement, the authors rated the effect of THA as clinically irrelevant. No effect whatever was observed by Molloy et al.⁷⁴ in a multiple crossover study with treatment periods of three weeks. Neither the overall evaluation nor a detailed analysis of individual patients revealed any indications of effects.

Positive results, on the other hand, were obtained in the trial conducted by Davis et al.⁷⁵ The 215 patients who had responded to tacrine in a preliminary crossover phase were subsequently treated for six weeks in a parallel study. By comparison with the placebo controls, the tacrine group showed a slight, but significant, decrease in mental decline (ADAS cognitive subscale). Two of the three quality-of-life assessment scales used indicated changes in favor of tacrine: Progressive Deterioration Scale (PDS) and Activities of Daily Living (ADL). The changes in the MMSE were slight and statistically not significant, and the clinician's global assessment (CGIC) likewise failed to detect any effects. In a similar, but more prolonged (12-week) parallel study by Farlow et al.,⁷⁶ very much the same results were obtained: the ADAS cognitive subscale indicated some retardation of cognitive decline, but the MMSE showed no changes. In contrast to the study by Davis, however, the physicians' and caregivers' global ratings were significantly better. In a crossover study by Eagger et al.,⁷⁷ in which 468 patients were treated for considerably longer (13 weeks) than those in Molloy's study,⁷⁴ the MMSE

and the AMTS (Abbreviated Mental Test Score), but not the ADL, revealed an effect of tacrine.

The effects in the MMSE were consistent with the findings of Gauthier et al.,⁷³ but not with those of Farlow et al.⁷⁶ and Davis et al.⁷⁵; the absence of effects in the ADL were at variance with the results observed by Davis et al.⁷⁵

Recent studies disclosed the entire range of possible effects. Distinctly positive effects emerged from a 30-week parallel study by Knapp et al.⁷⁸ In this study with an initial population of 663 patients, all three primary outcome measures (ADAS cognitive subscale, Clinicians' Interview-Based Impression, and Final Comprehensive Consensus Impression) showed significant effects of tacrine. In addition, positive effects, among others, were demonstrated by the Progressive Deterioration Scale and the MMSE, but not the ADL. The effects indicated by the MMSE were in agreement with those noted by Gauthier et al.,⁷³ Egger et al.,⁷⁷ and Davis et al.,⁷⁵ but contrary to those seen by Farlow et al.⁷⁶ and Molloy et al.⁷⁴ Although consistent with the findings of Egger et al.,⁷⁷ the absence of effects in the ADL conflicted with those of Davis et

al.⁷⁵ Exactly the opposite, i.e., no indications of any effect whatever, emerged from the study by Maltby et al.⁷⁹ with an initial population of 57 patients and a 36-week duration of treatment. Neither the Caregivers' rating-based scales nor the cognitive scales showed signs of changes. Halfway between positive and negative results lie the findings reported by Wilcock et al.⁸⁰ In a 2 × 3-month crossover study in 41 patients these authors noted positive trends in favor of tacrine, but statistically the differences were scarcely significant. In a study with 154 patients, Wood et al.⁸¹ likewise merely observed positive trends, but there was no significant effect of tacrine in the overall group analysis. The results nevertheless indicate that there were individual responders. The same applies to a 3 × 6-week crossover study of Alzheimer patients conducted by Gustafson⁸² in which there was no detectable overall effect, but individual responders were noted. It is, above all, the enrichment studies that confirm the existence of a subset of responders, although even after the enrichment not all patients respond to the treatment. In the light of these findings and in view of the need to optimize the therapy, it is surprising that scarcely any efforts have been made to establish a pharmacological,

biochemical, and endocrinological profile that would serve to identify likely responders.

To sum up, although there are clear indications that cholinesterase inhibitors do exert clinical effects, it is equally clear that only a certain number of patients respond to the treatment. The use of enriched-design studies often makes the proportion of responders appear larger than it really is. As with nootropics, longer durations of therapy improve the chances of evoking demonstrable effects. The psychometric scales and tests employed were in most cases not comparable with those used in the nootropic trials. In the few studies in which comparable scales and tests (MMSE, ADL) were used, the effects observed were of roughly the same magnitude as those produced by the nootropics. Although the methodology was much more nearly uniform than in the nootropics studies, there was no test that yielded consistently positive results in all trials.

V. PRECLINICAL EFFECTS OF THE NOOTROPICS IN THE LIGHT OF CLINICAL FINDINGS

Before considering the extent to which the clinical data meet the expectations based on preclinical findings, I must stress once again that the clinical investigations were exclusively aimed at showing whether or not the preparations exerted any therapeutic effects. For that reason a wide battery of tests was used, comprising both behavioral aspects and cognitive performance. The somewhat unfortunate efforts of many authors to make use of data from animal experiments in explaining the rationale of their studies and discussing the clinical results should not be allowed to obscure the fact that neither were the studies designed to validate the preclinical results, nor were the clinical results in any way adjusted to serve that purpose.

In the vast majority of the preclinical studies, a design was used in which the experimental animals were exposed to the learning situation while under the influence of the drugs and then tested for retention 24 hours later, either still, or no longer, under the influence of the drugs. In the clinical studies, however, retention performance was tested after short-term intervals, i.e., either

immediately after acquisition or after a lapse of 10 minutes. The several hours' delay preceding the emergence of detectable memory-facilitating effects that has been observed in the most recent animal experiments⁴⁻²⁴ strongly emphasizes the crucial importance of allowing long enough retention intervals, provided only, of course, that the clinical effect and the memory facilitation observed in animals come about by way of the same mechanism. What the long-term memory tests used in the clinical studies detected was not the influence of the substances on long-term storage, but their influence on retrieval from LTM, i.e., on the recall of information acquired while not under the influence of the drugs. Often, learning capacity was tested before and at the end of the treatment period: i.e., performance without the influence of the drugs was then compared with performance while under the acute influence of the drugs. There is thus still no sound scientific evidence of the predictive validity of the animal procedures. This aspect should be examined in specifically designed clinical investigations.

The various reports nevertheless do contain at least a few allusive remarks consistent with the expectations based on animal experiments. In the study with oxiracetam by Dager et al.,⁵⁹ for example, there is a sentence reading: "although long term recall improved only negligibly, his long term memory storage (learning capacity) and recognition memory were moderately enhanced." Similarly McLean et al.⁵⁶ state that: "The most dramatic demonstration of improvement with pramiracetam ... occurred in the selective reminding test-delayed recall, long term memory retrieval and long term storage." Last, but not least, there are a number of reports concerning the effects of piracetam in dyslexic children that possibly point to effects on LTM storage. In a double-blind, placebo-controlled study by Wilsher et al.⁵² the children showed greater facility in reading and comprehension after a 36-week phase of treatment with piracetam. It is very probable that the improved performance at the end of the treatment period reflects, not an acute effect on memory retrieval, but rather an improved availability of the knowledge acquired throughout the duration of treatment, i.e., long-term retention of information acquired under the influence of piracetam. This view is strongly supported

by the fact that the combination of psychological training and nootropic therapy proved particularly effective, not only in dyslexic children, but also in other forms of cognitive underperformance.³³ Moreover, it appears very likely that the effects observed after long-term treatment of Alzheimer patients might, at least partially, be based on such effects, too.

However, the many reports on an improvement in noncognitive aspects in individual studies or patients make it seem improbable that nootropics act exclusively on LTM storage. It is conceivable that the effect comes about via a modification of general processes that play an important role in the performance of brain cells. The improvement in long-term storage would then be only one of the measurable consequences. The reason for the usually modest extent of the clinical effects could be that the action of the substances is confined to cells that are still functionally competent. But since the individual patient's specific pattern of functional deficits reflects the impairment of the neuronal circuits essential to this function, it may be that the aspect most impaired through degeneration also affords the least room for improvement. This applies equally to cognitive and noncognitive performances. It is therefore perfectly conceivable that while measurable effects in one aspect or another may be detectable in a wide-ranging psychometric investigation, these aspects may be of little therapeutic relevance to the symptoms that are particularly disabling for the patient.

VI. SYNTHESIS AND OUTLOOK

Given the observed overall positive effects of the nootropics and their occasionally quite distinct effects in individual patients, this category of compounds would appear useful. The results available so far give no indication that tacrine is superior to the nootropics, or vice versa. The effects of these drugs seem to be similar, although the complication that the double-blind nature in connection with cholinomimetics is very probably wishful thinking (discriminative stimulus properties,⁸⁴ side effects, e.g., reference 74) has been completely left out of consideration. In the absence of comparative studies, the tacit assump-

tion that the cholinomimetics are more effective most likely reflects the superficial plausibility of the underlying hypothesis rather than the existing clinical results. Together, the clinical results present a mirror image of the preclinical profile.

In order to maximally exploit the available therapeutic possibilities, it would be desirable to give priority to the characterization of a subgroup of patients likely to respond to a particular therapy. The steroid dependence of the memory-facilitating effect of the nootropics^{23,31} opens up a practical possibility in view of the fact that a very large percentage of Alzheimer patients have elevated plasma cortisol concentrations.⁸⁵ This approach would, of course, be valid only if the memory-enhancing effects seen in preclinical studies and the effect observed in patients come about by way of the same mechanism. This brings us back to the question of the validity of the preclinical models, which urgently need clarifying by clinical trials specifically designed for that purpose.

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EVALUATION OF THE EFFICACY OF PIRACETAM IN TREATING INFORMATION PROCESSING, READING AND WRITING DISORDERS IN DYSLEXIC CHILDREN

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Piracetam, a new class of drug (nootropil) thought to enhance specific cognitive skills, was given in a 3300 mg daily dose to half of a group of fifty-five dyslexic boys aged 8-13 years, in a 12-week, double-blind, placebo-controlled study. The other half of the subjects received placebo. All subjects met the following criteria: normal intelligence, normal educational opportunities, no severe emotional problems, no neurological handicaps, good physical health, not taking other psychotropic medication, and scoring at least one and one half years below their mental age equivalent on the Gilmore Oral Reading Test. Non-verbal (auditory and visual) and verbal (spelling and memory) skills were examined, and reading, spelling, language and writing abilities were measured using standardized instruments. Compared to the placebo control group, individuals treated with Piracetam did not show statistically significant improvements above their baseline scores on measures of perception, memory, language, reading accuracy or comprehension, or writing accuracy. However, reading speed and numbers of words written in a timed period were significantly enhanced in subjects treated with Piracetam as compared to placebo. Effective reading and writing ability, taking both rate and accuracy into consideration, were also significantly improved in the Piracetam as compared to the placebo treatment group. The medication was well-tolerated and medical examinations showed no significant adverse reactions. These results encourage further study of Piracetam to determine more precisely the mechanism of action by which specific cognitive skills are affected.

INTRODUCTION

Recent reviews of chemotherapeutic treatment of learning disabilities have emphasized that the perceptual and behavioral changes induced by drugs do not necessarily lead to improved academic performance (Aman, 1980; Werry, 1981). This conclusion has been based primarily on research with central nervous system stimulants such as methylphenidate (Ritalin) and dextroamphetamine (dexamphetamine). Such stimulants have been shown to improve attention span (Barkley, 1977; Barkley and Jackson, 1977), memory (Sprague, 1972; Werry

and Aman, 1975), and impulsivity and social behavior (Barkley and Cunningham, 1980; Conners and Werry, 1979). However, studies of educational abilities using standardized reading, spelling and arithmetic tests have failed to demonstrate any significant differences in the performance of treated children (Quinn and Rapoport, 1975; Weiss et al., 1975) or non-hyperactive children (Gittelman-Klein and Klein, 1976; Aman and Werry, 1982).

This discrepancy between the drug-induced improvements in behavioral control and the absence of change in school-performance may be due in part to the way each child is assigned the proper dosage. In the past, clinicians and investigators have assumed that the optimal dosage to improve

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behavior would coincide with the levels of drug needed for improved learning. Gittleman-Klein and Klein (1975) demonstrated, however, that there was no association between improvements in behavior and increases on academic test scores among children treated with Ritalin. Sprague and Sleator (1977) have proposed an inverted U-shaped functional relationship between the medication dosage and performance on cognitive or behavioral tasks. There is a zone of peak-enhancement or actual deterioration of the performance. Their studies have suggested that zones of peak-enhancement are not the same for cognitive and behavioral tasks. The optimal zone for social tasks requires a slightly higher dosage than the optimal zone for cognitive tasks. Thus, the best dosage for cognitive tasks appears to be too low to enhance social functioning, whereas the optimal zone for social enhancement is too high a dosage for improving cognitive skills. Since stimulants are usually prescribed for improving social behavior, children taking these medications may be receiving dosages that are too high for enhancing cognitive skills.

To avoid the ambiguities of such dosage-dependent effects, many investigators have focused their efforts on the study of cognitive effects due to psychotropic medications. Recent attention has been given to a new class of psychoactive drugs called nootropils. Piracetam, a nootropic substance, has been studied for its facilitation of learning and memory consolidation (UCB, 1980). Chemically, Piracetam (2-oxo-pyrrolidine-acetamide) shows a kinship to γ -aminobutyric acid (GABA) and appears to have no stimulating or sedating effects (Stegink, 1972; Calliauw and Marchau, 1975). Dimond (1975) and Dimond and Brouwers (1976) report that Piracetam increased verbal learning and improved performance on coding and short-term memory tasks with normal adult subjects. Other researchers have also noted that Piracetam significantly enhances performance on a variety of tasks which assessed presumed left-hemispheric functioning (Squitieri et al., 1975; Mindus et al., 1976). As such, Piracetam may be a particularly appropriate drug for treating children with some forms of learning disabilities including dyslexia, since many such children have been shown to have relatively poor perceptual and

short-term memory abilities (Rudel and Denckla, 1974; Tallal, 1980a; Tallal, 1980b) and poor coding and naming abilities (Symmes and Rapoport, 1972; Denckla and Rudel, 1976).

Three studies have tested the effects of Piracetam on learning-disabled populations. The first study reported was by Wilsher et al. (1979), who used adult dyslexics as subjects. In this study, 16 adult dyslexics were matched on the basis of their WAIS IQ scores with 14 control subjects for a 3-week placebo-controlled, double-blind, crossover trial of 4800 mg daily dose of Piracetam. The dyslexic subjects met the criteria outlined by Thomson (1977). Since subjects in this study demonstrated significant carryover effects due to the crossover design, Wilsher et al. only examined results from the first period of treatment to avoid the confounding effects from previous exposure to Piracetam. In comparison to placebo treatment, results showed that in the dyslexic group who received Piracetam verbal learning improved by almost twice that of the non-dyslexic control group receiving Piracetam (15% compared to 8.6%). The test used was a serial memory verbal learning task with 10 three-letter nonsense syllables. In addition, the number of instances that a subject learned the nonsense syllable and then forgot it on the very next trial dropped by almost half among the dyslexic group treated with Piracetam (-47.1%), but was not changed in the dyslexic placebo treatment group.

Simeon et al. (1980) were the first to test the efficacy of Piracetam on learning skills of children. They treated 29 'learning disordered' boys between the ages of 8 and 14 with a 4800 mg daily dose of Piracetam in a double-blind, crossover placebo-controlled 4-week study. All children were at least one year behind their age group in either reading, spelling or arithmetic on the Wide Range Achievement Test (WRAT) and all had a Full Scale WISC-R IQ of at least 85. Their findings on measures of global behavior and learning were non-significant, although the author points out that the short duration of treatment, carryover effects due to the crossover design, and the small number of patients in various treatment subgroups made statistical analyses difficult to interpret.

In a second study by Wilsher et al. (1985), 46

dyslexic boys aged 8 to 13 years were treated in an 8-week, double-blind, placebo-controlled trial of 3300 mg daily of Piracetam. All subjects met the following criteria: they had a Full Scale WISC-R IQ greater than 90, a Reading or Spelling Age of at least two years behind their mental age based on the WISC-R, normal educational opportunities, no severe emotional problems, normal hearing and normal vision, and no gross neurological deficits. The children were tested on their reading ability (speed, accuracy, and comprehension) and a 5-min free-writing sample was taken to measure the total number of words written and the percentage of spelling mistakes. *T*-test comparisons between the means of the two treatment groups at the beginning and the end of the 8 weeks showed no significant differences on any of the dependent measures. However, further analysis comparing the mean treatment changes from baseline, using the difference between the post- and pretreatment scores for each subject, revealed improvements in reading speed and accuracy and total words written in individuals treated with Piracetam. In all 3 studies, the Piracetam medication was extremely well-tolerated.

The present study was designed to replicate and extend the findings of Wilsher et al. (1984). More rigorous patient-selection inclusion and exclusion criteria were used. Drug dosage and regimen were equivalent, but the clinical trial was extended to 12 weeks and additional subjects, test sites, and psychometric tests were included.

METHODS

Subjects

Six different centers participated in the study. At our site in San Diego, 61 developmentally reading-disabled children were studied over a one and a half year-period, from the spring of 1981 to the summer of 1982. All children attended school during the course of the study and met the following criteria: (1) They were male and between the ages of 8 years, 0 months and 13 years, 11 months old at the initial visits. (2) They had a Full Scale IQ score of 80 or more on the Wechsler Intelligence Scale for Children-Revised (WISC-R) with a

Performance Scale IQ or a Verbal Scale IQ of 90 or more, obtained within 9 months of the initial visit. (3) They had a Reading Quotient of less than or equal to 0.85. (4) English was their primary language. (5) Informed consent was obtained from both patient and parent or legal guardian. (6) They had normal audiological and ophthalmological functioning. (7) There was no significant neurological handicap. (8) They had no severe emotional disturbance as a primary symptom. (9) There was no severe educational deprivation. (10) They had no clinically significant laboratory abnormalities, nor any medical conditions which might put the patient at additional risk or interfere with the conduct of the study. (11) They had no history of significant adverse reaction or hypersensitivity to Piracetam. (12) They were not involved in any therapies which might interfere with the evaluation of efficacy and safety, including: psychostimulant medication within 6 months of the initial visit, concomitant drug therapy with psychostimulants or any drug for emotional disturbance, concomitant therapy with Tofranil for any indication, investigational drug therapy within one month of the initial visit, or concomitant chronic treatment with bronchodilators which have central stimulant activity.

The Reading Quotient was calculated as equal to: Reading Age \times 100% by Chronological Age \times Full Scale WISC-R IQ. The Reading Age was derived from the Accuracy Score of the Gilmore Oral Reading Test — Form C. Grade Scores from the Gilmore were converted to Age Scores using Table II provided in the Gates-McKillop Oral Reading Test. Abnormal audiological functioning was defined as a loss of greater than 20 dB in either ear for two frequencies in the normal range (500, 1000, 2000, 3000, 4000 Hz, using pure tones). Abnormal ophthalmological functioning was defined as less than 20/40 corrected vision in both eyes as tested by the American Optical E Chart. Significant neurological handicaps were defined as any of the following: acquired neurological disease, classical neurological signs with functional impairment or seizures within the last 5 years. The patients had not received anticonvulsant therapy for at least two years prior to the initial visit. Educational and emotional evaluations were made

by the medical staff following usual clinical practice. Four subjects were dropped from the study: one moved, one suffered from an asthma attack and was treated with bronchodilators (in violation with the protocol) and two were removed from the study due to medical complications unrelated to study medication (both were taking placebo). The fact that a child was currently receiving academic remedial assistance or had received such tutoring in the past did not preclude entry into the study.

Procedures

Placebo and Piracetam treatments were randomly divided among 6 groups of 10 subjects, each on a double-blind basis with the restriction that there be equal numbers of each treatment within each of the 6 groups. Patients were then assigned to one of the 6 groups on the basis of their age; that is, 8-year-olds were assigned to Group One, 9 years olds to Group Two, and so forth. When all the treatment medication had been used up within a group, the patient was assigned to the group with the fewest members. Patients received either 3.3 g of Piracetam daily or matching placebo syrup. Each dose of test medication was 5 ml, administered before breakfast and again before the evening meal. A 5 ml dose of active medication contained 1.65 g of Piracetam. No dosage adjustments were allowed.

The study consisted of 5 visits. An initial screening visit usually occurred one week prior to the start of treatment. The treatment period was 12 weeks long, with follow-up visits after 2 weeks, 6 weeks, and 12 weeks of treatment. At week 4 and week 9, the patient's parents were contacted to review dosage instructions and to determine whether any adverse effects had been observed.

At the initial screening, patients were tested to determine their eligibility. Hearing and visual acuity tests were given, a developmental history taken, IQ testing was done as needed, and the Gilmore Oral Reading Test was also administered to provide a calculation of the Reading Quotient. Assessment of education experience and emotional health was also performed at this time.

A complete physical examination was performed by a physician at the second or induction visit and again at the last visit. A medical history

was taken during the second visit and abbreviated physical examinations were performed at the second and sixth week visits. Observations for possible adverse effects and assessment of general health were emphasized. Laboratory evaluations were obtained at the induction visit, the 6-week, and the 12-week visits. The laboratory tests included hematology, urinalysis and blood chemistry to test for possible adverse side-effects.

Tests

All 6 study centers followed the same protocol and used a common battery of tests to measure drug efficacy. In addition, each site conducted additional 'special studies'. Only the results from the common test battery and special study conducted at the San Diego site are reported in this paper. The common test battery was administered at the induction and final (week 12) visits, while the special study tests were given at the induction and week 6 visit. At the San Diego Center, all testing for an individual patient was administered by the same tester and took approximately 1½ h. These tests included: the Gilmore Oral Reading Test — Form C at the initial visit and Form D at the final visit —, Information for Reading Accuracy, Comprehension and Rate were included; the Digit Span subtest of the WISC-R, both digits forwards and backwards administered via a tape recording; the Gates-McKillop Syllabication subtest — Form 1 at the induction and Form 2 at the 12-week visit; the Wide Range Achievement subtest for Spelling; a 5-min free-writing sample was taken to include the total number of words, number of words misspelled and the number of occurrences of the most frequently written word; the Rapid Automatized Naming Test (Denckla and Rudel, 1976); a behavioral assessment in the testing situation made at the induction and 12-week visits on a rating scale of 1 to 4 (1 being excellent, 4 being poor), measuring distractibility from following instructions, social appropriateness, cooperativeness, attention and general motor activity; and a parent's global assessment of the child's behavior obtained at the 12-week visit on a rating scale of 1-5, where 1 is much improved and 5 is much worse, considering their behavior at home, interaction with peers and school reports concern-

g behavior and performance in evaluating the change from the start of the study.

In addition to these common tests, we conducted additional special studies. Subjects were given the Repetition Test, developed by Tallal (1980), with 3 sets of stimuli: (1) non-verbal auditory tones (75 ms duration), differing in fundamental frequency; (2) non-verbal visual nonsense shapes (75 ms duration); and (3) auditory stop-nonsonant vowel syllables (ba/da) with 40 ms duration formant transitions. The Repetition Test has been shown to be a highly sensitive measure of perceptual and memory functioning. In addition, it is theoretically based on a model of perception and is comprised of a series of substests designed to assess levels of perception and memory in a hierarchical manner (see Tallal, 1980, for a detailed description of these procedures). Four dependent measures were made on each of the 3 versions of the Repetition Test. Subjects were scored for the total number of correct trials, the number of correct trials using interstimulus intervals (ISI's) of 1000 ms, the number of trials using ISI's less than 1000 ms and the number of trials needed to reach criterion. Improvements in trials to criterion scored indicate an increased rate of learning stimulus-response associations. Increases in scores on trials with short ISI's suggest an improvement in rate of processing and temporal sequencing abilities. Improvements in the longer ISI scores suggest an increase in short-term and serial memory.

In addition to these experimental perceptual and memory tests, subjects were also given the Wechsler Test (DeRenzi and Vignolo, 1962) to assess receptive language comprehension skills and a word-associate visual memory test designed for this study. In the visual memory test the tester instructed the child by saying, 'I would like to see how well you can remember different pairs of pictures. I will show you two pictures, one after the other. Try to remember them as a pair that go together'. Testing took place in two parts, a learning and a recall section. During the learning section, children were presented with pairs of pictures arranged as a set. Children were presented with sets of 2, 4, 6 and then 8 pairs. If a child successfully recalled all pairs within a set, they moved to the next higher set and were tested. If any failure

occurred, the final testing took place using the next lowest set; e.g., failure on set 6, final testing on set 5. During the learning portion, children were presented with pairs of pictures, one after the other, until the set was completed. Each pair was presented for 3 s with an intertrial interval of two seconds. After all of the pictures in a set had been presented, the child's recall abilities were tested in the following way: the second picture of each pair was grouped, mixed and then laid down on the table in front of the child. Using the same order as presented in the learning portion of the test, the first picture of each pair was presented to the child, and he was asked to find the picture that goes with it among the pictures laid down on the table in front of him. This procedure was continued until all pictures had been matched. Children were scored for the total number of correctly matched pictures. Improvements on this test suggest increases in visual learning and recall.

RESULTS

From the initial sample of 61 children, 57 successfully completed the study. From this group, two children had poor compliance during the last 6 weeks of the clinical trial period (below 70% as measured from the remaining bottled medication). Consequently, they were removed from the data analysis leaving 55 children, 28 from the piracetam treatment group and 27 in the placebo treatment group.

Table I presents the demographic and baseline characteristics of the Piracetam and placebo treatment groups. *T*-test and χ^2 comparisons between the two groups showed no significant demographic differences. Note that a high percentage of the children were actively receiving remedial tutoring for their reading problems (ca. 70%).

Table II shows the baseline scores for the Piracetam- and placebo-treated groups on the common test battery. Note that the Gilmore Oral Reading test was scored in two ways. First, individual reading ability for accuracy, comprehension and rate was scored. Second, because by reading more slowly, accuracy and comprehension may be improved or vice versa, composite reading scores

TABLE I

Demographic and baseline characteristics

Patient characteristic	Piracetam (n = 28)	Placebo (n = 27)	P
Age, years			
Mean	11.1	11.4	$t = -0.05$ n.s.
S.D.	1.9	1.6	
WISC-R, VSIQ			
Mean	97.8	98.0	$t = -0.1$ n.s.
S.D.	10.9	10.8	
WISC-R, PSIQ			
Mean	107.2	107.1	$t = 0.0$ n.s.
S.D.	11.2	12.1	
WISC-R, FSIQ			
Mean	102.4	102.5	$t = -0.1$ n.s.
S.D.	9.6	11.2	
Reading quotient			
Mean	0.73	0.72	$t = 0.9$ n.s.
S.D.	0.07	0.07	
Reading class			
Tutoring	20	20	$\chi^2 = 0.0$ n.s.
No tutoring	8	7	
Relatives			
Dyslexic	15	21	$\chi^2 = 0.5$ n.s.
Non-dyslexic	10	6	

n.s. = not significant, $P > 0.05$.

were calculated to reflect the interaction between reading speed, and reading accuracy and comprehension. A composite score for 'effective reading accuracy' was calculated by multiplying the percentage of words read correctly by the reading rate. Similarly, 'effective reading comprehension' scores were calculated by multiplying the percentage of correctly answered comprehension questions by the reading rate (Jackson, 1980). Scores are multiplied rather than added together, because they use different units of measurement. Composite reading scores are always a positive number and reflect a child's total reading effort.

T-test comparisons between groups at baseline showed non-significant difference on all but one measure. The placebo group performed significantly better than the Piracetam group at baseline on the percentage of spelling errors in the free-writing test ($t = 2.64$, $P < 0.01$). There were no

other significant baseline differences between groups on the common test battery.

Table III gives the baseline scores for the Piracetam- and placebo-treated groups on the experimental test battery. *T*-test comparisons between groups at baseline again showed no significant difference on all but one measure. The placebo group performed significantly better than the Piracetam group on the Paired Associate Visual Memory Test at baseline ($t = 2.0$, $P < 0.05$). There were no other baseline differences on the experimental test battery.

To assess the effect of drug treatment, the mean change from baseline was calculated for each subject on each measure and then averaged and compared for each treatment group.

Table IV shows the mean change from baseline (posttest-pretest scores) for each measure in the common test battery for the Piracetam and placebo groups. As seen in Fig. 1 for individual reading scores, the Piracetam group demonstrated a statistically significant improvement over the placebo group (at the $P < 0.003$ level of accuracy) on their reading rate from the Gilmore test. The Piracetam group increased their reading speed by almost 8 words per min (+10%) whereas the placebo group decreased by 3 words per min (-4%), leaving a difference of almost 11 words per min between the

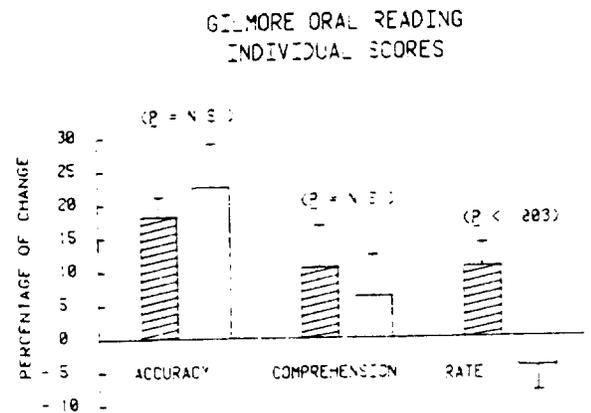


Fig. 1. Percentage of change from baseline (posttest minus pretest scores) made by the Piracetam and placebo treatment groups are shown for the accuracy, comprehension and rate scores of the Gilmore Oral Reading Test.

TABLE II

Baseline scores for the Piracetam and placebo groups on the common test battery.

Test name	Piracetam	Placebo	t-test
Timed oral reading			
Accuracy (grade rating)	3.3	3.1	n.s.
Reading comprehension (grade rating)	4.8	4.9	n.s.
Reading rate (words/min)	76.9	77.6	n.s.
Timed composite reading (5 correct x rate)			
Accuracy	6774.3	6883.9	n.s.
Comprehension	6646.3	6683.3	n.s.
Digit span (scaled score)	7.2	7.2	n.s.
Deles-McKillop syllabication (raw score)	11.6	12.1	n.s.
Words written (total)	41.0	44.1	n.s.
Percent of spelling errors ^b	21.5	12.3	$P < 0.01^a$
Reaction color ^b	42.3	46.7	n.s.
Reaction number ^b	31.4	35.0	n.s.
Reaction symbol ^b	32.4	37.1	n.s.
Reaction object ^b	61.3	65.0	n.s.

^a One-tailed test of significance; ^b reduction in score indicates improvement.

TABLE III

Baseline scores for the Piracetam and placebo groups on the experimental test battery.

Test name	Piracetam	Placebo	t-test
Non-verbal —			
Visual test			
Long ISI's	23.4	23.4	n.s.
Short ISI's	10.9	11.5	n.s.
Verbal test —			
Tables			
Long ISI's	13.5	12.7	n.s.
Short ISI's	7.1	6.8	n.s.
Verbal test —			
Non-verbal auditory			
Long ISI's	19.2	21.4	n.s.
Short ISI's	11.3	13.1	n.s.
Verbal test —			
Verbal associate			
Memory test	18.0	24.5	$P < 0.05^a$
Verbal test —			
Picture test			
P ₁	9.6	9.6	n.s.
P ₂	17.7	18.2	n.s.

^a One-tailed test of significance.

GILMORE ORAL READING
COMPOSITE SCORES
PERCENT CORRECT X WORDS PER MINUTE

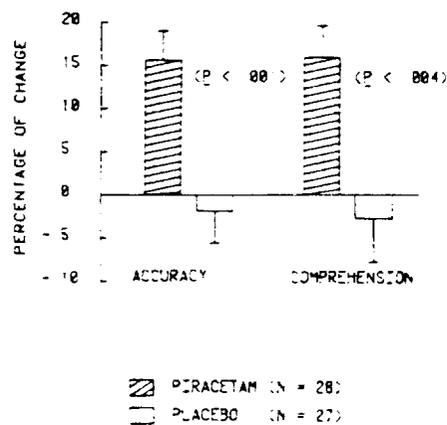


Fig. 2. The Composite Reading scores, derived by multiplying the percentage correct by the number of words read per min. on the Gilmore Oral Reading test are shown for the Piracetam and placebo treatment groups. Percentage change from baseline (posttest minus pretest composite scores) are shown separately for accuracy and comprehension.

TABLE IV

Mean change from baseline score for the Piracetam and placebo groups on the common test battery

Test name	Mean change from base-line (post- pretest score)			d.f.	P ^a
	Piracetam	Placebo	t		
Gilmore oral reading					
Accuracy (grade rating)	0.6	0.7	-0.55	53	0.29
Reading comprehension (grade rating)	0.5	0.3	0.40	53	0.34
Reading rate (words/min)	8.0	-3.4	2.39	53	0.003
Gilmore composite reading (% correct x rate)					
Accuracy	1055.6	-132.1	3.43	53	0.001
Comprehension	1054.0	-189.7	2.98	53	0.003
Digit span (scaled score)	0.9	0.3	1.03	53	0.15
Gates-McKillop syllabication (raw score)	2.2	2.9	-0.83	53	0.21
Wrat spelling (grade rating)	0.2	0.3	-0.49	53	0.31
Words written (total)	6.1	2.2	1.08	51	0.14
Percent of spelling errors ^b	-4.1	7.4	-2.51	51	0.008
Ran color ^b	-1.9	-1.3	-0.30	53	0.38
Ran number ^b	-1.6	-2.5	0.70	53	0.24
Ran letter ^b	-2.1	-3.1	0.55	53	0.29
Ran object ^b	-3.4	-1.3	-0.73	53	0.24

^a A one-tailed test of significance; ^b reduction in score indicates improvement.

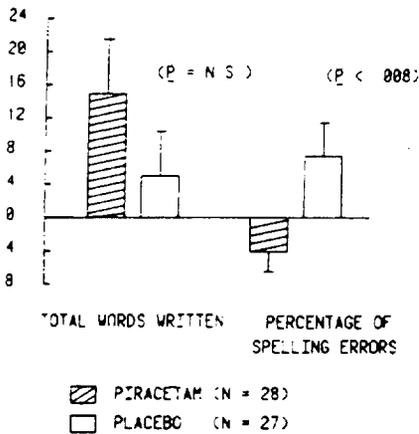
two groups. This increase in reading speed for the Piracetam group was accompanied by improved reading accuracy and comprehension, although similar gains were also found in the placebo group and, thus, cannot be ascribed to drug effect. There were no significant differences between groups on reading accuracy or comprehension.

Composite reading test scores shown in Fig. 2 demonstrate that the Piracetam group significantly improved their effective reading by 16% during the course of the study, on both their effective reading accuracy and comprehension scores, whereas the placebo group decreased on both composite reading scores. This difference in performance between the two treatment groups was highly significant (effective reading accuracy, $t = 3.43$, $P < 0.001$; effective reading comprehension, $t = 2.98$, $P < 0.004$).

A comparison of composite and individual reading scores reveals that although the placebo group did increase in their reading accuracy and comprehension this was accomplished at the expense of their reading speed which decreased, producing very little effective change in their overall reading performance. The Piracetam group, on the other hand, not only improved their reading accuracy and comprehension but also simultaneously was able to increase their reading rate. This resulted in significant gains in their overall reading performance.

Fig. 3 shows that on the Free-Writing Test, both groups showed an increase in the total number of words written. The Piracetam group improved 15% whereas the placebo group showed only a 5% gain, although this difference was not statistically significant. The Piracetam group, how-

WRITING SAMPLE (5 MINUTES)
PERCENTAGE OF CHANGE FROM BASELINE



3. Percentage of change from baseline (posttest minus test scores) made by the Piracetam and placebo treatment groups are shown for the 5-min free-writing sample. The total number of words written in 5 min by each treatment group, as well as the percentage of spelling errors are graphed.

sistent with previous findings, showing no significant medical abnormalities among the Piracetam-treated subjects. The double-blind rating of drug tolerance by the physician indicated that Piracetam was well-tolerated by the children (mean rating = 1.1 (± 0.1), 1 excellent, 4 poor). Except for the one child who suffered from an asthma attack, all the children who were treated with Piracetam remained healthy.

DISCUSSION

These results confirm some of the previous findings of Wilsher et al. (1984) that Piracetam increases the rate of reading and of writing accuracy. The amount of changes found in this present study are comparable to the results obtained by Wilsher. In Wilsher's 8-week study, subjects improved their reading rate by 5%. The amount of change found in the present 12-week study is proportional to Wilsher's data with a 10% improvement in reading rate. This finding, seen in the light of Wilsher's previous data, suggests that the degree of Piracetam-induced improvement in reading and writing may be related to the duration of treatment. However, improvement over time was not assessed directly in the present study. Additional studies will be necessary to establish the effects of dose-duration.

The present study failed to confirm Wilsher's previous findings of drug-improved reading accuracy. The lack of improvement may be due in part to some very large placebo responders; in fact, the largest improvement in reading accuracy (79%) was found in a member of the placebo group.

Substantial changes in reading accuracy and comprehension ability occurred over the course of the study for many of the dyslexic children in both the Piracetam- and placebo-treated groups. This was somewhat unexpected as the reading skills of dyslexic children as a group are known to be difficult to remediate. These marked changes in reading suggest that perhaps the attention and positive reinforcement given to the children in the study, together with the expressed goal of helping them improve their reading skill by using a unique method, a medication, added to the improvement

er, did show significant improvement over the placebo group in the accuracy of their spelling ($P < 0.008$). The Piracetam group decreased the percentage of spelling errors (number of errors/total words written) by 4% whereas the placebo group increased in spelling errors by over 7%. These figures change, however, if one placebo "outlier" subject, who scored well above the rest of the group (83%), is removed from the analysis. Then the placebo group shows only a 4.5% increase in spelling errors ($P < 0.02$). Nevertheless, the trends remain the same. Overall, the Piracetam group not only increased in their writing speed, but also improved in their spelling accuracy. The placebo group's increase in writing speed, however, was offset by additional spelling errors.

Analysis of the mean change from baseline (pretest-posttest scores) for each measure in the experimental test battery for the Piracetam and placebo groups showed that there were no significant differences found between treatment groups on any of the experimental perceptual, memory or language measures given.

Results from laboratory evaluations of blood chemistry, hematology and urinalysis were con-

made. It is of considerable interest that the improvements noted in the placebo-treated group mirror the instructions given to them on reading and writing tests.

On the Gilmore reading test children were told to read the passages as well as they could. Although the children on placebo did improve their reading accuracy and comprehension, as instructed to do, they did so by slowing down their rate of reading (over their baseline reading rate) to achieve this improvement. Thus, they had to lose ground in rate in order to gain it in accuracy and comprehension. The dyslexics on Piracetam, on the other hand, did not need to resort to this strategy to achieve improvement in reading accuracy and comprehension. Rather, they were able to significantly increase their reading rate as well as their accuracy and comprehension over their original baseline performance. That is, they did not have to lose ground in order to gain ground. They gained both speed and improved accuracy and comprehension over the course of the study. The percentages of subjects in the Piracetam and placebo treatment groups showing gains and losses in reading accuracy and rate are shown in Fig. 4.

On the writing sample subjects were told to

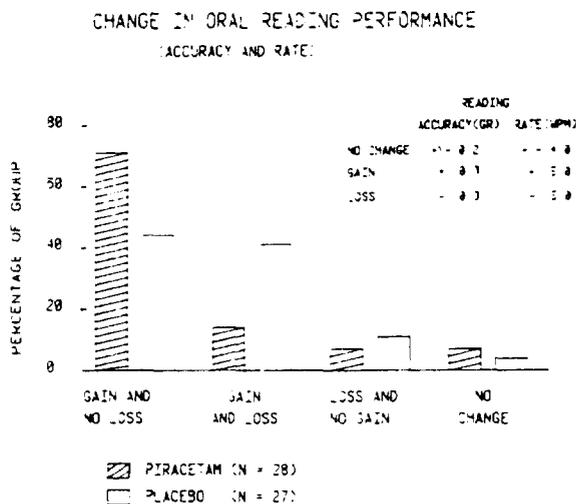


Fig. 4. Composite reading scores, derived by multiplying reading accuracy by rate (words read per min), on the Gilmore Oral Reading test are graphed to show the percentage of the Piracetam and placebo treatment group who made gains and losses in effective reading ability over the course of the study.

write as much as they could during a specified time-period. The placebo-treated children did just that. They increased the number of words written over their original baseline performance. However, as was found in reading, they made this gain at the expense of something else, in this case an increased number of spelling errors. The dyslexics on Piracetam did not show this 'lose-to-gain' pattern. Rather, they increased both the number of words written as well as decreasing the number of spelling errors they made. Even though the only significant difference between groups noted at baseline was the number of spelling errors made, with the Piracetam group making more errors than the placebo group, by the end of the study this order was reversed. The Piracetam group made fewer spelling errors than the placebo group.

Some of the measures in the special perceptual, memory and receptive language studies suffered from ceiling effects, as most of the subjects found these tests to be relatively easy, indicating adequate perceptual, memory and language abilities for their age. Most of the subjects performed at the top of the scale on all subtests of the Repetition Test as well as on all 5 parts of the Token Test, indicating normal perception and receptive language abilities at the onset of the study, hence leaving little room for improvement. Only 4 subjects scored at least one standard deviation below the mean on the Token Test, suggesting that Mattis et al.'s (1975) language disorder syndrome was poorly represented in this dyslexic sample. Subjects also scored highly on perceptual subtests of all 3 Repetition Tests, indicating that they had no difficulty in discriminating between the different auditory or visual stimuli. A subgroup of 19 subjects did have difficulty discriminating between the two computer-synthesized speech syllables /ba/ and /da/ with 40 ms formant transitions. On the Repetition Test however, perhaps due to the very small sample size, a χ^2 -test indicated no significant differences between Piracetam and placebo groups on this test. Contrary to previous findings (Dimond, 1975; Wilsher et al., 1979), subjects taking Piracetam did not demonstrate statistically significant improvements in their short-term and serial memory skills, although some differences between non-verbal and verbal stimuli were found.

sing non-verbal stimuli, treatment groups showed no significant differences on the total number of correct stimulus series recalled in the auditory modality of the Repetition Test. In the visual modality, subjects on placebo found it easier to call the proper sequence of the visual nonsense-paired stimuli, as demonstrated by their improved scores for total correct trials with long ISI's. In contrast, when test items could be verbally rehearsed, as in the Paired Associate Visual Memory Test, which used namable pictures as stimuli, and the Digit Span subtests, the Piracetam-treated group's mean final performance and change from baseline was almost twice that of the placebo group on both tests (Fig. 5). The difference between groups, however, was not statistically significant in either case. These trends toward improved memory for verbally mediated material suggest that a significant improvement in verbal memory scores might be realized with a larger sample size, a longer duration drug trial, or more stringent measures. In addition, Piracetam's effect on memory could be mediated by drug-dosage. A larger (e.g. 4800 mg/day) dosage might produce significant results, since previous findings used a dosage in this range.

MEMORY TESTS

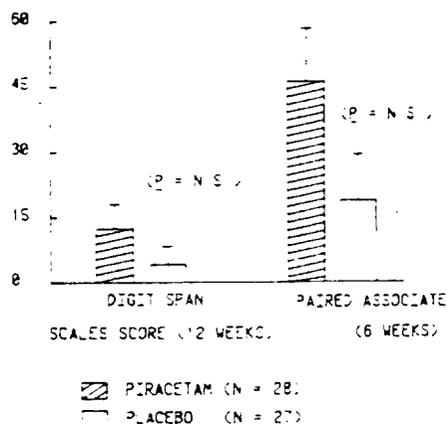


Fig. 5. The percentage of change from baseline (posttest minus pretest scores) made by the Piracetam and placebo treatment groups on two verbal memory tests, digit span and paired associate, are shown.

This pattern of results calls for a much closer examination of the different stages of memory that may be affected by Piracetam. Future studies should examine possible material-specific effects of Piracetam on various memory components, such as working capacity, rehearsal strategies, retrieval, retention and recall. In addition, the questions of dosage-dependent memory effects should be investigated.

Subject selection procedures may also have important implications for drug studies with dyslexic children. Several different subgroups of reading- or language-impaired children, exhibiting different profiles in the areas of perceptual, memory and language functions, have been described (see Tallal and Stark, 1982, for review). Baseline test scores suggest that the majority of reading-impaired children participating in this study did not have significant perceptual, memory or receptive language deficits associated with their reading disability. Thus, it was difficult to assess the potential therapeutic efficacy of Piracetam in treating such deficits in the present study. In order to better assess Piracetam's ability to effect perceptual, memory or receptive language deficits, it will be important to select a group of reading- or language-impaired children who show significant deficits in these areas at baseline testing. Comparisons between different subgroups of reading-impaired children, selected on the basis of specified behavioral profiles, may be an important factor in assessing the effects of nootropils on learning- and language-impaired children.

In summary, Piracetam appears to improve verbal fluency, as demonstrated by increased rates of reading and writing accuracy. These trends encourage a potential role for Piracetam in the clinical remediation of dyslexia, although questions about drug-dosage, duration of treatment, possible interaction with other remedial procedures, differential effects on various subgroups of learning-impaired children and selectivity of drug-response remain unanswered. Some of these issues are being investigated presently.

One final note of caution — given the number of analyses performed, some of the results obtained could be interpreted as chance occurrences. Selective replication of these findings with a differ-

ent group of dyslexic children is necessary to validate these results.

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The Effects of Nootropics on Memory: New Aspects for Basic Research

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Summary

The mechanism through which nootropics of the piracetam type (i.e., piracetam itself and its analogues oxiracetam, pramiracetam, and aniracetam) improve memory is still uncertain. Its elucidation will, however, not only mark an advance in the treatment of cognitive disorders, but also shed light on the basic processes of memory storage. Although the great majority of the findings available so far seem to suggest cholinergic mechanisms, divergent results are obtained whenever parallel experiments are performed with two or more of these compounds. More recent observations indicate that interactions with steroids take place. All four compounds are inactive in adrenalectomized laboratory animals; chemical blockade of the adrenal cortex with aminoglutethimide and pretreatment with epoxymexrenon, a potent mineralocorticoid antagonist, eradicated the memory-enhancing effect of all four substances.

Wirkungen der Nootropika auf das Gedächtnis: Neue Aspekte für die Grundlagenforschung

Es besteht noch immer keine Gewißheit darüber, auf welche Weise die Nootropika des Piracetamtyps (Piracetam und dessen Analogverbindungen Oxiracetam, Pramiracetam und Aniracetam) das Gedächtnis verbessern. Die Klärung dieser Frage würde nicht nur einen Fortschritt bei der Behandlung kognitiver Störungen darstellen, sondern auch die der Gedächtnisspeicherung zugrundeliegenden Vorgänge erhellen. Obwohl die große Mehrzahl der bislang verfügbaren Befunde auf cholinergische Mechanismen hinweisen, werden widersprüchliche Ergebnisse erzielt, sobald parallele Experimente mit zwei oder mehreren dieser Verbindungen durchgeführt werden. Neuere Beobachtungen scheinen auf Wechselwirkungen mit Steroiden hinzuweisen: alle vier Verbindungen sind bei adrenalectomierten Labortieren unwirksam; sowohl eine chemische Blockierung der Nebennierenrinde durch Aminoglutethimid als auch eine Vorbehandlung mit Epoxymexrenon (einem potenten Mineralokortikoidantagonisten) blockierte die gedächtnisverbessernde Wirkung aller vier Substanzen.

The elucidation of biochemical bases and the regulation of memory is one of the greatest challenges in neurobiology. It is therefore hardly surprising that every year hundreds of papers are published dealing with some particular facet of memory. Our knowledge of the subject matter increases almost daily, but more in width than in depth. We now know of many transmitters, receptors, and modulators that play some part in memory processing; but each new finding is soon relativized by the realization that it is not generally valid, but simply sometimes true under certain limiting conditions. In this field, progress tends to follow the discovery of a new pharmacological tool, e.g., a new specific receptor blocker or activator, or an enzyme inhibitor. Consequently, the prevalent method in efforts to identify the mechanisms and the neuronal networks operative in memory processing relies on the testing of mechanistically specific preparations for potential effects on memory in animal models. For example, the NMDA blockers (MK 801, AP5, and AP7) that recently became available encouraged studies of the influence of NMDA blockade on

learning and memory and speculation about the possible involvement of this type of receptor in memory processing (Morris et al., 1986). In the meantime, it has become evident that the responses seen under NMDA blockade only apply in certain circumstances and to certain processes of memory (Mondadori et al., 1989). Thus, while the assortment of transmitters involved in memory processing increases, that does nothing to alter the fact that almost every pharmacological manipulation of the CNS has some influence on certain, though not all, forms of learning and memory (Mondadori, 1987).

The opposite way of seeking insight into the processes of memory consists in characterizing biochemically the substances known to affect memory, and then attempting to correlate certain components of their biochemical profile with their effect on memory. The memory-blocking effects of certain antibiotics such as puromycin, anisomycin, and cycloheximide, for instance, inspired a very large number of studies of the possible relations between inhibition of protein synthesis – scientifically the most appealing aspect – and memory (for a review see, for example, Davies and Squire, 1984). The underlying mode of action has, however, always remained conjectural, because these antibiotics exert many other known

effects (see, for example, *Flexner and Goodman, 1975; Rainow et al., 1979*) and quite probably just as many other unknown effects that might equally well be responsible for the disturbance of memory, or at least contribute to it. The possibility that the known biochemical effect under scrutiny may not be responsible for the observed effect on memory, or that that effect may be due to the interplay of several discrete effects, must always be taken into consideration, even in studies using the abovementioned "specific tools": failure to do so makes false conclusions unavoidable.

One practicable and valid approach to the experimental investigation of mechanisms underlying memory storage, or the regulation of memory storage, may be afforded by the piracetam-like nootropics. These are interesting preparations, above all because they exert distinct, positive effects on various manifestations of memory, yet provoke few or no side-effects. The fact that they have so far been found to display scarcely any effects in most of the traditional assays used in biochemistry laboratories may make them appear all the more or all the less attractive, depending on the viewpoint of the observer. If, however, as has already been suggested (*Giurgea, 1973, 1982*), they do act specifically on cognitive processes or on the structures and mechanisms responsible for cognitive processes, then the elucidation of their mode of action might represent a very significant advance. The following remarks, illustrated by a selection of experimental observations, will be concerned with the progress made to date along this line of research and the possibilities emerging from it.

Neuropharmacological findings

The first experimentally demonstrable effect of piracetam, the prototype substance, on the CNS was inhibition of central nystagmus in the rabbit (*Giurgea et al., 1967*). In retrospect, however, the vast majority of the experimental pre-clinical findings seem to be indicative of effects on cognitive processes, in particular on learning and memory in a very wide variety of forms. Piracetam, for instance, diminishes the disruptive effect of a cerebral electroshock on the orientation of rats in a water maze (*Giurgea and Mouravieff Lesuisse, 1972*). Many other authors have also observed anti-amnesic effects of piracetam and related substances: distinct protective effects against the disturbance of memory following cerebral electroshocks in passive- and active-avoidance tests on mice and rats were noted by *Cumin et al. (1982)* after treatment with aniracetam and piracetam, and by *Mondadori et al. (1986)* after treatment with oxiracetam and piracetam. *Sara (1980)* observed similar responses to etiracetam. *Butler et al. (1987)* described anti-amnesic effects of a whole series of piracetam analogues, including pramiracetam. Numerous observations have also been made of direct positive effects on learning and memory: aniracetam and piracetam (*Yamada et al., 1985; Wolthuis, 1971*), etiracetam (*Sara, 1980*) and oxiracetam (*Mondadori et al., 1986*) were found to exert direct effects on acquisition and retention performance in rats and mice in passive- and active-avoidance paradigms; pramiracetam increased the acquisition rate in a 16-armed radial maze (*Murray and Fibiger, 1986*) and in a place navigation test (Morris maze) (*Poschel et al., 1985*); positive effects of aniracetam were demonstrated in matching-to-sample tests (*Pontecorvo et al., 1985*). All these findings are supplemented and indirectly supported by observations of a facilitating effect of piracetam on inter-

hemispherical transfer (*Buresova and Bures, 1976*), on augmentation of paradoxical sleep in rats (*Wetzel, 1985*), on increased theta power in the hippocampal EEG, and on a reduction in the power of cortical slow waves (*Poschel et al., 1985*).

Interesting and biochemically inexplicable observations indicate that both piracetam and oxiracetam intensify the anticonvulsive effects of anti-epileptics such as carbamazepine (*Mondadori et al., 1984; Mondadori and Schmutz, 1986; Hawkins and Mellanby, 1986*).

Biochemical effects of piracetam-like nootropics

There are relatively few data available on the biochemical effects of the piracetam-like nootropics. For a long time, the observation by *Nickolson and Wolthuis (1976)* that piracetam stimulates adenylate kinase activity was the sole measured biochemical effect. *Woelk (1979)* then showed that piracetam increased the incorporation of ^{32}P in phosphatidylinositol and phosphatidyl chloride in glia cells and neurons. *Grau et al. (1987)* reported an increase in glucose utilization under hypoxic conditions and accelerated recovery of the EEG. *Poschel et al. (1983)* demonstrated that neither piracetam nor pramiracetam bound to muscarinic cholinergic receptors; nor did binding occur in a dopamine assay with haloperidol. The uptake of GABA and serotonin was not affected by piracetam or by pramiracetam. *Pugsley et al. (1983)* found no evidence of activity in traditional pharmacological assays. No effects were detectable on the concentrations of noradrenaline, dopamine, 5-HT, or 5-HIAA in the cortex or midbrain of the rat. At very high doses (200 mg/kg i.p.), piracetam increased striatal HV without affecting DA levels, indicating that it augments the turnover of DA. Pramiracetam, however, did not increase DA turnover. Receptor assays revealed no affinity of either piracetam or pramiracetam for DA, muscarinic, alpha 1,2- and beta 1,2-adrenergic, 5-HT₁, 5-HT₂, GABA, adenosine, and benzodiazepine receptors. On the other hand, it was shown (*Pugsley et al., 1983; Shih and Pugsley, 1985*) that pramiracetam increased high-affinity choline uptake into hippocampal synaptosomes. The effective doses were 44 and 88 mg/kg i.p.: neither higher nor lower doses were active. Surprisingly enough, piracetam at 100 and 300 mg/kg and aniracetam between 10 and 200 mg/kg both had no effect on high-affinity choline uptake. These results with piracetam are slightly at variance with the observations reported by *Pedata et al. (1984)*. These latter authors found that both oxiracetam and piracetam exerted positive effects on high-affinity choline uptake in the rat cortex and hippocampus. The discrepancy may have been due to the timing of the determinations.

The above cholinergic effects are supplemented by findings made by *Spignoli and Pepeu (1986)* which demonstrated that oxiracetam prevented the decrease in the acetylcholine content of the cortex and hippocampus induced by cerebral electroshock treatment (piracetam was inactive). Further observations show that piracetam reduces scopolamine-induced amnesia (*Piercey et al., 1987*) and, according to one interesting report (*Pilch and Müller, 1988*), elevates the muscarinic cholinergic receptor density in the frontal cortex of aged rats.

Taken as a whole, this selection of findings might at first glance give the impression that the piracetam-like nootropics act by way of cholinergic mechanisms. This conclusion is all the more plausible because there is a very large body of literature on the significance of cholinergic mechanisms in learning and memory (see, for example, *Drachman, 1978; Bartus, 1980*). On closer scrutiny of the available results, however, it becomes plainly evident that there is not one single report in which several piracetam-like nootropics tested concurrently have actually been found to produce the same effects. The observed effects, insofar as they have been studied, are not common to all nootropics (*Shih and Pugsley, 1985; Spignoli and Pepeu, 1986*). Considering their similarity in structure as well as in their pharmacological profiles of activity on learning and memory, it seems quite likely (or at least quite possible) that all representatives of this class modulate memory via the same mechanism. Failing any definite evidence to the contrary, this is certainly reason enough to continue the search for one common mechanism of action shared by all the substances belonging to this class.

Are steroids involved in the mediation of nootropic effects?

Even if allowance is made for individual variations dependent on their particular pharmacokinetics, it is still true to say that whenever neuropharmacological agents are administered systemically the brain is flooded with active substance. One may well wonder what chance there is of improving the performance of such a complex and finely tuned organ by so crude a method. On the other hand, there are indications pointing to the existence of endogenous physiological mechanisms that can, under certain circumstances, heighten the performance of the memory: flash-bulb memories (see e.g. *Brown and Kulik, 1977*), i.e. abnormally sharp recollections of certain events mostly associated with highly emotional states, are a good example. If such mechanisms do in fact exist, then they obviously deserve to be regarded as potential targets for pharmacological interventions. In this context, account must also be taken of the possibility that the selective physiological activation of certain neuronal mechanisms in the brain proceeds via peripheral mediators. Nor can one simply dismiss the further possibility that the memory facilitation induced by nootropic drugs may come about through modulation of such processes. Since the pituitary-adrenal axis plays a significant part in emotional states, it seemed important to find out whether piracetam-like nootropics retained their activities in adrenalectomized animals. They did not: oxiracetam, piracetam, aniracetam, and pramiracetam showed no memory-enhancing effects in adrenalectomized mice (*Mondadori and Petschke, 1987*). A series of further studies proved that the blockade of their activities was not an effect of dosage: even significantly higher doses of the nootropics were ineffective after adrenalectomy (*Mondadori, Ducret and Petschke, 1989, in press*); Accordingly, the next question was whether the products of the adrenal medulla or of the cortex are the critical components in the activity of nootropics. To answer that question the animals were pretreated with aminoglutethimide, which is an inhibitor of several cytochrome-P450-mediated hydroxylation steps in steroid biosynthesis in the adrenal cortex: e.g. 18-hydroxylation of corticosterone (i.e. aldosterone biosynthesis), side-chain cleavage (i.e. conversion of cholesterol to preg-

nenolone), and 11-hydroxylation (i.e. glucocorticoid biosynthesis) (for a review see *Santen et al., 1981*). Exactly as adrenalectomy, this pretreatment rendered the four piracetam-like nootropics inactive. Aminoglutethimide itself had no effects on the retention performance of the mice. These data provided the first indication of the involvement of products of the adrenal cortex in the mediation of the effects of the piracetam-like nootropics. It must be conceded that aminoglutethimide is not entirely devoid of effects on the adrenal medulla: increases in catecholamine levels have been observed (*Duckworth and Kitabchi, 1971*). To exclude this possibility, mice were pretreated with epoxymexrenon. Pretreatment with this specific mineralocorticoid antagonist (*de Gasparo et al., 1987*) gave similar results: the memory-enhancing effects of the piracetam-like nootropics were completely blocked; and again the drug itself had no effect on memory. These findings prove that steroids can play a role in the mediation of nootropic effects. Furthermore, these were the first pharmacological experiments in which all four prototype substances behaved in exactly the same way. (*Mondadori et al, 1989, in press*)

It is interesting to note that certain other substances also lose their memory-modulating activities in the absence of the adrenals: e.g. amphetamine and hydroxyamphetamine (*Martinez et al., 1980*) and vasopressin (*Borellet et al., 1983*). However, the effects of these drugs appear to be dependent on the function of the adrenal medulla.

Although autoradiographic studies of the rat brain give the impression that oxiracetam does not readily penetrate the blood-brain barrier (*Mondadori and Petschke, 1987*), the above-mentioned findings as a whole cannot be taken as evidence that the piracetam-like nootropics act peripherally. Amongst various other possible mechanisms (see also *Mondadori and Petschke, 1987*), it is conceivable that activation of steroid receptors in the brain may be a prerequisite for the efficacy of the piracetam-like nootropics; in other words, steroids may mediate the action of nootropics on memory. The converse is equally plausible, i.e. that these preparations directly or indirectly modulate the effects of certain steroids on memory. There is ample evidence to show that steroids can exert an influence on memory (see for example, *Micheau et al., 1985; Bohus and de Kloet, 1981*). A new facet emerging from the authors' experiments is that aldosterone-receptor-mediated activity may play a part in memory processing or its regulation.

How these effects come about is unclear; but extrapolation from findings on the peripheral effects of steroids discloses a particularly fascinating aspect. It has been demonstrated that in various organs steroids affect specific gene expression by modulating the rate of transcription of a specific set of genes (*Yamamoto, 1985; Schütz, 1988*). It would therefore be extremely interesting to know whether piracetam-like nootropics can exert direct effects on gene transcription, or modulate the action of steroids on gene transcription. There are already a number of publications on the effects of steroids on protein synthesis (*Arenander and Vallis, 1980; Eigen et al., 1980; Nesiler et al., 1981; Mileusnic et al., 1986*). Since it is known that protein synthesis plays an important part in the formation of memory traces (for a review see *Davies and*

Squire, 1984), it is conceivable that nootropics may improve memory via modulation of protein synthesis.

The present observations, which suggest that steroids may be involved in the mediation of the nootropic action of the piracetam derivatives, do not contradict the reported findings on their cholinergic effects, since the possibility that steroids may interact with cholinergic mechanisms cannot simply be dismissed.

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Picamilon appears to be more effective than Hydergine or vinpocetin in improving blood flow to the cerebral vessels. Picamilon readily crosses the blood-brain barrier to protect neurons against the effects of diminished oxygen flow. It also produces cognitive-enhancing effects.

The combination of these effects provides an entirely new method of dealing safely with several causes of neurological aging. Picamilon is approved as a pharmaceutical product in Russia, but is really a vitamin-like compound consisting of a niacin analog (n-nicotinoyl) uniquely bonded to GABA (gamma aminobutyric acid). When niacin is bound to GABA, it creates a molecule that readily penetrates the blood-brain barrier to enhance cerebral and peripheral circulation. What enables picamilon to work so well is the synergism between the niacin and GABA molecules.

Suggested dose: One tablet, two to three times a day.
If cognitive enhancing results do not occur in 30 days, double the dose.

PIRACETAM

Piracetam is a derivative of the amino acid GABA that increases the sensitivity of receptors in the brain involved in memory and learning. Piracetam is called a nootropic drug because of its ability to enhance the mind. Studies in both animals and humans have demonstrated that Piracetam can improve memory, increase attention and cognition, improve spatial learning, and enhance motor mechanisms. Piracetam is one of the most popular "smart drugs" that is used to increase intelligence, information processing ability, concentration, memory, and creativity. It has been shown to harmonize and synchronize the spheres of the brain by anchoring information within the brain.

Suggested dose: Piracetam should be used in doses ranging from 1600 to 2400 mg a day taken first thing in the morning.

RETIN A

Retin A is a highly publicized vitamin A derivative that stimulates skin cell renewal, increasing the creation of youthful cells at the skin's surface. Retin A may produce side effects such as minor irritation. People using Retin A should stay out of the sun and use a sunblock for normal sunlight exposure, because Retin A increases skin sensitivity to sunlight.

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TITLE: Piracetam-induced changes in the functional activity of neurons as a possible mechanism for the effects of nootropic agents.

AUTHOR: Verbnyi YaI; Derzhiruk LP; Mogilevskii AYa

AUTHOR AFFILIATION: Physical-Technical Low Temperature Institute, National Academy of Sciences of Ukraine, Khar'kov.

SOURCE: Neurosci Behav Physiol 1996 Nov-Dec;26(6):507-15

NLM CIT. ID: 97173873

ABSTRACT: Studies were carried out on the effects of piracetam (4-20 mM) on the electrical activity of identified neurons in the isolated central nervous system of the pond snail in conditions of single-electrode intracellular stimulation and recording. Piracetam-induced changes were seen in 60-70% of the neurons studied. Different parameters showed different sensitivities to piracetam: the most frequent changes were in the action potential generation threshold, the slope and shape of the steady-state voltage-current characteristics of neuron membranes, and the appearance of piracetam-induced transmembrane ion currents. Nifedipine and cadmium ions, both of which are calcium channel blockers, generally reversed or weakened the effects of piracetam on the changes seen in test cells. This indicates that the effects of piracetam result from its action on calcium channels; selective changes in calcium channels may determine which piracetam-induced effects appear at the cellular level. It is hypothesized that the piracetam-sensitive cellular plasticity mechanisms may make a significant contribution to its nootropic action at the behavioral level.

MAIN MESH SUBJECTS: Lymnaea/*PHYSIOLOGY
Neurons/*DRUG EFFECTS
Nootropic Agents/ANTAGONISTS & INHIB/*PHARMACOLOGY
Piracetam/ANTAGONISTS & INHIB/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: **Animal**
Cadmium/PHARMACOLOGY
Calcium Channel Blockers/PHARMACOLOGY
Electrophysiology
Ganglia, Invertebrate/CYTOLOGY/PHYSIOLOGY
In Vitro
Membrane Potentials/DRUG EFFECTS/PHYSIOLOGY
Nifedipine/PHARMACOLOGY
Parietal Lobe/CYTOLOGY/DRUG EFFECTS
Patch-Clamp Techniques

PUBLICATION TYPES: **JOURNAL ARTICLE**

LANGUAGE: **Eng**

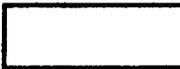
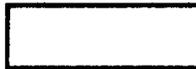
REGISTRY NUMBERS: **0 (Calcium Channel Blockers)**

0 (Nootropic Agents)

21829-25-4 (Nifedipine)

7440-43-9 (Cadmium)

7491-74-9 (Piracetam)



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TITLE: Nootropic drugs and brain cholinergic mechanisms.

AUTHOR: Pepeu G; Spignoli G

AUTHOR AFFILIATION: Department of Preclinical and Clinical Pharmacology, University of Florence, Italy.

SOURCE: Prog Neuropsychopharmacol Biol Psychiatry 1989;13 Suppl:S77-88

NLM CIT. ID: 90139561

ABSTRACT: 1. This review has two aims: first, to marshal and discuss evidences demonstrating an interaction between nootropic drugs and brain cholinergic mechanisms; second, to define the relationship between the effects on cholinergic mechanisms and the cognitive process. 2. Direct or indirect evidences indicating an activation of cholinergic mechanisms exist for pyrrolidinone derivatives including piracetam, oxiracetam, aniracetam, pyroglutamic acid, tenilsetam and pramiracetam and for miscellaneous chemical structures such as vinpocetine, naloxone, ebitatide and phosphatidylserine. All these drugs prevent or revert scopolamine-induced disruption of several learning and memory paradigms in animal and man. 3. Some of the pyrrolidinone derivatives also prevent amnesia associated with inhibition of acetylcholine synthesis brought about by hemicholinium. Oxiracetam prevents the decrease in brain acetylcholine and amnesia caused by electroconvulsive shock. Oxiracetam, aniracetam and pyroglutamic acid prevent brain acetylcholine decrease and amnesia induced by scopolamine. Comparable bell-shaped dose-effect relationships result for both actions. Phosphatidylserine restores acetylcholine synthesis and conditioned responses in aging rats. 4. The mechanisms through which the action on cholinergic systems might take place, including stimulation of the high affinity choline uptake, are discussed. The information available are not yet sufficient to define at which steps of the cognitive process the action on cholinergic system plays a role and which are the influences of the changes in cholinergic function on other neurochemical mechanisms of learning and memory.

MAIN MESH SUBJECTS: Acetylcholine/*METABOLISM
Brain/DRUG EFFECTS/*METABOLISM
Psychotropic Drugs/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Animal Receptors, Cholinergic/DRUG EFFECTS/METABOLISM Scopolamine/PHARMACOLOGY Synapses/DRUG EFFECTS/PHYSIOLOGY

PUBLICATION TYPES: JOURNAL ARTICLE REVIEW REVIEW, TUTORIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Receptors, Cholinergic) 51-34-3 (Scopolamine) 51-84-3 (Acetylcholine)



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TITLE: Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice.

AUTHOR: Pilch H; Muller WE

AUTHOR AFFILIATION: Psychopharmacological Laboratory, Central Institute of Mental Health, Mannheim, Federal Republic of Germany.

SOURCE: Psychopharmacology (Berl) 1988;94(1):74-8

NLM CIT. ID: 88158509

ABSTRACT: Chronic treatment (2 weeks) with piracetam (500 mg/kg, once daily PO) elevated m-cholinoceptor density in the frontal cortex of aged (18 months) female mice by about 30-40%, but had no effect on m-cholinoceptor density in the frontal cortex of young (4 weeks) mice. The effect of piracetam on m-cholinoceptor density as determined by the specific binding of tritiated QNB was not affected by concomitant daily treatment with either choline (200 mg/kg) or scopolamine (4 mg/kg). It is concluded that the effect of piracetam on m-cholinoceptor density could explain the positive effects which have been reported for combinations of cholinergic precursor treatment with piracetam on memory and other cognitive functions in aged experimental animals and patients and could also represent part of the possible mechanism of action of piracetam alone.

MAIN MESH SUBJECTS: Aging/*METABOLISM
Cerebral Cortex/DRUG EFFECTS/*METABOLISM
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY
Receptors, Muscarinic/*DRUG EFFECTS

ADDITIONAL MESH SUBJECTS: Animal
Atropine/PHARMACOLOGY
Female
Male
Mice
Oxotremorine/PHARMACOLOGY
Quinuclidinyl Benzilate/PHARMACOLOGY
Scopolamine/PHARMACOLOGY

**PUBLICATION JOURNAL ARTICLE
TYPES:**

LANGUAGE: Eng

**REGISTRY
NUMBERS:** 0 (Pyrrolidinones)
0 (Receptors, Muscarinic)
51-34-3 (Scopolamine)
51-55-8 (Atropine)
6581-06-2 (Quinuclidinyl Benzilate)
70-22-4 (Oxotremorine)
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Stroke

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TITLE: Treatment of acute ischemic stroke with piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group.

AUTHOR: De Deyn PP; Reuck JD; Deberdt W; Vlietinck R; Orgogozo JM

AUTHOR AFFILIATION: Department of Neurology, Middelheim Hospital, Antwerp, Belgium.

SOURCE: Stroke 1997 Dec;28(12):2347-52

NLM CIT. ID: 98074088

ABSTRACT:

BACKGROUND AND PURPOSE: Piracetam, a nootropic agent with neuroprotective properties, has been reported in pilot studies to increase compromised regional cerebral blood flow in patients with acute stroke and, given soon after onset, to improve clinical outcome. We performed a multicenter, randomized, double-blind trial to test whether piracetam conferred benefit when given within 12 hours of the onset of acute ischemic stroke to a large group of patients. **METHODS:** Patients received placebo or 12 g piracetam as an initial intravenous bolus, 12 g daily for 4 weeks and 4.8 g daily for 8 weeks. The primary end point was neurologic outcome after 4 weeks as assessed by the Orgogozo scale. Functional status at 12 weeks as measured by the Barthel Index was the major secondary outcome. CT scan was performed within 24 hours of the onset of stroke but not necessarily before treatment. Analyses based on the intention to treat were performed in all randomized patients (n = 927) and in an "early treatment" population specified in the protocol as treatment within 6 hours of the onset of stroke but subsequently redefined as less than 7 hours after onset (n = 452). **RESULTS:** In the total population, outcome was similar with both treatments (the mean Orgogozo scale after 4 weeks: piracetam 57.7, placebo 57.6; the mean Barthel Index after 12 weeks: piracetam 55.8, placebo 53.1). Mortality at 12 weeks was 23.9% (111/464) in the piracetam group and 19.2% (89/463) in the placebo group (relative risk 1.24, 95% confidence interval, 0.97 to 1.59; P = .15). Deaths were fewer in the piracetam group in those patients in the intention-to-treat population admitted with primary hemorrhagic stroke. Post hoc analyses in the early treatment subgroup showed differences favoring piracetam relative to placebo in mean Orgogozo scale scores after 4 weeks (piracetam 60.4, placebo 54.9; P = .07) and Barthel Index scores at 12 weeks (piracetam 58.6, placebo 49.4; P = .02). Additional analyses within this subgroup, confined to 360 patients with moderate and severe stroke (initial Orgogozo scale score < 55), showed significant improvement on piracetam in both outcomes (P < .02). **CONCLUSIONS:** Piracetam did not influence outcome when given within 12 hours of the onset of acute ischemic stroke. Post hoc analyses suggest that piracetam may confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate and severe degree. A randomized, placebo-controlled, multicenter study, the Piracetam Acute Stroke Study II (PASS II) will soon begin.

**MAIN MESH
SUBJECTS:**

Cerebral Ischemia/*DRUG THERAPY/MORTALITY
Cerebrovascular Disorders/*DRUG THERAPY/MORTALITY
Neuroprotective Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Nootropic Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS: Acute Disease
Aged
Aged, 80 and over
Double-Blind Method
Female
Human
Male
Middle Age
Support, Non-U.S. Gov't
Survival Analysis
Treatment Outcome

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE
MULTICENTER STUDY
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Neuroprotective Agents)
0 (Nootropic Agents)
7491-74-9 (Piracetam)



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dyslexia



TITLE: The effects of piracetam in children with ~~dyslexia~~

AUTHOR: Di Ianni M; Wilsher CR; Blank MS; Conners CK; Chase CH; Funkenstein HH; Helfgott E; Holmes JM; Lougee L; Maletta GJ; et al

SOURCE: J Clin Psychopharmacol 1985 Oct;5(5):272-8

NLM CIT. ID: 86009005

ABSTRACT: Following previous research which suggests that piracetam improves performance on tasks associated with the left hemisphere, a 12-week, double-blind, placebo-controlled study of developmental dyslexics was conducted. Six study sites treated 257 dyslexic boys between the ages of 8 and 13 years who were significantly below their potential in reading performance. Children were of at least normal intelligence, had normal findings on audiologic, ophthalmologic, neurologic, and physical examination, and were neither educationally deprived nor emotionally disturbed. Piracetam was found to be well tolerated in this study population. ~~Children treated with piracetam showed improvements in reading speed.~~ No other effects on reading were observed. In addition, ~~improvement in auditory sequential short-term memory~~ was observed in those piracetam-treated patients who showed relatively poor memory at baseline. It is suggested that longer term treatment with piracetam may result in ~~additional improvements~~.

MAIN MESH SUBJECTS: Dyslexia/*DRUG THERAPY
Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE
Pyrrolidinones/*THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS: Adolescence
Child
Clinical Trials
Depression/CHEMICALLY INDUCED
Human
Male
Memory Disorders/DRUG THERAPY
Memory, Short-Term
Support, Non-U.S. Gov't

PUBLICATION TYPES: CLINICAL TRIAL
CONTROLLED CLINICAL TRIAL
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Pyrrolidinones)
7491-74-9 (Piracetam)





TITLE: Piracetam and **dyslexia**: effects on reading tests.

AUTHOR: Wilsher CR; Bennett D; Chase CH; Conners CK; DiIanni M; Feagans L; Hanvik LJ; Helfgott E; Koplewicz H; Overby P; et al

SOURCE: J Clin Psychopharmacol 1987 Aug;7(4):230-7

NLM CIT. ID: 87308901

ABSTRACT: Previous research has suggested that **dyslexics treated with piracetam have shown improvements in reading skills, verbal memory and verbal conceptualizing ability, feature analysis and processing of letter-like stimuli.** Two hundred twenty-five dyslexic children between the ages of 7 years 6 months and 12 years 11 months whose reading skills were significantly below their intellectual capacity were enrolled in a multicenter, 36-week, double-blind, placebo-controlled study. Children of below average intelligence, with abnormal findings on audiologic, ophthalmologic, neurologic, psychiatric, and physical examinations, who were emotionally disturbed or educationally deprived and who had recently been treated with psychoactive medication were excluded from the trial. **Piracetam was well tolerated, with no serious adverse clinical or laboratory effects reported. Piracetam-treated children showed significant improvements in reading ability (Gray Oral Reading Test) and reading comprehension (Gilmore Oral Reading Test).** Treatment effects were evident after 12 weeks and were sustained for the total period (36 weeks).

MAIN MESH SUBJECTS: Dyslexia/*DRUG THERAPY/PSYCHOLOGY
Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE
Pyrrolidinones/*THERAPEUTIC USE
*Reading

ADDITIONAL MESH SUBJECTS: Child
Clinical Trials
Double-Blind Method
Female
Human
Male
Random Allocation
Support, Non-U.S. Gov't

PUBLICATION TYPES: CLINICAL TRIAL
CONTROLLED CLINICAL TRIAL
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Pyrrolidinones)
7491-74-9 (Piracetam)



cognition



TITLE: An overview of pharmacologic treatment of **cognitive decline** in the aged.

AUTHOR: Reisberg B; Ferris SH; Gershon S

SOURCE: Am J Psychiatry 1981 May;138(5):593-600

NLM CIT. ID: 81204750

ABSTRACT: The most widely known substances that have been investigated for treating cognitive deterioration in the aged are cerebral vasodilators, Gerovital H3, psychostimulants, "nootropics," neuropeptides, and neurotransmitters. The rationale for the choice of specific agents has shifted as our conceptions regarding the origins of cognitive decline have changed; we now know that most cognitive deterioration occurs independently of arteriosclerotic vascular changes. Substances currently being investigated because of their effects on brain electrophysiology, on neurohumoral processes, or on central neurotransmitters show promise.

MAIN MESH SUBJECTS: Cognition Disorders/*DRUG THERAPY

ADDITIONAL MESH SUBJECTS: Anticoagulants/THERAPEUTIC USE
Clinical Trials
Comparative Study
Dihydroergotoxine/THERAPEUTIC USE
Human
Hyperbaric Oxygenation
Methylphenidate/THERAPEUTIC USE
Parasympathomimetics/THERAPEUTIC USE
Peptides/THERAPEUTIC USE
Piracetam/THERAPEUTIC USE
Procaine/THERAPEUTIC USE
Support, U.S. Gov't, P.H.S. Vasodilator Agents/THERAPEUTIC USE

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE
REVIEW

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Anticoagulants)
0 (Parasympathomimetics)
0 (Peptides)
0 (Vasodilator Agents)
11032-41-0 (Dihydroergotoxine)
113-45-1 (Methylphenidate)
12663-50-2 (Gerovital H3)
59-46-1 (Procaine)
7491-74-9 (Piracetam)

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TITLE: Profound effects of combining choline and piracetam on ~~memory~~ **enhancement** and cholinergic function in aged rats.

AUTHOR: Bartus RT; Dean RL 3d; Sherman KA; Friedman E; Beer B

SOURCE: Neurobiol Aging 1981 Summer;2(2):105-11

NLM CIT. ID: 82058347

ABSTRACT:

In an attempt to gain some insight into possible approaches to reducing age-related memory disturbances, aged Fischer 344 rats were administered either vehicle, choline, piracetam or a combination of choline or piracetam. Animals in each group were tested behaviorally for retention of a one trial passive avoidance task, and biochemically to determine changes in choline and acetylcholine levels in hippocampus, cortex and striatum. Previous research has shown that rats of this strain suffer severe age-related deficits on this passive avoidance task and that memory disturbances are at least partially responsible. Those subjects given only choline (100 mg/kg) did not differ on the behavioral task from control animals administered vehicle. Rats given piracetam (100 mg/kg) performed slightly better than control rats (p less than 0.05), but rats given the piracetam/choline combination (100 mg/kg of each) exhibited retention scores several times better than those given piracetam alone. In a second study, it was shown that twice the dose of piracetam (200 mg/kg) or choline (200 mg/kg) alone, still did not enhance retention nearly as well as when piracetam and choline (100 mg/kg of each) were administered together. Further, repeated administration (1 week) of the piracetam/choline combination was superior to acute injections. Regional determinations of choline and acetylcholine revealed interesting differences between treatments and brain area. Although choline administration raised choline content about 50% in striatum and cortex, changes in acetylcholine levels were much more subtle (only 6-10%). No significant changes following choline administration were observed in the hippocampus. However, piracetam alone markedly increased choline content in hippocampus (88%) and tended to decrease acetylcholine levels (19%). No measurable changes in striatum or cortex were observed following piracetam administration. The combination of choline and piracetam did not potentiate the effects seen with either drug alone, and in certain cases the effects were much less pronounced under the drug combination. These data are discussed as they relate to possible effects of choline and piracetam on cholinergic transmission and other neuronal function, and how these effects may reduce specific memory disturbances in aged subjects. The results of these studies demonstrate that the effects of combining choline and piracetam are quite different than those obtained with either drug alone and support the notion that in order to achieve substantial efficacy in aged subjects it may be necessary to reduce multiple, interactive neurochemical dysfunctions in the brain, or affect activity in more than one parameter of a deficient metabolic pathway.

**MAIN MESH
SUBJECTS:**

*Aging
Choline/ANALYSIS/*PHARMACOLOGY
Memory/*DRUG EFFECTS
Parasympathetic Nervous System/*PHYSIOLOGY
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Acetylcholine/ANALYSIS/SECRETION
Animal
SUBJECTS: Brain Chemistry/DRUG EFFECTS
Male
Rats
Rats, Inbred F344

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Pyrrolidinones)
51-84-3 (Acetylcholine)
62-49-7 (Choline)
7491-74-9 (Piracetam)

National Library of Medicine: IGM Full Record Screen



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TITLE: Piracetam-induced facilitation of interhemispheric transfer of visual information in rats.

AUTHOR: Buresova O; Bures J

SOURCE: Psychopharmacologia 1976;46(1):93-102

NLM CIT. ID: 76152798

ABSTRACT: The effect of Piracetam (UCB 6215, 2-pyrrolidoneacetamide) on learning mediated by transcommissural information flow was studied in hooded rats. Acquisition of monocular pattern discrimination was faster in drug-treated rats (100 mg/kg, 30 min before training) than in untreated controls. Subsequent relearning with one hemisphere functionally eliminated by cortical spreading depression showed that the strength of the primary engram formed under Piracetam in the hemisphere contralateral to the trained eye remained unaffected but that the secondary trace (in the ipsilateral hemisphere) was considerably improved and almost equalled the primary one (savings increased from 20-30% to 50-60%). Learning with uncrossed optic fibers was unaffected by the drug. Interhemispheric transfer of lateralized visual engrams acquired during functional hemidecortication was facilitated by Piracetam administration preceding the five transfer trials performed with the untrained eye open (imperative transfer). Piracetam was ineffective when the trained eye was open during transfer trials (facultative transfer). After a visual engram had been lateralized by 5 days of monocular overtraining, Piracetam facilitated formation of the secondary engram induced by 3 interocular transfer trials. It is concluded that Piracetam enhances transcommissural encoding mechanisms activated in the initial stage of monocular learning and in some forms of interhemispheric transfer, but does not affect the transcommissural readout. This effect is interpreted as a special case of the Piracetam-induced facilitation of the phylogenetically old mechanisms of redundant information storage which improve liminal or subnormal learning.

MAIN MESH SUBJECTS: Form Perception/*DRUG EFFECTS
Pattern Recognition, Visual/*DRUG EFFECTS
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY
Transfer (Psychology)/*DRUG EFFECTS

ADDITIONAL MESH SUBJECTS: Animal
Corpus Callosum/PHYSIOLOGY
Discrimination Learning/DRUG EFFECTS
Male
Memory/DRUG EFFECTS
Overlearning/DRUG EFFECTS
Perceptual Masking
Rats
Spreading Cortical Depression

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng



TITLE: Some effects of piracetam (UCB 6215, Nootropyl) on ~~chronic~~
schizophrenia.

AUTHOR: Dimond SJ; Scammell RE; Pryce IG; Huws D; Gray C

SOURCE: Psychopharmacology (Berl) 1979 Sep;64(3):341-8

NLM CIT. ID: 80057401

ABSTRACT: A study is described of effects of a nootropic drug on chronic schizophrenia. The nootropic drugs act on the central nervous system with the cerebral cortex as their target. Chronic schizophrenic patients on the drug showed **improvement in object naming and in tests** where the patient was required to indicate the number of times he had been tapped. Improvements were also noted in **learning and memory tasks**. In dichotic listening the patients showed a reduction in the amount of incorrect verbal responses produced. ~~There were no improvements in symptom rating or social behaviour rating.~~ These results suggest some cognitive improvement but little if any change in the disease state of the patient.

MAIN MESH SUBJECTS: Piracetam/*THERAPEUTIC USE
Pyrrolidinones/*THERAPEUTIC USE
Schizophrenia/*DRUG THERAPY

ADDITIONAL MESH SUBJECTS: Adult
Chronic Disease
Clinical Trials
Dichotic Listening Tests
Double-Blind Method
Female
Human
Male
Middle Age
Motor Skills/DRUG EFFECTS
Psychiatric Status Rating Scales
Schizophrenic Psychology

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE

LANGUAGE: Eng

National Library of Medicine: IGM Full Record Screen

TITLE: Increase in the power of **human memory** in normal man through the use of drugs.

AUTHOR: Dimond SJ; Brouwers EM

SOURCE: Psychopharmacology (Berl) 1976 Sep 29;49(3):307-9

NLM CIT. ID: 77079535

ABSTRACT: Nootropyl (Piracetam) a drug reported to facilitate learning in animals was tested for its effect on man by administering it to normal volunteers. The subjects were given 3x4 capsules at 400 mg per day, in a double blind study. Each subject learned series of words presented as stimuli upon a memory drum. No effects were observed after 7 days but after 14 days, verbal learning had significantly increased.

MAIN MESH SUBJECTS: Memory/*DRUG EFFECTS
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Female
Human
Male
Stimulation, Chemical
Verbal Learning/DRUG EFFECTS

PUBLICATION TYPES: CLINICAL TRIAL
CONTROLLED CLINICAL TRIAL
JOURNAL ARTICLE

LANGUAGE: Eng

National Library of Medicine: IGM Full Record Screen

TITLE: Piracetam facilitates retrieval but does not impair extinction of bar-pressing in rats.

AUTHOR: Sara SJ; David-Remacle M; Weyers M; Giurgea C

SOURCE: Psychopharmacology (Berl) 1979 Mar 14;61(1):71-5

NLM CIT. ID: 79180683

ABSTRACT: Rats were trained on a continuously reinforced bar-press response for water reward. Seven days later they were retested for retention, with or without pretest injection of the nootropic drug, piracetam. **Drug-treated animals had significantly shorter response latencies than saline-treated animals. The results are interpreted as a facilitation of retrieval processes after forgetting.** The experiment was extended under extinction conditions and it was found that after three sessions there was a tendency to facilitate extinction when response latency is used as the extinction index. The clinical interest of a drug which facilitates the retrieval aspect of the memory process without impairing extinction is discussed.

MAIN MESH SUBJECTS: Conditioning, Operant/*DRUG EFFECTS
Extinction (Psychology)/*DRUG EFFECTS
Memory/*DRUG EFFECTS
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Animal
Male
Rats
Water Deprivation

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng



TITLE: Piracetam impedes hippocampal neuronal loss during withdrawal after ~~chronic alcohol intake~~.

AUTHOR: Brandao F; Paula-Barbosa MM; Cadete-Leite A

AUTHOR AFFILIATION: Department of Anatomy, Porto Medical School, Portugal.

SOURCE: Alcohol 1995 May-Jun;12(3):279-88

NLM CIT. ID: 95367208

ABSTRACT: In previous studies we have demonstrated that **prolonged ethanol consumption induced hippocampal neuronal loss**. In addition, we have shown that withdrawal after chronic alcohol intake augmented such degenerative activity leading to increased neuronal death in all subregions of the hippocampal formation but in the CA3 field. In an attempt to reverse this situation, we tested, during the withdrawal period, the effects of piracetam (2-oxo-1-pyrrolidine acetamide), a cyclic derivative of gamma-aminobutyric acid, as there is previous evidence that it might act as a neuronoprotective agent. The total number of dentate granule, hilar, and CA3 and CA1 pyramidal cells of the hippocampal formation were estimated using unbiased stereological methods. We found out that in animals treated with piracetam the numbers of dentate granule, hilar, and CA1 pyramidal cells were significantly higher than in pure withdrawn animals, and did not differ from those of alcohol-treated rats that did not undergo withdrawal. **These data suggest that piracetam treatment impedes, during withdrawal, the pursuing of neuronal degeneration.**

MAIN MESH SUBJECTS: Ethanol/*ADVERSE EFFECTS
Hippocampus/*DRUG EFFECTS/PATHOLOGY
Neurons/*DRUG EFFECTS
Piracetam/*PHARMACOLOGY
Substance Withdrawal Syndrome/*PATHOLOGY

ADDITIONAL MESH SUBJECTS: Analysis of Variance
Animal
Cell Count/DRUG EFFECTS
Diet
Male
Rats
Rats, Sprague-Dawley
Support, Non-U.S. Gov't

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 64-17-5 (Ethanol)
7491-74-9 (Piracetam)



5

TITLE: Does piracetam counteract the ECT-induced memory dysfunctions in depressed patients?

AUTHOR: Mindus P; Cronholm B; Levander SE

SOURCE: Acta Psychiatr Scand 1975 Jun;51(5):319-26

NLM CIT. ID: 75201625

ABSTRACT: A double-blind, intra-individual cross-over comparison of the effect of piracetam on retrograde memory impairment as measured by the KS memory test battery was performed in connection with second and third Bi-ECT in 18 patients diagnosed as suffering from depression. The seizure duration and the post-ECT EEG patterns were examined visually and the post-ECT confusion time was measured. Piracetam was given orally in the dose of 4.8 g/day for 3 days. No significant effects were obtained on memory scores, electrical stimulus duration, EEG pattern or post-ECT confusion time. The findings may indicate that the protective effect of piracetam shown in animal electroconvulsive stimulation (ECS) is due to a counteraction of the disturbing effect of hypoxia on memory functions. It is concluded that more information is needed as regards the pharmacokinetics and the mode of action of the drug.

MAIN MESH SUBJECTS: Depression/*THERAPY
Electroconvulsive Therapy/*ADVERSE EFFECTS
Memory/*DRUG EFFECTS
Memory Disorders/*ETIOLOGY/PREVENTION & CONTROL
Piracetam/*PHARMACOLOGY/THERAPEUTIC USE
Pyrrolidinones/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Adult
Aged
Clinical Trials
Drug Evaluation
English Abstract
Female
Human
Male
Middle Age
Placebos

PUBLICATION TYPES: CLINICAL TRIAL
CONTROLLED CLINICAL TRIAL
JOURNAL ARTICLE

LANGUAGE: Eng



TITLE: Effects of oxiracetam on learning and memory in animals: comparison with piracetam.

AUTHOR: Mondadori C; Classen W; Borkowski J; Ducret T; Buerki H; Schade A

SOURCE: Clin Neuropharmacol 1986;9 Suppl 3:S27-38

NLM CIT. ID: 87244092

ABSTRACT: The effects of oxiracetam and piracetam were compared in learning and memory tests in rats and mice. In the dose range examined, the two nootropics were equally active in reducing the amnesia induced by cerebral electroshock in the mouse. Step-down retention performance, however, was distinctly improved by oxiracetam but unaffected by piracetam, no matter whether it was given before or immediately after the learning trial. Oxiracetam also improved acquisition performance in aged (24- to 27-month-old) rats in an active-avoidance situation at doses of 30 and 100 mg/kg i.p. whereas piracetam showed no effect at 100 mg/kg i.p.

MAIN MESH SUBJECTS: Avoidance Learning/*DRUG EFFECTS
Memory/*DRUG EFFECTS
Piracetam/*PHARMACOLOGY
Pyrrolidines/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Aging/PHYSIOLOGY
Animal
Comparative Study
Drug Administration Schedule
Electroshock
Mice
Rats

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Pyrrolidines)
0 (Pyrrolidinones)
62613-82-5 (oxiracetam)
7491-74-9 (Piracetam)



Order Documents	Other Years 52 71 67	Log off IGM		
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A. INGREDIENT NAME:

QUINACRINE HYDROCHLORIDE

B. Chemical Name:

3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine Dihydrochloride;
Mepacrine Hydrochloride; Quinacrinium Chloride
2-Chloro-5-(Omega-Diethylamino-Alpha-Methylbutylamino)-7-Methoxyacridine
Dihydrochloride
3-Chloro-9-(4'-Diethylamino-1'-Methylbutylamino)-7-Methoxyacridine Dihydrochloride
6-Chloro-9-((4-(Diethylamino)-1-Methylbutyl)Amino)-2-Methoxyacridine
Dihydrochloride
3-Chloro-7-Methoxy-9-(1-Methyl-4-Diethylaminobutylamino)Acridine Dihydrochloride
2-Methoxy-6-Chloro-9-(4-Diethylamino-1-Methylbutylamino)

C. Common Name:

Acrichine, Acriquine, Akrichin (Czech), Arichin, Atabrine, Atabrine Dihydrochloride,
Atabrine Hydrochloride, Atebrin, Atebrine, AtebrinHydrochloride, Chemiochin, Chinacrin,
Chinacrin Hydrochloride, Crinodora, Dial, Erion, Italchin, malaricida, Mecryl, Mepacrine
Dihydrochloride, Mepacrine Hydrochloride, Methoquine, Acridine Dihydrochloride,
Metochin, Metoquin, Metoquine, Palacrin, Palusan, Pentilen, Quinacrine Dihydrochloride,
Quinacrine Hydrochloride

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 100.12%
98 %

E. Information about how the ingredient is supplied:

Bright Yellow, Crystalline Powder. It is odorless and has a bitter taste.

F. Information about recognition of the substance in foreign pharmacopeias:

Pharmacopeias. In Arg., Belg., Br., Braz., Eur., Fr., Ger., Hung., Ind., It., Mex., Neth.,
Nord., Pol., Rus., Span., Swiss., Turk., and U. S.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

Tablets

I. Information about strength:

100mg - 900mg

J. Information about route of administration:

Orally

K. Stability data:

Melting Point: 257 C (DEC)

Incompatible with alkalis, nitrates, and oxidizing agents.

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

The Drugs & Cosmetics Act 1940 and the rules thereunder
From 39 Rule 150 E (i)

Certificate No. VCL/ 17/97-98.

30-2193
53219

1. Name of the manufacturer : M/s. Vipor Chemicals, Baroda-390 010.
 2. Licence No. : G/152
 3. Date of Receipt : 03-07-97.
 4. Name of Sample : HEPACRINE HYDROCHLORIDE B.P.
 5. (a) Batch No. (b) Quantity Submitted (c) Total Quantity Mfgd / Purchased (d) Date of Manufacture (e) Date of Expiry
- | | | | | |
|-----|----------|---|----------|------------|
| 025 | 2x 15gm. | - | JULY '97 | JUNE '2002 |
|-----|----------|---|----------|------------|

6. RESULTS OF ANALYSIS As per B.P.

Description	: Yellow Crystalline Powder
Solubility	: Comply
Identification	: A, B, C, D Comply
Acidity	: PH of 2% solution : 4.0
3-Chloro -7-Methoxy Acridine	: Complies
Water	: 006.8 %
Sulphated Ash	: 000.07%
Assay	: 100.12%

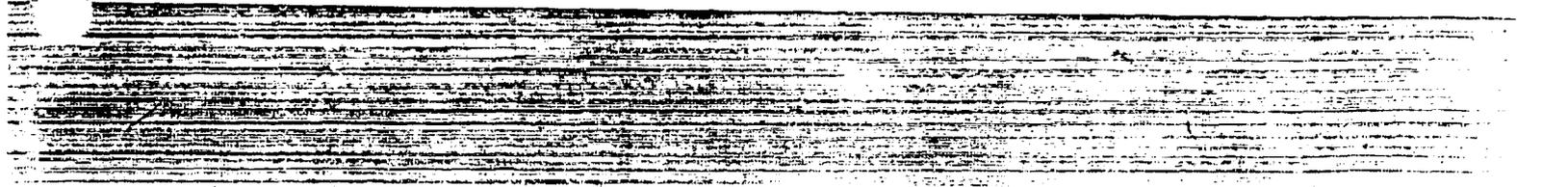


D

Report : In the opinion of the undersigned, the sample referred to above is of STANDARD QUALITY/ is ~~not of standard quality~~ as defined in the Act and the rules made thereunder.

9/97

The opinion is in respect of the tests carried out and mentioned above.



QUALITY CONTROL REPORT

CHEMICAL NAME.:QUINACRINE HYDROCHLORIDE USP _____

MANUFACTURE LOT NO.:025

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP___/BP___/MERCCK___/NF___/MART.___/CO.SPECS.___.

1)DESCRIPTION.:

IF — BRIGHT YELLOW, CRYSTALLINE POWDER. IS ODORLESS AND HAS A BITTER TASTE.

2) SOLUBILITY.:

SPARINGLY SOLUBLE IN WATER; SOLUBLE IN ALCOHOL.

3)MELTING POINT.:

MELTS AT ABOUT 250 DEGREES WITH DECOMPOSITION.

4)SPECIFIC GRAVITY.:

5)IDENTIFICATION.:

- A)COMPLIES (A) AS PER IR SPECTRUM USP XXII.
- B)COMPLIES (C) AS PER USP XXII.
- C)A SOLUTION 1 IN 100 HAS A PH ABOUT 4.5.

PASSES.: _____

FAILS.: _____

COMMENTS.:QUINACRINE DIHYDROCHLORIDE IS ALSO KNOWN AS QUINACRINE HCL.

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

----- IDENTIFICATION -----

PRODUCT #: 22299-2 NAME: QUINACRINE DIHYDROCHLORIDE HYDRATE,
98%

CAS #: 69-05-6

MF: C23H30CLN3O

SYNONYMS

C { ACRICHINE * ACRIQUINE * AKRICHIN (CZECH) * ARICHIN * ATABRINE *
ATABRINE DIHYDROCHLORIDE * ATABRINE HYDROCHLORIDE * ATEBRIN *

ATEBRINE * ATEBRIN HYDROCHLORIDE * CHEMIOCHIN * CHINACRIN *
CHINACRIN
HYDROCHLORIDE *

B { (2-CHLORO-5-(OMEGA-DIETHYLAMINO-ALPHA-METHYLBUTYLAMINO)
-7-METHOXYACRIDINE DIHYDROCHLORIDE *)

3-CHLORO-9-(4'-DIETHYLAMINO-1'-
METHYLBUTYLAMINO)-7-METHOXYACRIDINE DIHYDROCHLORIDE *

6-CHLORO-9-((4-
(DIETHYLAMINO)-1-METHYLBUTYL)AMINO)-2-METHOXYACRIDINE
DIHYDROCHLORIDE

*

3-CHLORO-7-METHOXY-9-(1-METHYL-4-DIETHYLAMINO)ACRIDINE

DIHYDROCHLORIDE * [CRINODORA * DIAL * ERION * ITALCHIN * MALARICIDA *

MECRYL * MEPACRINE DIHYDROCHLORIDE * MEPACRINE HYDROCHLORIDE *

METHOQUINE *] C

2 { (2-METHOXY-6-CHLORO-9-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO))
ACRIDINE DIHYDROCHLORIDE * METOCHIN * METOQUIN * METOQUINE *

B { PALACRIN

* PALUSAN * PENTILEN * QUINACRINE DIHYDROCHLORIDE * QUINACRINE

HYDROCHLORIDE * 866 R.P. * SN 390 *

----- TOXICITY HAZARDS -----

RTECS NO: AR7875000

ACRIDINE, 6-CHLORO-9-((4-(DIETHYLAMINO)-1-METHYLBUTYL)AMINO)-2-

METHOXY-, DIHYDROCHLORIDE

TOXICITY DATA

ORL-RAT LD50:660 MG/KG

JPETAB 91,157,47

IVN-RAT LD50:29 MG/KG

JPETAB 91,157,47

IUT-RAT LD50:100 MG/KG

IJEBA6 16,1074,78

ORL-MUS LD50:557 MG/KG

JPETAB 91,157,47

IPR-MUS LD50:189 MG/KG

JPETAB 91,133,47

SCU-MUS LD50:212 MG/KG

ABEMAV 1,317,41

IVN-MUS LD50:38 MG/KG JPETAB 91,157,47
ORL-RBT LD50:433 MG/KG JPETAB 91,157,47
IVN-RBT LD50:9 MG/KG JPETAB 91,157,47
IVN-GPG LD50:14 MG/KG JPETAB 91,157,47

REVIEWS, STANDARDS, AND REGULATIONS

NOES 1983: HZD X4102; NIS 1; TNF 66; NOS 3; TNE 987; TFE 508
EPA GENETOX PROGRAM 1988, NEGATIVE: SPERM MORPHOLOGY-MOUSE

EPA GENETOX PROGRAM 1988, INCONCLUSIVE: MAMMALIAN MICRONUCLEUS

TARGET ORGAN DATA

PERIPHERAL NERVE AND SENSATION (FLACCID PARALYSIS WITHOUT ANESTHESIA)

BEHAVIORAL (ALTERED SLEEP TIME)

BEHAVIORAL (SOMNOLENCE)

BEHAVIORAL (TOXIC PSYCHOSIS)

BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)

VASCULAR (OTHER CHANGES)

LUNGS, THORAX OR RESPIRATION (RESPIRATORY DEPRESSION)

LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)

IMMUNOLOGICAL INCLUDING ALLERGIC (ANAPHYLAXIS)

PATERNAL EFFECTS (SPERMATOGENESIS)

MATERNAL EFFECTS (OVARIES, FALLOPIAN TUBES)

MATERNAL EFFECTS (UTERUS, CERVIX, VAGINA)

MATERNAL EFFECTS (MENSTRUAL CYLCE CHANGES OR DISORDERS)

MATERNAL EFFECTS (OTHER EFFECTS ON FEMALE)

EFFECTS ON FERTILITY (FEMALE FERTILITY INDEX)

EFFECTS ON FERTILITY (PRE-IMPLANTATION MORTALITY)

EFFECTS ON FERTILITY (POST-IMPLANTATION MORTALITY)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

MAY CAUSE EYE IRRITATION.

MAY CAUSE SKIN IRRITATION.

TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES.

IN CASE OF CONTACT, IMMEDIATELY WASH SKIN WITH SOAP AND COPIOUS

AMOUNTS OF WATER.

IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

WASH CONTAMINATED CLOTHING BEFORE REUSE.

----- PHYSICAL DATA -----

← MELTING PT: 257 C (DEC)

APPEARANCE AND ODOR

YELLOW POWDER

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

----- REACTIVITY DATA -----

INCOMPATIBILITIES

STRONG OXIDIZING AGENTS

STRONG ACIDS

MAY DISCOLOR ON EXPOSURE TO LIGHT.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

TOXIC FUMES OF:

CARBON MONOXIDE, CARBON DIOXIDE

NITROGEN OXIDES

HYDROGEN CHLORIDE GAS

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

EVACUATE AREA.

WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS

COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN

IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

CHEMICAL SAFETY GOGGLES.

RUBBER GLOVES.

NIOSH/MSHA-APPROVED RESPIRATOR.

SAFETY SHOWER AND EYE BATH.

USE ONLY IN A CHEMICAL FUME HOOD.

DO NOT BREATHE DUST.

DO NOT GET IN EYES, ON SKIN, ON CLOTHING.

WASH THOROUGHLY AFTER HANDLING.

TOXIC.

KEEP TIGHTLY CLOSED.

LIGHT SENSITIVE

STORE IN A COOL DRY PLACE.

HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

WEAR SUITABLE PROTECTIVE CLOTHING.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT
PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL
NOT BE

HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM
CONTACT WITH THE

ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR
ADDITIONAL

TERMS AND CONDITIONS OF SALE

Packaging and storage—Preserve Pyroxylin loosely packed in cartons, protected from light.

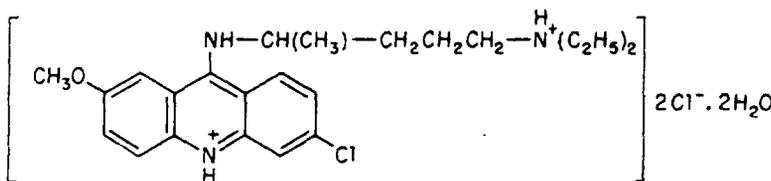
CATEGORY—Pharmaceutic necessity for COLLODION.

Quinacrine Hydrochloride *

A
B

QUINACRINE HYDROCHLORIDE

3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine Dihydrochloride; Mepacrine Hydrochloride; Quinacrinium Chloride



$C_{23}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$

Mol. wt. 508.94

Quinacrine Hydrochloride contains not less than 98 per cent of $C_{23}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$.

E Description—Quinacrine Hydrochloride occurs as a bright yellow, crystalline powder. It is odorless and has a bitter taste.

Solubility—One Gm. of Quinacrine Hydrochloride dissolves in about 35 ml. of water. It is soluble in alcohol.

Identification—

A: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add a slight excess of ammonia T.S.: a yellow to orange, oily precipitate of quinacrine base is formed which adheres to the wall of the vessel and is soluble in ether.

B: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add 1 ml. of diluted nitric acid: a yellow crystalline precipitate is formed.

C: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add 1 ml. of mercuric chloride T.S.: a yellow precipitate is formed.

D: The filtrate from the precipitate, obtained in Identification test A, acidified with nitric acid, responds to the tests for Chloride, page 901.

pH—The pH of a solution of Quinacrine Hydrochloride (1 in 100) is about 4.5.

Water, page 942—Determine the water content of Quinacrine Hydrochloride by drying at 105° for 4 hours or by the Karl Fischer method: it contains not less than 6 per cent and not more than 8 per cent of water.

Residue on ignition, page 912—The residue on ignition of 200 mg. of Quinacrine Hydrochloride is negligible.

Assay—Transfer to a 100-ml. volumetric flask about 250 mg. of Quinacrine Hydrochloride, accurately weighed, dissolve it in 10 ml. of water, then add 10 ml. of a solution prepared by dissolving 25 Gm. of sodium acetate and 10 ml. of glacial acetic acid in water to make 100 ml. Add exactly 50 ml. of 0.1 N potassium dichromate and water to make 100 ml., stopper the flask, mix thoroughly, and filter through a dry filter paper into a dry flask, rejecting the first 15 ml. of the filtrate. Measure 50 ml. of the subsequent filtrate into a glass-stoppered flask, add 15 ml. of hydrochloric acid and 20 ml. of potassium iodide T.S., stopper the flask, mix the contents gently, and allow to stand in the dark for 5 minutes. Add 75 ml. of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate, adding starch T.S. as the end-point is neared. Perform a blank determination with the same quanti-

LIN

otton

he action of a mixture of nitric chiefly of cellulose tetranitrate

, matted mass of filaments, resembling e touch. It is exceedingly flammable, with a luminous flame. When kept in is decomposed with the evolution of ue.

owly but completely in 25 parts of a f alcohol. It is soluble in acetone and n these solutions by water.

ut 500 mg. of Pyroxylin, accurately ld water, and ignite the Pyroxylin at at the dish to redness, and cool: not

3m. of Pyroxylin with 20 ml. of water not have an acid reaction to litmus. on a steam bath, and dry the residue of residue remains.

ties of the same reagents and in the same manner (see *Residual Titrations*, page 832). Each ml. of 0.1 N potassium dichromate is equivalent to 8.482 mg. of $C_{33}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$.

Packaging and storage—Preserve Quinacrine Hydrochloride in tight, light-resistant containers.

CATEGORY—Anthelmintic; antimalarial; antiprotozoan.

DOSE—USUAL—Suppressive—

Antimalarial—100 mg.

Therapeutic—

Antimalarial and antiprotozoan—200 mg. every 6 hours for 5 doses, then 100 mg. three times a day for 6 days.

Anthelmintic—500 mg. with 500 mg. of sodium bicarbonate in a single dose.

Quinacrine Hydrochloride Tablets

QUINACRINE HYDROCHLORIDE TABLETS

Quinacrine Hydrochloride Tablets contain not less than 93 per cent and not more than 107 per cent of the labeled amount of $C_{33}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$.

Identification—

A: Powder a sufficient number of Quinacrine Hydrochloride Tablets, equivalent to about 250 mg. of quinacrine hydrochloride, and extract with two 15-ml. portions of hot water, filtering after each extraction. To 5 ml. of the extract add ammonia T.S., and remove the oily precipitate so formed by extraction with two 10-ml. portions of ether. The water layer, acidified with nitric acid, responds to the tests for *Chloride*, page 901.

B: To the remaining portion of the water extract obtained in *Identification test A* add 2 ml. of ammonia T.S.: a yellow, oily precipitate forms. Shake the mixture with several 10-ml. portions of chloroform until the water layer is practically colorless. Evaporate the combined chloroform solutions on a steam bath in a small beaker, and add to the residue 3 ml. of hot water and 2 ml. of diluted hydrochloric acid, moistening the sides of the beaker with the liquid and stirring with a glass rod. Allow to stand for 30 minutes, then filter, wash the crystals with ice-cold water until the last washing is practically neutral to litmus, and dry at 105° for 2 hours: the crystals so obtained respond to *Identification tests B* and *C* under *Quinacrine Hydrochloride*, page 599.

Disintegration—Quinacrine Hydrochloride Tablets meet the requirements of the *Disintegration Test for Tablets*, page 936, in not more than 1 hour.

Weight variation—Quinacrine Hydrochloride Tablets meet the requirements of the *Weight Variation Test for Tablets*, page 945.

Assay—Weigh a counted number of not less than 20 Quinacrine Hydrochloride Tablets, and reduce them to a fine powder without appreciable loss. Weigh accurately a portion of the powder, equivalent to about 200 mg. of quinacrine hydrochloride, and place it in a separator with 25 ml. of water and 3 ml. of diluted hydrochloric acid. Extract the suspension with two 15-ml. portions of chloroform, and wash the chloroform extracts in a second separator with 10 ml. of water. Discard the washed chloroform, and add the water in the second separator to the suspension of tablet

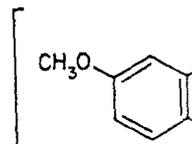
material. Make the extract completely with successive portions of cotton moistened with water. The extract is colorless. Evaporate the extract to dryness in a steam bath until the residue is completely with the aid of 2 ml. of water. Proceed as directed in *Identification test B* then add 10 ml. of water. This is equivalent to 8.482 mg. of quinacrine hydrochloride.

Packaging and storage—Preserve in tight, light-resistant containers.

Tablets available—Quinacrine Hydrochloride Tablets in the following amounts of quinacrine hydrochloride:

CATEGORY and DOSE

Q



$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$

Quinidine Sulfate is a species of *Cinchona* alkaloid, Flückiger (Fam. *Rubiaceae*).

Description—Quinidine Sulfate occurs as a white, crystalline powder, cohering in masses. It is soluble in water and alcohol. Its solutions are colorless to light. Its solutions are slightly bitter.

Solubility—One Gm. of Quinidine Sulfate is soluble in about 10 ml. of alcohol.

Identification—

A: Acidify a solution of Quinidine Sulfate in water. The resulting solution has a characteristic bitter taste.

B: To 5 ml. of a solution of Quinidine Sulfate in water, add 1 ml. of ammonia T.S., and the solution becomes green color due to the formation of a complex.

C: To 5 ml. of a solution of Quinidine Sulfate in water, add 1 ml. of ammonia T.S., and stir with a glass rod. A white precipitate is formed, which is soluble in water.

D: Quinidine Sulfate has a specific rotation of +100° (the anhydrous basis, d₂₀²⁰). Quinidine Sulfate in each

1378-w

Chloroquine. Cyclochin; Haloquine. 4-(7-Chloro-4-aminino)-2,6-bis(dihexylaminomethyl)phenol.
C₁₆H₁₂N₂O₂S = 497.1.

CAS — 14594-33-3.

A yellow crystalline powder with a bitter taste. Practically insoluble in water; readily soluble in dilute acids; insoluble in dilute alkalis. Protect from light.

Uses. Cycloquine resembles chloroquine in its action and has been used in the USSR for the suppression and treatment of malaria. A dose of 300 mg has been given weekly for the suppression of malaria and 300 mg has been given daily for three days in the treatment of acute attacks.

1379-e

Diformyldapson. DFD; DFDD; Diformyldiaminodiphenylsulphone. 4,4'-Disulphonylbisformanilide.
C₁₈H₁₂N₂O₂S = 304.3.

CAS — 6784-25-4.

A crystalline solid. M.p. 267° to 269°. Practically insoluble in water; soluble 1 in about 200 of dimethyl sulphoxide. It is most stable at pH 6.

Uses. Diformyldapson has been used as an antimalarial in doses of 400 to 800 mg weekly, but is given with chloroquine, primaquine, or pyrimethamine, since it has no action on gametocytes.

Diformyldapson had an approximate half-life of 84 hours.— W. Peters, *Postgrad. med. J.*, 1973, 49, 573.

Diformyldapson in doses of 3.2 g twice weekly for 4 weeks damaged the red blood cells in 25 subjects. Smaller doses did not appear to cause haemolysis.— S. A. Cucinell et al., *J. clin. Pharmacol.*, 1974, 14, 51.

Malaria. Diformyldapson was considered to protect volunteers more effectively against the Vietnam Smith strain of *P. falciparum* than against the Chesson strain of *P. vivax*. There were no reports of methemoglobinemia in patients receiving diformyldapson in conjunction with chloroquine.— Clyde, D.F. et al., *Milit. Med.*, 1971, 136, 836, per *Trop. Dis. Bull.*, 1972, 69, 593. See also *idem*, *Milit. Med.*, 1970, 135, 527.

Diformyldapson 100 to 800 mg weekly given with chloroquine alone, or with chloroquine and primaquine, suppressed the Smith strain of falciparum malaria in 41 of 45 men and the Brai strain in 9 men. The combination appeared to be more effective than treatment with chloroquine and primaquine, or than pyrimethamine 25 mg weekly which suppressed the Brai, but not the Smith strain.— D. F. Clyde et al., *Am. J. Trop. Med. Hyg.*, 1971, 20, 1, per *Trop. Dis. Bull.*, 1971, 68, 1153.

Diformyldapson given weekly with chloroquine protected 5 of 8 volunteers against falciparum malaria. Better results were noted when volunteers were given dapson daily with chloroquine or chloroquine and primaquine weekly.— D. Willerson, *Am. J. Trop. Med. Hyg.*, 1972, 21, 138, per *J. Am. med. Ass.*, 1972, 220, 1382.

Diformyldapson, 400 to 800 mg with pyrimethamine 25 mg, both given weekly, was considered to provide effective prophylaxis against chloroquine-resistant *P. falciparum* and against *P. vivax*. No toxic side-effects were noted.— D. F. Clyde et al., *Milit. Med.*, 1973, 138, 418, per *Trop. Dis. Bull.*, 1974, 71, 15.

1380-b

Hydroxychloroquine Sulphate (B.P.)

Hydroxychloroquine Sulfate (U.S.P.); Oxichlorochin Sulphate; Win 1258-2. 2- $\{N-[4-(7\text{-Chloro-4-quinolylamino})\text{pentyl}]-N\text{-ethylamino}\}$ ethanol sulphate.

C₁₈H₂₆ClN₂O, H₂SO₄ = 433.9.

CAS — 118-42-3 (hydroxychloroquine); 747-36-4 (sulphate).

Ph. *zooetias*. In Br. and U.S.

A pale or almost white odourless crystalline powder with a bitter taste. There are 2 forms, one melting at about 198° and the other at about 240°. Hydroxychloroquine sulphate 100 mg is approximately equivalent to 77 mg of hydroxy-

chloroquine base. Soluble 1 in 5 of water; practically insoluble in alcohol, chloroform, and ether. A 1% solution in water has a pH of 3.5 to 5.5. Protect from light.

Adverse Effects, Treatment, Precautions, and Resistance. As for Chloroquine, p.395.

Hydroxychloroquine was given in an average dose of 800 mg daily for up to 4½ years to 94 patients with lupus erythematosus, rheumatoid arthritis, or scleroderma. The patients had not previously received chloroquine, amodiaquine, mepacrine, or quinine. Corneal deposition occurred in 26 patients; it was reversible in 20, persistent in 3, and 3 were lost to follow-up. There was a rapid rise in incidence after 150 g had been given. One patient who had received 770 g over 26½ months developed retinopathy. A second case of probable retinopathy was subsequently seen in a further patient.— R. V. Shearer and E. L. Dubois, *Am. J. Ophthalmol.*, 1967, 64, 245.

Ocular toxicity in 3 of 99 patients after long-term treatment with hydroxychloroquine.— R. I. Rynes et al., *Arthritis Rheum.*, 1979, 22, 832.

Uses. Hydroxychloroquine sulphate has an antimalarial action similar to that of chloroquine (see p.396) but it is mainly used in the treatment of systemic and discoid lupus erythematosus and rheumatoid arthritis. Treatment is usually started with about 400 to 800 mg daily in divided doses with meals and the dose is reduced to about 200 to 400 mg when a response occurs. In malaria, a suppressive dose of 400 mg every 7 days is used, and in treating an acute attack a dose of 800 mg has been used, followed after 6 to 8 hours by 400 mg and a further 400 mg on each of the 2 following days. Children may be given a weekly suppressive dose equivalent to 5 mg of base per kg body-weight, while for treatment an initial dose of 10 mg per kg may be given, following by 5 mg per kg 6 hours later and again on the second and third days.

In the treatment of giardiasis, the usual dose is 200 mg thrice daily for 5 days.

Hydroxychloroquine sulphate has been used in the treatment of polymorphous light eruptions. The dose is as for rheumatoid arthritis.

Porphyria. Hydroxychloroquine, 400 mg weekly for several months, had been reported to be safe and effective in the treatment of porphyria cutanea tarda.— F. De Matteis, *Br. J. Derm.*, 1972, 87, 174.

Thrombo-embolic disorders. Of 565 patients who underwent surgery 284 received an injection of hydroxychloroquine sulphate 200 mg with their premedication and then 200 mg eight-hourly by mouth or by injection until discharge from hospital. From postoperative observations and by phlebography it appeared that hydroxychloroquine could be useful in reducing the incidence of deep-vein thrombosis and pulmonary embolism.— A. E. Carter et al., *Br. med. J.*, 1971, 1, 312.

The incidence of deep-vein thrombosis after surgery was 5% in 107 patients given hydroxychloroquine sulphate compared with 16% in 97 controls. The dose was 1.2 g by mouth in 3 divided doses in the 24 hours before surgery followed by 400 mg every 12 hours after surgery until discharge.— A. E. Carter and R. Eban, *Br. med. J.*, 1974, 3, 94.

For discussions, see A. S. Gallus and J. Hirsh, *Drugs*, 1976, 12, 132; A. G. G. Turpie and J. Hirsh, *Br. med. Bull.*, 1978, 34, 183.

Preparations

Hydroxychloroquine Sulfate Tablets (U.S.P.). Tablets containing hydroxychloroquine sulphate.

Hydroxychloroquine Tablets (B.P.). Tablets containing hydroxychloroquine sulphate. They are sugar-coated.

Plaquenil (Winthrop, UK). Hydroxychloroquine sulphate, available as tablets of 200 mg. (Also available as Plaquenil in Aust., Austral., Belg., Canad., Denm., Fin., Fr., Iceland, Ital., Neth., Norw., Swed., Switz., USA).

Other Proprietary Names

Ercoquin (Denm., Norw., Swed.); Quensyl (Ger.).

1381-v

Mefloquine Hydrochloride. WR 142490.

(±)-α-[2,8-Bis(trifluoromethyl)-4-quinoly]-α-(2-piperidyl)methanol hydrochloride.

C₁₇H₁₆F₆N₂O, HCl = 414.8.

CAS — 53230-10-7 (mefloquine); 51773-92-3 (hydrochloride).

Adverse Effects. Epigastric discomfort has been reported after doses of 1 g, and nausea and dizziness after doses of 1.75 or 2 g.

Uses. Mefloquine hydrochloride is a 4-quinolinemethanol compound which has schizonticidal activity against malaria parasites. It is active against chloroquine-resistant falciparum malaria.

Malaria. A preliminary study in 17 subjects of the use of mefloquine hydrochloride in single 1-g doses as a prophylactic against drug-resistant malaria.— K. H. Rieckmann et al., *Bull. Wild Hlth Org.*, 1974, 51, 375.

Thirty-five non-immune volunteers infected with 1 of 3 strains of *Plasmodium falciparum*, 2 of them drug-resistant, were treated with a single oral dose of mefloquine hydrochloride 0.4, 1, or 1.5 g. The infection was cured in 2 of 12 given 0.4 g, 13 of 15 given 1 g, and 8 of 8 given 1.5 g. In 5 partially-immune volunteers infected with *P. vivax* cures were achieved with single doses of 0.4 or 1 g in two, but infection reappeared in the remaining 3 subjects and was subsequently cured with chloroquine and primaquine.— G. M. Trenholme et al., *Science*, 1975, 190, 792.

None of 21 volunteers bitten by 10 to 15 mosquitoes heavily infected with *P. falciparum* developed malaria when given mefloquine hydrochloride 250 or 500 mg weekly, 500 mg every 2 weeks, or 1 g every 4 weeks. Doses of 250 mg weekly suppressed *P. vivax* infections during drug administration but malaria appeared when treatment ceased.— D. F. Clyde et al., *Antimicrob. Ag. Chemother.*, 1976, 9, 384.

Of 39 patients with chloroquine-resistant falciparum malaria, 36 (92%) were cleared of infection with no recrudescence after treatment with quinine, sulfadoxine, and pyrimethamine, by the regimen of A.P. Hall (*Br. med. J.*, 1975, 2, 15; see under Quinine, p.405), while all of 35 were cleared by treatment with quinine followed by a single dose of mefloquine hydrochloride 1.5 g (one patient received only 1 g). Side-effects in 40 patients given mefloquine were: abdominal pain (7), anorexia (6), diarrhoea (6), dizziness (9), nausea (3), vomiting (9), and weakness (3). Side-effects were minimal or absent if at least 12 hours elapsed after the last dose of quinine.— A. P. Hall et al., *Br. med. J.*, 1977, 1, 1626.

Animal studies of the antimalarial activities of 4-quinolinemethanols including mefloquine and a report of the US Army Malaria Research Program.— L. H. Schmidt et al., *Antimicrob. Ag. Chemother.*, 1978, 13, 1011.

Of 37 patients with chloroquine-resistant falciparum malaria all were radically cured by a single dose of mefloquine hydrochloride 1.5 g. Side-effects (nausea, vomiting, diarrhoea, dizziness, headache) could probably be reduced by a formulation designed to slow absorption.— E. B. Doberstyn et al., *Bull. Wild Hlth Org.*, 1979, 57, 275.

Metabolism. Preliminary study in 1 subject given a single dose of mefloquine indicated relatively rapid absorption, extensive distribution, and prolonged elimination phases. Mefloquine was reported to be extensively bound to plasma proteins and to be concentrated in erythrocytes.— J. M. Grindel et al., *J. pharm. Sci.*, 1977, 66, 834.

The kinetics of mefloquine hydrochloride.— R. E. Desjardins et al., *Clin. Pharmac. Ther.*, 1979, 26, 372.

1382-g

Mepacrine Hydrochloride (B.P., Eur. P.).

Mepacrine Hydrochloridum; Acrinamine; Quinacrine Hydrochloride (U.S.P.); Quinacrinium

Chloride; Acrichinum; Antimalarinae Chlorhydras; Chinacrina. 6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate.

C₂₃H₃₀Cl₂N₂O, 2HCl, 2H₂O = 508.9.

CAS — 83-89-6 (mepacrine); 69-05-6 (dihydrochloride, anhydrous); 6151-30-0 (dihydrochloride, dihydrate)

Pharmacopoeias. In Arg., Belg., Br., Braz., Eur., Fr., Ger., Hung., Ind., Int., It., Mex., Neth., Nord., Pol., Rus., Span., Swiss, Turk., and U.S.

A bright yellow odourless crystalline powder with a bitter taste. M.p. about 250° with decomposition. Soluble 1 in 35 to 40 of water; soluble in alcohol; slightly soluble in dehydrated alcohol; very slightly soluble in chloroform; practically insoluble in acetone and ether. A 2% solution in water has a pH of 3 to 5. **Incompatible with alkalis, nitrates, and oxidising agents.** Store in airtight containers. Protect from light.

Incompatibility. Mepacrine hydrochloride was incompatible with amaranth, benzylpenicillin, sodium alginate, sodium aminosulphate, sodium carboxymethylcellulose, sodium lauryl sulphate, and thiomersal.—*J. Am. Pharm. Ass., Pract. Pharm. Edn.*, 1952, 13, 658.

Adverse Effects. Minor effects liable to arise with ordinary doses are dizziness, headache, and mild gastro-intestinal disturbances. Most patients develop a yellow discoloration of the skin. Large doses may give rise to nausea and vomiting and occasionally to transient mental disturbances. A few patients develop chronic dermatoses after prolonged administration of the drug; these may be either lichenoid, eczematoid, or exfoliative in type. Deaths from exfoliative dermatitis and from hepatitis have been reported. The use of mepacrine over prolonged periods may give rise to aplastic anaemia.

Adverse effects of intrapleural instillation include fever and chest pain caused by the inflammatory reaction.

The toxicity arising from prolonged administration has contributed to the decline in the use of mepacrine in malaria.

Two patients had convulsions a few hours after the intrapleural administration of mepacrine hydrochloride 400 mg for malignant effusions. One developed status epilepticus and died; the other was successfully controlled with phenobarbitone intravenously and phenytoin by mouth.—*I. Borda and M. Krant, J. Am. med. Ass.*, 1967, 201, 1049.

Mepacrine hydrochloride 100 mg daily had been reported to cause haemolytic anaemia in certain individuals with a deficiency of glucose-6-phosphate dehydrogenase. The reaction was not considered clinically significant under normal circumstances (e.g. in the absence of infection).—*E. Beutler, Pharmac. Rev.*, 1969, 21, 73. A patient with rheumatoid arthritis treated with mepacrine hydrochloride for about 20 years had developed a blue-black discoloration of the hard palate, the nail beds, and the skin over the shins. The colour disappeared when mepacrine was stopped and reappeared when it was restarted.—*M. J. Egorin et al., J. Am. med. Ass.*, 1976, 236, 385.

Treatment of Adverse Effects. As for Chloroquine, p.396.

Precautions. Mepacrine enhances the toxicity of the 8-aminoquinoline derivatives such as primaquine by inhibiting their metabolism.

Mepacrine might interfere with fluorimetric estimations of plasma hydrocortisone.—*J. Millhouse, Adverse Drug React. Bull.*, 1974, Dec., 164.

Absorption and Fate. Mepacrine is absorbed from the gastro-intestinal tract and appears in the blood within 2 hours. It becomes concentrated in liver, pancreas, spleen, and lung, and higher concentrations occur in red and white blood cells than in plasma, but it also permeates into all body fluids and crosses the placenta. It has a biological half-life of about 5 days and is excreted only very slowly in the urine and faeces. Mepacrine hydrochloride was bound to serum proteins *in vitro*.—*G. A. Luty, Toxic. appl. Pharmac.*, 1978, 44, 225.

Uses. Mepacrine was formerly widely used for the suppression and treatment of malaria but it has been superseded for these purposes by chloroquine and other more recently introduced antimalarials. Doses ranged from 100 mg daily for suppression and from 900 mg reducing to 300 mg daily for treatment. Mepacrine hydrochloride is used in the treatment of giardiasis; 100 mg thrice

daily for 7 days is usually effective, though relapses may occur. A suggested dose for children is 2.7 mg per kg body-weight thrice daily.

It has been used for the expulsion of tapeworms; 100 mg is given at intervals of 5 minutes until a total dose of 1 g is reached.

Instillations of mepacrine hydrochloride or mesylate are used in the symptomatic treatment of neoplastic effusions in the pleura or peritoneum but the treatment is associated with a high frequency of toxic effects.

For the use of mepacrine as an anthelmintic, see A. Davis, *Drug Treatment in Intestinal Helminthiases*, Geneva, World Health Organization, 1973.

Giardiasis. Mepacrine 100 mg thrice daily for 5 to 7 days was usually effective in the treatment of giardiasis, although a second course might be required. The dose for children under 4 years old was one-quarter of the adult dose.—*Br. med. J.*, 1974, 2, 347.

A 95% cure-rate was obtained in giardiasis after treatment with mepacrine hydrochloride 100 mg thrice daily for 7 days. Dosages in children were: under 1 year, 33 mg thrice daily; 1 to 4 years, 50 mg twice daily; 4 to 8 years, 50 mg thrice daily; over 8 years, 100 mg thrice daily, all for 7 days.—*M. S. Wolfe, J. Am. med. Ass.*, 1975, 233, 1362.

Further references: *G. T. Moore et al., New Engl. J. Med.*, 1969, 281, 402; *Med. Lett.*, 1976, 18, 39; *R. E. Raizman, Am. J. dig. Dis.*, 1976, 21, 1070.

Malignant effusions. The value of local instillations of mepacrine in controlling effusions in advanced disseminated neoplastic disease was studied in 60 patients. For pleural effusions, an initial dose of 50 to 100 mg was followed by 200 to 400 mg daily for 4 or 5 days; patients with ascites received 100 to 200 mg followed by 400 to 800 mg daily for 3 to 5 days. The mepacrine was dissolved in 10 ml of the effusion fluid which was then re-injected. Of 33 patients clinically evaluated for 2 months or more, objective control of the effusion was maintained in 27 for 2 to 26 months. Fever, often accompanied by leucocytosis and persisting for a few hours to 10 days after completion of treatment, was noted in about half the patients.—*J. E. Ulmann et al., Cancer*, 1963, 16, 283.

Thirteen patients with neoplastic effusions were treated with mepacrine hydrochloride in doses of 100 to 200 mg daily by local instillations for pleural effusions, and 200 to 400 mg daily for ascites, usually for 3 to 5 days. Clinical benefit with favourable objective changes in all measurable criteria of the disease was seen in 9 patients for periods of up to 27 months. Mild local toxicity was frequent but haematopoietic depression did not occur. No consistent cytolytic changes of tumour cells were observed and response was attributed to the inflammation and fibrosis produced.—*M. R. Dollinger et al., Ann. intern. Med.*, 1967, 66, 249.

There was a response in 8 of 12 patients with malignant pleural effusions given mepacrine by instillation in small daily doses, and in 19 of 27 given mepacrine as a single dose through a thoracostomy tube. More disturbing and serious toxicity occurred in the second group.—*E. R. Borja and R. P. Pugh, Cancer*, 1973, 31, 899.

A beneficial effect (less than 500 ml fluid drawn at each pleurocentesis in 3 months) was achieved on 9 of 14 occasions after the instillation of mepacrine (100, 200, and 200 mg respectively on 3 occasions in 1 week), on 4 of 15 occasions after thiotepa (20 mg per instillation), and on 1 of 9 occasions after pleurocentesis alone. Fever and chest pain were limiting factors; mepacrine was suitable if the patient's condition and prognosis was good; otherwise thiotepa or pleurocentesis were preferred.—*J. Mejer et al., Scand. J. resp. Dis.*, 1977, 58, 319.

Further references: *J. A. Hickman and M. C. Jones, Thorax*, 1970, 25, 226; *M. Lee and D. A. Boyes, J. Obstet. Gynaec. Br. Commonw.*, 1971, 78, 843.

Pneumothorax. A patient with cystic fibrosis was treated for pneumothorax on the left side by the instillation of mepacrine hydrochloride 100 mg in 15 ml saline into the intrapleural space on 4 consecutive days. This procedure was repeated 12 months later for pneumothorax on the right. There was no recurrence of pneumothorax on either side before the patient died 11 months after the second treatment after several relapses of chronic pulmonary disease.—*J. Kattwinkel et al., J. Am. med. Ass.*, 1973, 226, 557. See also *R. E. Jones and S. T. Giammona, Am. J. Dis. Child.*, 1976, 130, 777.

Tubal occlusion. Two to 4 ml of a 30% aqueous suspension of mepacrine hydrochloride instilled transvaginally once in the immediate postmenstrual phase of 2 consecutive cycles induced tubal occlusion in 93% of 134

women.—*Advances in Methods of Fertility Regulation, Tech. Rep. Ser. Wild Hlth Org. No. 527*, 1973.

Sixty women desiring sterilisation were treated by the application, by cannula within the uterus, of 1 g of mepacrine hydrochloride suspended in 7 ml of sterile water. Of 52 available for examination 4 months later, 22 had bilateral tubal patency and 3 unilateral patency, a further 6 were pregnant. The low success-rate of a single application indicated limited usefulness.—*C. Israngkun et al., Contraception*, 1976, 14, 75.

Warts. A local injection technique was used in the treatment of warts in children. A 4% solution of mepacrine, in doses of 0.1 to 0.2 ml, was injected into the healthy skin at the base of the wart, 3 to 6 warts being treated at each session. The injections were repeated twice if no response followed the first injection. The treatment was successful in 97 of 112 patients. It sometimes caused slight transient pain.—*A. I. Lopatin, Pediatriya*, 1966, 45, 71, per *Abstr. Wild Med.*, 1966, 40, 446.

Preparations

Mepacrine Tablets (B.P.). Tablets containing mepacrine hydrochloride. Protect from light.

Quinacrine Hydrochloride Tablets (U.S.P.). Tablets containing mepacrine hydrochloride. Store in airtight containers.

Proprietary Names

Atabrine (*Winthrop, Canad.*); Atabrine Hydrochloride (*Winthrop, USA*).

Mepacrine hydrochloride was formerly marketed in certain countries under the proprietary name Quinacrine (*May & Baker*).

1383-q

Mepacrine Mesylate. Mepacrine Methanesulphonate (*B.P.C. 1963*).

$C_{21}H_{30}ClN_3O_2 \cdot 2CH_3SO_2H \cdot H_2O = 610.2$.

CAS — 316-05-2 (anhydrous).

Bright yellow odourless crystals with a bitter taste. Mepacrine mesylate 120 mg is approximately equivalent to 100 mg of mepacrine hydrochloride. Soluble 1 in 3 of water and 1 in 36 of alcohol. A 2% solution in water has a pH of 3 to 5. Protect from light. Solutions should not be heated, or stored for any length of time.

Uses. Mepacrine mesylate has actions similar to those of mepacrine hydrochloride, but as it is more soluble than the hydrochloride it has been administered by intramuscular injection in the treatment of severe malaria. A dose of 360 mg has been given in 2 to 4 ml of Water for Injections.

It is given by intrapleural or intraperitoneal instillation in the treatment of neoplastic effusions.

Preparations

Mepacrine Methanesulphonate Injection (B.P.C. 1963). Mepacrine Mesylate Injection. A sterile solution of mepacrine mesylate in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in Water for Injections.

Mepacrine mesylate was formerly marketed in certain countries under the proprietary name Quinacrine Soluble (*May & Baker*).

1384-p

Pamaquin (B.P. 1953). Gametocidum; Pamachin; Pamaquine Embonate. Plasmoquinum; SN 971 8-(4-Diethylamino-1-methylbutylamino)-6-methoxyquinoline 4,4'-methylenebis(3-hydroxy-2-naphthoate). $C_{42}H_{54}N_4O_7 = 703.8$.

CAS — 491-92-9 (base); 635-05-2 (embonate).

A yellow to orange-yellow odourless powder with a bitter taste. Practically insoluble in water; soluble 1 in 20 of alcohol.

Uses. Pamaquin was formerly used in the treatment of malaria but has been superseded by primaquine phosphate.

A. INGREDIENT NAME:

SILVER PROTEIN MILD NF

B. Chemical Name:

C. Common Name:

Argentum Crede, Collargol (9CI), Colloidal Silver, Stillargol, Vitargénol, Aust.:
Coldargan, Fr.: Pastaba, Ger.: Coldargan, Ital.: Arscolloid, Bio-Arscolloid, Corti-
Ascolloid, Rikosilver, Rinatipiol, Rinovit Nube.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specifications)</i>	<i>(Results)</i>
Assay: (after ignition)	19.0-23.0%	19.74%

E. Information about how the ingredient is supplied:

Brown, Dark-Brown, or almost black, odorless, lustrous scales or granules, somewhat hygroscopic, and is affected by light.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Belg., Cz., Fr., Hung., It., and Jpn.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Isenberg, S., Apt, L., and Yoshimuri. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Archives of Ophthalmology*, 1983; 101(5): 764-765.

Apt, L. and Isenberg, S. Chemical preparation of skin and eye in ophthalmic surgery: an international survey. *Ophthalmic Surgery*, 1982; 13(12): 1026-1029.

H. Information about dosage forms used:

Liquid

I. Information about strength:

1-20%

J. Information about route of administration:

Nasal
Ophthalmic

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

PRODUCT: SILVER PROTEIN MILD
RELEASE #: N

LOT # :B61695G18

30-1263

51149

GRADE:NFXIII
CODE:D5785

SPECIFICATIONS

RESULT

1. DESCRIPTION	Black granules	Conforms
2. Identification	To pass test	Passes test
3. Solubility	To pass test	Passes test
4. Assay (after ignition) D	<u>19.0 - 23.0%</u>	<u>19.74%</u>
5. Ionic silver	No turbidity	Conforms
6. Distinction from strong silver protein	To pass test	Passes test

ATTENTION: TONY HATCHETT

Date :06/23/97

10762

Prepared by : A. HAZARI

Approved by :  6/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: SILVER PROTEIN MILD NF *A*

MANUFACTURE LOT NO.: C64051D10

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

E - (BROWN, DARK-BROWN, OR ALMOST BLACK, ODORLESS, LUSTROUS SCALES OR GRANULES; SOMEWHAT HYGROSCOPIC, AND IS AFFECTED BY LIGHT.

2) SOLUBILITY.:

FREELY SOLUBLE IN WATER. ALMOST INSOLUBLE IN ALCOHOL, CHLOROFORM AND IN ETHER.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

- A) COMPLIES (B) AS PER NF 10th EDITION 1955.
- B) COMPLIES (C) AS PER NF 10th EDITION 1955.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

----- IDENTIFICATION -----

PRODUCT #: 29824-7 NAME: SILVER PROTEIN, MILD
CAS #: 9015-51-4

SYNONYMS

U ARGENTUM CREDE * COLLARGOL (9CI) * COLLOIDAL SILVER *

----- TOXICITY HAZARDS -----

RTECS NO: VW3675000

SILVER, COLLOIDAL

TOXICITY DATA

ORL-MUS LD50:100 MG/KG JPPMAB 2,20,50

REVIEWS, STANDARDS, AND REGULATIONS

ACGIH TLV-TWA 0.01 MG(AG)/M3 85INA8 5,529,86

MSHA STANDARD-AIR:TWA 0.01 MG(AG)/M3 DTLVS* 3,231,71

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES
(RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE
INFORMATION.

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

MAY CAUSE EYE IRRITATION.

MAY CAUSE SKIN IRRITATION.

TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND
TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH COPIOUS

AMOUNTS OF WATER FOR AT LEAST 15 MINUTES WHILE REMOVING
CONTAMINATED

CLOTHING AND SHOES.

IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL
RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS
CONSCIOUS.

CALL A PHYSICIAN.

WASH CONTAMINATED CLOTHING BEFORE REUSE.

----- PHYSICAL DATA -----

APPEARANCE AND ODOR

DARK-BROWN OR BLACK FLAKES

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING
TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

----- REACTIVITY DATA -----

INCOMPATIBILITIES

STRONG OXIDIZING AGENTS

PROTECT FROM LIGHT.

ACIDS

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

TOXIC FUMES OF:

CARBON MONOXIDE, CARBON DIOXIDE

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

EVACUATE AREA.

WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS

COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN
IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR,
CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

SAFETY SHOWER AND EYE BATH.

USE ONLY IN A CHEMICAL FUME HOOD.

DO NOT BREATHE DUST.

AVOID CONTACT WITH EYES, SKIN AND CLOTHING.

AVOID PROLONGED OR REPEATED EXPOSURE.

WASH THOROUGHLY AFTER HANDLING.

TOXIC.

KEEP TIGHTLY CLOSED.

LIGHT SENSITIVE

STORE IN A COOL DRY PLACE.

TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE

POSSIBLE).

WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.

REGULATORY INFORMATION

20.0% SILVER COMPOUND

THIS PRODUCT IS SUBJECT TO SARA SECTION 313 REPORTING REQUIREMENTS.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE

HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE

ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL

TERMS AND CONDITIONS OF SALE

Sesame Oil (7368-w)

Acete de Ajonjol; Benne Oil; Gingelly Oil; Oleum Sesami; Sesam Oil.

Pharmacopoeias. In Aust., Belg., Br., Chin., Eur., Fr., Ger., It., Jpn., Neth., Port., and Swiss. Also in USNF.

Standards of Ph. Eur. apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

The fixed oil obtained from the ripe seeds of *Sesamum indicum* (Pedaliaceae) by expression or extraction and subsequent refining. It is a clear pale yellow oil, almost odourless and with a bland taste with a fatty-acid content consisting mainly of linoleic and oleic acids. It solidifies to a buttery mass at about -4°.

Slightly soluble to practically insoluble in alcohol; miscible with carbon disulphide, chloroform, ether, and petroleum spirit. Store at a temperature not exceeding 40° in well-filled airtight containers. Protect from light.

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been observed.

Shellac (285-x)

904; Gomme Laque; Lacca; Lacca in Tabulis; Schellack.

Pharmacopoeias. In Fr. and Ger. Also in USNF.

Includes Purified Shellac and White Shellac (Bleached).

Shellac is obtained by purification of the resinous secretion of the insect *Laccifer lacca* Kerr (Coccidae). The USNF describes 4 grades: Orange Shellac is produced by filtration in the molten state or by a hot solvent process, or both; removal of the wax produces Dewaxed Orange Shellac; Regular Bleached (White) Shellac is prepared by dissolving the secretion in aqueous sodium carbonate, bleaching with hypochlorite, and precipitating with sulphuric acid; removal of the wax by filtration during the process produces Refined Bleached Shellac.

Practically insoluble in water; very slowly soluble in alcohol 85% to 95% (w/w); soluble in ether, 13% to 15%, and in aqueous solutions of tetrahydroamines, alkalis, and borax. Store preferably at a temperature not exceeding 8°.

Shellac is used as an enteric coating for pills and tablets, but integration time has been reported to increase markedly on age.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USNF 18: Pharmaceutical Glaze.

Siam Benzoin (273-c)

Benjoin du Laos; Benzoe Tonkinensis.

Pharmacopoeias. In Aust., Chin., Fr., It., and Swiss. Also in many pharmacopoeias under the title benzoin and should not be confused with Sumatra Benzoin. Hung., Jpn., and US allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

A balsamic resin from *Styrax tonkinensis* (Styracaceae) and containing not more than 10% of alcohol (90%)-insoluble matter.

Yellowish-brown to rusty brown compressed pebble-like tears with an agreeable, balsamic, vanilla-like odour. The tears are separate or very slightly agglutinated, milky white on fracture, and brittle at ordinary temperatures, but softened on heating.

Siam benzoin has been used similarly to Sumatra benzoin (p.17) and has been used as a preservative and was formerly used in the preparation of benzoinated lard.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Compound Tincture; Podophyllum Resin Topical Solution.

Proprietary Preparations

Multi-ingredient preparations. Austral.: Benzoin Spray⁺; Cold Sore Lotion⁺; Ital.: Onda Balsamica⁺; Spain: Vahos Balsamicos⁺.

Silver (5316-v)

E174.

CAS = 107.8682.

CAS — 7440-22-4.

Pharmacopoeias. In Swiss.

A pure white, malleable and ductile metal.

Silver possesses antibacterial properties and is used topically either as the metal or as silver salts. It is not absorbed to any great extent and the main problem associated with the metal

The symbol + denotes a preparation which is actively marketed

is argyria, a general grey discoloration. Silver is used as a colouring agent for some types of confectionery. It is also used as Argentum Metallicum in homeopathy.

Numerous salts or compounds of silver have been employed for various therapeutic purposes, including silver acetate (p.1751), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganite, silver nitrate (p.1751), silver-nylon polymers, silver protein (p.1751), and silver sulphadiazine (p.273).

A report of reversible neuropathy associated with the absorption of silver from an arthroplasty cement.¹

1. Vik H, et al. Neuropathy caused by silver absorption from arthroplasty cement. *Lancet* 1985; i: 872.

Coating catheters with silver has been reported to reduce the incidence of catheter-associated bacteriuria,² but other studies have reported increased infection.³

1. Lundeborg T. Prevention of catheter-associated urinary-tract infections by use of silver-impregnated catheters. *Lancet* 1986; ii: 1031.

2. Johnson JR, et al. Prevention of catheter-associated urinary tract infections with a silver oxide-coated urinary catheter: clinical and microbiologic correlates. *J Infect Dis* 1990; 162: 1145-50.

3. Riley DK, et al. A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. *Am J Med* 1995; 98: 349-56.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Austral.: Micropur, Canad.: Tabanil; Ger.: Dulcargant; Silargetent⁺.

Multi-ingredient preparations. Austral.: Sima-Varix Bandage⁺; Simanite⁺; Fr.: Siérilet T au Cuivre Argent⁺; Ger.: Adsorgant⁺; Grüne Salbe "Schmidt" N; Ital.: Actisorb Plus; Agipi⁺; Katoderm; Katoxy⁺; Nova-T; Silver-Nova T⁺; Spain: Argentocromo; UK: Actisorb Plus.

Silver Acetate (5319-p)

Argenti Acetas.

CH₃COOAg = 166.9.

CAS — 563-63-3.

Pharmacopoeias. In Aust. and Hung.

Silver acetate has been used similarly to silver nitrate as a disinfectant. It has also been used in antismoking preparations.

References

1. Jensen EJ, et al. Serum concentrations and accumulation of silver in skin during three months' treatment with an anti-smoking chewing gum containing silver acetate. *Hum Toxicol* 1988; 7: 535-40.

2. Gourlay SG, McNeill JJ. Antismoking products. *Med J Aust* 1990; 153: 699-707.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

UK: Tabmint.

Silver Nitrate (5321-h)

Argenti Nitras; Nitrato de Plata; Nitrato de Prata.

AgNO₃ = 169.9.

CAS — 7761-88-8.

Pharmacopoeias. In Aust., Belg., Br., Cz., Eur., Fr., Ger., Hung., Int., It., Jpn., Neth., Port., Swiss, and US.

The standards of Ph. Eur. apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

Colourless or white transparent crystals or crystalline odourless powder. On exposure to light in the presence of organic matter, silver nitrate becomes grey or greyish-black.

Soluble 1 in 0.4 of water and 1 in 30 of alcohol; its solubility is increased in boiling water or alcohol; slightly soluble in ether. A solution in water has a pH of about 5.5.

Silver nitrate is incompatible with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility. Store in airtight non-metallic containers. Protect from light.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose from the reaction of the silver nitrate with alkali released from the glass bottle which appeared to be soda-glass.¹

1. *PSGB Lab Report P/R0/6* 1980.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, sialorrhoea, diarrhoea, vomiting, coma, and convulsions.

A short lived minor conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness.

Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria, which though difficult to treat is considered to be mainly a cosmetic hazard, see under Silver (above).

Absorption of nitrite following reduction of nitrate may cause methaemoglobinemia. There is also a risk of electrolyte disturbances.

Treatment of these adverse effects is symptomatic.

Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.¹ After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The corneas had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibiotics and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Hornblass A. Silver nitrate ocular damage in newborns. *JAMA* 1975; 231: 245.

Pharmacokinetics

Silver nitrate is not readily absorbed.

Uses and Administration

Silver nitrate possesses disinfectant properties and is used in many countries as a 1% solution for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p.151) when 2 drops are instilled into each conjunctival sac of the neonate. However, as it can cause irritation, other agents are often used.

In stick form it has been used as a caustic to destroy warts and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical disinfectants and astringents in other conditions.

Silver nitrate (Argentum Nitricum; Argent. Nit.) is used in homeopathic medicine. It is also used in cosmetics to dye eyebrows and eye lashes in a concentration of not more than 4%.

Cystitis. Comment on silver nitrate irrigation having limited value in the management of haemorrhagic cystitis after radiotherapy.¹

1. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; i: 304-6.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Proprietary Preparations

Austral.: Howe's Solution⁺; Quit⁺; Ger.: Mova Nitrat; Pluralane; Spain: Argenpal.

Multi-ingredient preparations. Austral.: Super Banish; Spain: Argentofofenol; Switz.: Grafco; UK: AVOCA.

Silver Protein (5322-m)

Albumosesilber; Argentoproteinum; Argentum Proteinicum; Protargolum; Proteinato de Plata; Proteinato de Prata; Strong Protargin; Strong Protein Silver; Strong Silver Protein. CAS — 9007-35-6 (colloidal silver).

NOTE. Synonyms for mild silver protein include: Argentoproteinum Mite; Argentum Vitellinum; Mild Protargin; Mild Silver Protein; Silver Nucleinate; Silver Vitellin; Vitelinato de Plata and Vitelinato de Prata.

Pharmacopoeias. In Aust., Belg., Cz., Fr., Hung., It., and Jpn. Many of these pharmacopoeias include monographs on mild silver protein as well as on colloidal silver.

Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and have been used as eye drops and for application to mucous membranes. The mild form of silver protein is considered to be less irritating, but less active.

Colloidal silver which is also a preparation of silver in combination with protein has also been used topically for its antibacterial activity.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Sullargol; Viargérol.

Multi-ingredient preparations. Aust.: Coldargan; Fr.: Pastaba; Ger.: Coldargan⁺; Ital.: Arscolloid; Bio-Arscolloid; Corti-Arscolloid; Rikosilver; Rinantipol; Rinovit Nube.

Slippery Elm (5458-t)

Elm Bark; Slippery Elm Bark; Ulmus; Ulmus Fulva.

Pharmacopoeias. In US.

The dried inner bark of *Ulmus fulva* (= *U. rubra*) (Ulmaceae).

Slippery elm contains much mucilage and has been used as a demulcent.

Epidermal necrolysis. Based on the treatment of 10 cases, the following was suggested as treatment for toxic epidermal necrolysis: continuous moist compresses of silver nitrate solution 0.25 to 0.5%, with generous wrapping to prevent excessive cooling; daily electrolyte estimations; and daily debridement; after about the fourth day the compresses could be replaced by dexame-thasone/neomycin spray followed by inunction of wool alcohol ointment. A penicillin should be given routinely and steroids if vasculitis was present.— P. J. Koblenzer, *Archs Derm.*, 1967, 95, 608.

Herpes simplex. Silver nitrate 1% had little effect *in vitro* or *in vivo* against herpes simplex virus type 2.— V. R. Coleman *et al.*, *Antimicrob. Ag. Chemother.*, 1973, 4, 259. A further study.— F. Shimizu *et al.*, *ibid.*, 1976, 10, 57.

Hydatid cysts. Intrahepatic cysts of *Echinococcus granulosus* were treated with excellent results in 20 patients by freezing the operation area then administering silver nitrate 0.5% to destroy the scolices.— I. Nazarian and F. Saidi, *Z. Tropenmed. Parasit.*, 1971, 22, 188, per *Trop. Dis. Bull.*, 1971, 68, 1356.

Ophthalmia neonatorum. In a study of the incidence of ophthalmia neonatorum in 220 000 births, it was found that in 92 865 cases where preparations other than silver nitrate were used the frequency of gonococcal ophthalmia neonatorum was 0.07% whereas where silver nitrate was used the rate was 0.1%. Silver nitrate did not always suppress the development of the condition and seemed no more effective than other agents. While a drop of 1% silver nitrate solution did no harm, there was little evidence that it did any good.— *Lancet*, 1949, 1, 313.

Of the 49 states of the USA which had made regulations requiring routine prophylactic treatment of the eyes of newborn infants, 22 had specified silver nitrate applications. No evidence had been found to contra-indicate 1% silver nitrate drops when properly packed, handled, and administered. The increasing incidence of gonorrhoea had rendered continued routine prophylaxis necessary.— P. C. Barsam, *New Engl. J. Med.*, 1966, 274, 731. Fewer local reactions occurred with penicillin than with silver nitrate eye-drops. Penicillin for neonatal prophylaxis should not be abandoned, since it did not appear to sensitise infants.— G. Nathanson (letter), *ibid.*, 275, 280. Eye-drops containing less than 2% of silver nitrate were considered to be ineffective. Treatment was effective if applied early and prophylaxis was advised only in infants whose mothers were known or suspected to be infected.— E. B. Shaw (letter), *ibid.*, 281. See also P. Kober, *Medische Klin.*, 1967, 62, 424.

To prevent gonorrhoeal ophthalmia neonatorum, a 1% solution of silver nitrate was instilled at birth. The chemical conjunctivitis caused by silver nitrate was of short duration.— P. Thygeson, *J. Am. med. Ass.*, 1967, 201, 902.

For reports on the chemical conjunctivitis associated with instillation of silver nitrate eye-drops and recommendations for reduction of the incidence, see Adverse Effects (above).

Pneumothorax. Spontaneous pneumothorax was successfully treated in 132 patients by pleurodesis induced with silver nitrate; repeated pleurodesis was necessary in only 2 patients. It was suggested that this therapy should be used for patients with only small or no blebs visible on thoracoscopy, or with only mild pre-existing lung disease.— I. Anderson and H. Nissen, *Dis. Chest*, 1968, 54, 230, per *J. Am. med. Ass.*, 1968, 206, 681.

Wounds. Silver nitrate solution 0.5% was more effective against Gram-positive than Gram-negative bacteria in the treatment of nonthermal war wounds. The solution did not hinder wound healing or epithelialisation of split thickness skin grafts.— J. P. Connors *et al.*, *Archs Surg.*, Chicago, 1969, 98, 119, per *J. Am. med. Ass.*, 1969, 207, 580.

Preparations

Mitigated Silver Nitrate (B.P.C. 1968). Argenti Nitras Mitigatus; Mitigated Caustic; Argenti Nitras Dilutus. Silver nitrate 1 and potassium nitrate 2, fused together and suitably moulded for application as a caustic to warts and condylomas. Protect from light. A similar preparation is included in several pharmacopoeias.

Silver Nitrate Stain Remover (Univ. of Iowa). Thiourea ($\text{NH}_2\text{CS.NH}_2=76.12$) 8 g, citric acid monohydrate 8 g, water to 100 ml. It should be freshly prepared.

Toughened Silver Nitrate (B.P.). Argenti Nitras Induratus; Toughened Caustic; Fused Silver Nitrate; Lunar Caustic; Moulded Silver Nitrate; Stylus Argenti Nitrici. Silver nitrate 95 and potassium nitrate 5, fused together and suitably moulded.

White or greyish-white cylindrical rods or cones, which

become grey or greyish-black on exposure to light. Freely soluble in water; sparingly soluble in alcohol. Protect from light.

A similar preparation is included in several pharmacopoeias.

Toughened Silver Nitrate (U.S.P.). Contains not less than 94.5% of AgNO_3 , the remainder consisting of silver chloride. Store in airtight containers. Protect from light.

Creams

Silver Nitrate Cream. Silver nitrate, 0.5 or 2%, Xalifin-15 20%, water to 100%. The cream was stable with only slight discoloration when stored for 4 weeks in the dark at room temperature; at 0° to 4° there was no discoloration.— *Pharm. Soc. Lab. Rep.* P/68/15, 1968.

Eye-drops

Oculoguttæ Argenti Nitratis pro Neonatis (Dan. Disp.). Silver nitrate 670 mg, potassium nitrate 1.2 g, and Water for Injections, 98.13 g.

A similar preparation is included in *F.N.Belg.*

Silver Nitrate Eye-drops (B.P.C. 1954). Gutt. Argent. Nit. Silver nitrate 0.5% w/v, potassium nitrate 1.33% w/v, in Solution for Eye-drops.

Nord. P. has 1% w/w with potassium nitrate 1% w/w in Water for Injections.

Ointments

Unguentum Argenti Nitratis Compositum. Compound Silver Nitrate Ointment. An ointment with this title is included in several pharmacopoeias. It contains silver nitrate 1% and Peru balsam 5 to 10% usually in a basis of yellow soft paraffin or yellow soft paraffin and wool fat.

Ophthalmic Solutions

Silver Nitrate Ophthalmic Solution (U.S.P.). A solution of silver nitrate 0.95 to 1.05% in an aqueous medium. pH 4.5 to 6. It may contain sodium acetate as a buffer. Store in single-dose containers. Protect from light.

Solutions

Ammoniacal Silver Nitrate Solution (U.S.N.F. XII, 1965). Ammoniacal Silver Nitrate, Howe. A solution of diamminosilver nitrate was prepared from silver nitrate 704 g, water 245 ml, and strong ammonia solution to dissolve all but the last trace of precipitate (about 680 ml). It contains 28.5 to 30.5% w/w of Ag and 9 to 9.7% w/w of NH_3 . Store in small glass-stoppered containers or in ampoules. Protect from light.

This solution has been employed in dental surgery to deposit silver in exposed dentine or to fill up small crevices in the teeth. After the solution had been applied to the tooth it was followed by a reducing agent such as a 10% formaldehyde solution or eugenol to cause a deposit of metallic silver. The solution has also been employed in the treatment of fungous infections of the nails.

Solutio Argenti Nitratis cum Tetracaino (Nord. P.). Silver nitrate 200 mg, amethocaine nitrate 100 mg, and water 99.7 g.

Proprietary Names

Helvestensstifter (*Braun, Denm.*); Lapis (*DAK, Denm.*); Mova Nitrat Pipette (*Lindopharm, Ger.*).

5322-m

Silver Protein (B.P.C. 1968). Argentoproteinum; Strong Protein Silver; Strong Protargin; Argentum Proteinicum; Albumosilber; Protargolum; Proteinato de Plata; Proteinato de Prata.

CAS — 9015-51-4.

Pharmacopoeias. In *Arg.*, *Aust.*, *Belg.*, *Cz.*, *Fr.*, *Hung.*, *Ind.*, *Int.*, *It.*, *Jap.*, *Pol.*, *Port.*, *Roum.*, *Span.*, and *Turk.*

A brown odourless hygroscopic powder containing 7.5 to 8.5% of Ag.

Slowly soluble 1 in 2 of water; very slightly soluble in alcohol, chloroform, and ether. A solution in water is neutral to litmus. Solutions may be prepared by shaking the powder over the surface of cold water and allowing it to dissolve slowly, or by triturating the powder to a cream with water and diluting. Solutions are transparent and not coagulated by heat, nor precipitated by the addition of alkali, alkali sulphides, alkali salts, or albumin; they are relatively non-staining. Store in airtight containers. Protect from light.

Adverse Effects. As for Silver (above).

Uses. Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and are used as eye-drops in the treatment of conjunctivitis. Solutions are relatively non-irritant unless they contain more than 10% of silver protein.

Preparations

Silver Protein Eye-drops (B.P.C. 1963). Gutt. Argent. A solution of silver protein 5%, with phenylmercuric acetate or nitrate 0.002%, in water. Prepared by dissolving, aseptically, the silver protein in a solution of phenylmercuric acetate or nitrate 0.002% in water to the final sterilised container. They must be freshly prepared. They are adversely affected by alkali. Protect from light.

Proprietary Names

Stillargol (*Mayoly-Spindler, Fr.*).

5323-b

Mild Silver Protein (B.P.C. 1968). Argentoproteinum Mit. Argentum Vitellinum; Mild Silver Protein; Silver Nuclinate; Silver Vitellin; Mild Proteinato de Plata; Vitelinato de Prata.

NOTE. The name Mild Silver Protein is a compound because it is less bactericidal than Silver Protein, though it contains more silver.

Pharmacopoeias. In *Arg.*, *Belg.*, *Fr.*, *Ind.*, *Int.*, *It.*, *Jap.*, *Pol.*, *Roum.*, *Span.*, *Swiss.*, and *Turk.*

A hydroscopic brown powder or nearly black granules with a slight odour and taste, containing 23% of Ag.

Soluble slowly but completely in water, and soluble in alcohol, chloroform, and ether. A solution to light it is incompletely soluble in water. A solution in water is iso-osmotic with serum. Incompatible with cocaine hydrochloride, but compatible with atropine sulphate solution. Incompatible with acids, alkalis, tannins, and oxidising agents. Store in airtight containers. Protect from light.

Preservative for eye-drops. Phenylmercuric nitrate 0.005% was a suitable preservative for silver protein eye-drops sterilised by heating at 100° for 30 minutes.— M. Van Ooteghem, *Pharm. Belg.*, 1968, 45, 69.

Adverse Effects, Treatment, and Precautions. Silver (above).

Argyria. Argyria developed in an elderly patient on prolonged use of mild silver protein 10% nasal drops. W. A. Parker, *Am. J. Hosp. Pharm.*, 1971, 26, 100.

Uses. Mild silver protein solutions have properties similar to those of silver protein, though they contain even lower concentrations of silver and are consequently less irritant to the tissues. Silver protein may be used, therefore, in higher concentrations than silver protein, particularly in children, to avoid irritation of mucous membranes. Mild silver protein, usually 1 to 5%, is used as drops or as a spray in nasal infections. It has been applied as a 20% solution in conjunctivitis for the prophylaxis of ophthalmia neonatorum and solution to corneal ulcers.

Rhinitis. Mild silver protein (Argyrol) has been used for many years in children with chronic purulent rhinitis and has some value in encouraging nose blowing. The main disadvantage is the irreversible staining of kerchiefs and pillows.— D. F. N. Harrison, *J. Clin. Pharm.*, 1976, 16, 69.

Preparations

Mild Silver Protein Eye-drops (B.P.C. 1968). Argentoprot. Mit. A solution of mild silver protein 5% with phenylmercuric acetate or nitrate 0.002% in water. Prepared by dissolving, aseptically, the silver protein in a sterile 0.002% solution of phenylmercuric acetate or nitrate and transferring to the final container. The eye-drops must be freshly prepared. They are adversely affected by alkali. Protect from light. A.P.F. (Mild Silver Protein Eye-Drops) has silver protein 20% and phenylmercuric nitrate 0.002% in Water for Injections.

Silver Protein and Ephedrine Instillation (A.P.F.). Silver Protein and Ephedrine Nasal Drops. Mild silver protein 5 g, ephedrine 500 mg, phenylmercuric nitrate 5 mg, freshly boiled and cooled water to 100 ml. This should be recently prepared. Protect from light.

Proprietary Preparations

Argotone (*Rona, UK*). Contains mild silver protein and ephedrine hydrochloride 0.9% in 0.5% sodium chloride solution, available as Nasal Drops. Ready-Spray nasal spray in plastic atomisers.

Other Proprietary Names

Argincolor (*Fr.*); Argirol (*Spain*); Vitargol (*It.*)

ghly with hot 3 per cent hydro-
 ight of the precipitate so obtained
 er Iodide in tight, light-resistant

TRATE SOLUTION

moniacal Silver Nitrate, Howe

a solution of silver diammino
 quivalent of not less than 28.5
 and not less than 9.0 Gm. and

.....	704 Gm.
.....	245 ml.
.....	680 ml.
.....	1000 ml.

ortar and dissolve it in the puri-
 t m temperature and add
 e u all but the last trace of
 is last trace of precipitate from

ion is a clear, colorless, almost odorless
 ected by light. Its specific gravity is

ite Solution (1 in 10) responds to the
 ate, page 683.

Solution add a few drops of formalde-
 recipitate is immediately formed (*dis-*
nonium nitrates).

Silver Nitrate Solution (1 in 10) add
 filter, add 5 ml. of sodium hydroxide
 itmus blue.

remains free from even a transient blue

iacal Silver Nitrate Solution add 3 ml.
 he clear filtrate tested in a flame on a
 of sodium or potassium (*distinction from*

ml. of Ammoniacal Silver Nitrate Solu-
 water, 10 ml. of diluted nitric acid, and
 rate with 0.1 N ammonium thiocyanate.
 is equivalent to 10.79 mg. of Ag.

ut 1 ml. of Ammoniacal Silver Nitrate
 e sample to a Kjeldahl distillation flask

with 50 ml. of water, and add sufficient of the water to make a volume of 200 ml.;
 add 10 ml. of sodium sulfide T.S. and 20 ml. of a solution of sodium hydroxide (4
 in 10). Connect the flask to a condenser, the lower outlet tube of which dips
 beneath the surface of 50 ml. of 0.5 N sulfuric acid contained in a receiving flask.
 Distil the mixture until about 100 ml. of distillate has been collected, add methyl
 red T.S., and titrate the excess acid with 0.5 N sodium hydroxide. Each ml. of
 0.5 N sulfuric acid is equivalent to 8.516 mg. of NH₃.

The ratio between the percentage of ammonia and the percentage of silver
 closely approximates 1 to 3.16.

Packaging and storage—Preserve Ammoniacal Silver Nitrate Solution in small glass-
 stoppered, light-resistant containers, or in light-resistant ampuls.

FOR TOPICAL USE—Mix Ammoniacal Silver Nitrate Solution with a re-
 ducing agent, such as formaldehyde (1 in 10) or eugenol, to deposit
 the metallic silver, in a state of fine subdivision, in the desired area of the
 tooth.

CATEGORY—Protective (dental).

Silver Protein, Mild

MILD SILVER PROTEIN

Argentum Proteicum Mite

Mild Protargin

Mild Silver Protein is silver rendered colloidal by the presence of, or
 combination with, protein. It contains not less than 19 per cent and
 not more than 23 per cent of Ag.

*Caution: Solutions of Mild Silver Protein should be freshly prepared or
 contain a suitable stabilizer, and should be dispensed in amber-colored bottles!*

Description—Mild Silver Protein occurs as dark brown or almost black, shining
 scales or granules. It is odorless, is frequently hygroscopic, and is affected by
 light.

Solubility—Mild Silver Protein is freely soluble in water, but almost insoluble in
 alcohol, in chloroform, and in ether.

Identification—

A: Heat about 100 mg. of Mild Silver Protein in a porcelain crucible until all
 carbonaceous matter is burned off, warm the residue with 1 ml. of nitric
 acid, dilute with 10 ml. of water, and add a few drops of hydrochloric acid:
 a white precipitate is produced which dissolves in ammonia T.S.

B: Ferric chloride T.S. added to a solution of Mild Silver Protein (1 in 100)
 discharges the dark color and a precipitate is gradually produced.

C: To 10 ml. of a solution of Mild Silver Protein (1 in 100) add a few drops of
 mercury bichloride T.S.: a white precipitate is formed and the super-
 natant liquid becomes colorless or nearly so.

Ionic silver—To 10 ml. of a solution of Mild Silver Protein (1 in 100) add 2 ml. of a
 solution of sodium chloride (1 in 100): no turbidity is produced.

Distinction from strong silver protein—Dissolve 1 Gm. of Mild Silver Protein in 10
 ml. of water. Add, all at once, 7 Gm. of ammonium sulfate, and stir occasionally
 for 30 minutes. Filter through quantitative filter paper into a 50-ml. Nessler
 tube, returning the first portions of the filtrate to the filter, if necessary, to secure
 a clear filtrate, and allow the filter and precipitate to drain. Add to the clear
 filtrate 25 ml. of a solution of acacia (1 in 100). In a second 50-ml. Nessler tube
 dissolve 7 Gm. of ammonium sulfate in 10 ml. of water, and add to this solution
 25 ml. of the solution of acacia and 1.6 ml. of 0.01 N silver nitrate. To each tube

Database: Medline <1966 to present>

<1>

Unique Identifier

83203583

Authors

Isenberg S. Apt L. Yoshimuri R.

Title

Chemical preparation of the eye in ophthalmic surgery. II.
Effectiveness of mild silver protein solution.

Source

Archives of Ophthalmology. 101(5):764-5, 1983 May.

Abstract

Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.

<2>

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Authors

Apt L. Isenberg S.

Title

Chemical preparation of skin and eye in ophthalmic surgery:
an international survey.

Source

Ophthalmic Surgery. 13(12):1026-9, 1982 Dec.

Abstract

We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver

protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

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Chemical Preparation of the Eye in Ophthalmic Surgery

II. Effectiveness of Mild Silver Protein Solution

Sherwin Isenberg, MD; Leonard Apt, MD; Robert Yoshimuri, PhD

• Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.

(*Arch Ophthalmol* 1983;101:764-765)

Therapeutic properties of silver and its salts were recognized as early as the Roman Empire period. Jabir ibn Hayyan Geber, an Arabian physician of the eighth century, initiated the use of silver nitrate on the eye.¹ Carl Siegmund Franz Credé began the prophylactic application of silver nitrate on the eyes of newborn infants to prevent gonococcal conjunctivitis in 1884. After that, silver nitrate was used for other ophthalmic disorders, but it was found occasionally to cause

necrosis of conjunctival epithelial cells and a gray-black color when light reduced the salt to its metallic state. In addition, irritation, scarring of the conjunctiva, corneal opacification, and symblepharon occurred. In an attempt to reduce these problems, Albert C. Barnes, MD, and Hermann Hille, in 1902, developed a combination of silver nitrate and grain protein (Argyrol).² However, this drug also caused complications. In 1980, Spencer et al³ reported the clinical and histopathologic findings in one patient who drank this mild silver protein solution for years and in a second patient who applied mild silver protein drops to one eye for a long-term period.

A 20% mild silver protein solution is available for topical ocular use in the United States as a silver nitrate and gelatin colloid. The drug is available also abroad under a variety of proprietary names and formulations. It is classified in pharmacy textbooks as a local anti-infective agent.

The antimicrobial properties of this mild silver protein solution have been questioned for years.^{4,7} To our knowledge, there has been no controlled clinical study proving the antibiotic efficacy of this mild silver protein solution as part of the chemical preparation of the eye before surgery. Yet, in a recent international survey of ophthalmologists, Apt and Isenberg⁴ found that 22% of the respondents use this mild silver protein solution on the conjunctiva as part of the preoperative chemical preparation of the eye. We, therefore, conducted a masked study to investigate the effectiveness of this mild silver protein solution as

an antimicrobial agent in the preoperative preparation.

PATIENTS AND METHODS

Thirty-two patients undergoing ophthalmic surgery were studied. No patient had received preoperative antibiotic therapy or had an active infection at the time of surgery.

All subjects had the identical regimen of preoperative preparation. Initially, a sterile anaerobic transport swab was applied to either the inferonasal or inferotemporal conjunctival fornix of one eye and a second swab was applied to the conjunctiva of the same quadrant in the second eye. Twenty microliters (1 drop) of 20% mild silver protein solution then was instilled in the inferior conjunctival fornix of one randomly selected eye. This eye may have been the eye that was operated on when unilateral ocular surgery was performed. Hexachlorophene soap was applied equally to both eyelids, eyelid margins, cheeks, nose, eyebrow, and forehead. The inferior fornix of the eye into which the mild silver protein solution had been instilled was then irrigated with a normal saline solution, while the other eye had no irrigation. Gauze sponges moistened in a saline solution were used to rinse areas bearing hexachlorophene. Next, the quadrant of each inferior conjunctival fornix not previously cultured was cultured with a third and fourth sterile anaerobic transport swab. The choice of which portion of the fornix was cultured before and after the preparation was randomly assigned. Nursing personnel coded each specimen before bacteriologic analysis. The microbiologist had no knowledge of the exact origin of the specimen.

The swab was washed three times in 0.5 mL of Schaedler's broth and wrung out by pressing it along the sides of the tube. The swab was cultured in 10 mL of Schaedler's broth. Blood and chocolate agar each were inoculated with 0.1 mL of eluant and spread on the surface of the agar with a

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Table 1.—Mean Number of Colonies and Species of Bacteria Isolated per Subject

Eye		Mean \pm SD		% of Increase
		Before Preparation	After Preparation	
Colonies	Untreated	183 \pm 425	284 \pm 571	55
	Mild silver protein-treated	231 \pm 687	323 \pm 750	40
Species	Untreated	1.06 \pm 0.83	1.41 \pm 0.86	33
	Mild silver protein-treated	1.06 \pm 0.75	1.31 \pm 0.77	24

Table 2.—Number of Eyes in Which Culture Was Sterile

Type of Eye	No. of Eyes That Were Sterile		No. of Eyes That Remained Sterile
	Before Preparation	After Preparation	
Untreated	8	4	2
Mild silver protein-treated	7	5	1

glass rod. The blood agar plates were incubated for seven days at 35 °C in an anaerobic jar with a gas mixture of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen. The chocolate agar plates were incubated in 5% to 10% carbon dioxide at 35 °C. After incubation, the colonies were differentiated and enumerated by standard bacteriologic procedures.

RESULTS

Table 1 gives the mean number of colonies and species per subject isolated from untreated and experimental eyes before and after instillation of this mild silver protein solution. Although the number of colonies and species were greater after the preparation than before in both mild silver protein solution-treated and untreated eyes, in no case was the increase of actual numbers significant at the 5% level by Student's *t* test. The difference in the amount of increase of actual number in the untreated eye as opposed to the mild silver protein solution-treated eye also was not found to be significant at the 5% level.

The pattern of sterile cultures before and after chemical preparation of the eye is given in Table 2. Of all the eyes in this study, only three of the 15 that were sterile before preparation remained sterile after preparation.

The organisms cultured were diphtheroids, *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Candida albicans*, and *Klebsiella* sp.

COMMENT

This mild silver protein solution originally was intended to be an antimicrobial agent. The colloidal suspension liberates silver ions that alter the protein in the bacterial cell wall. It

also has been suggested that silver interferes with essential metabolic activity of bacteria.⁴ The silver in this mild silver protein solution ionizes poorly, and thus causes less irritation than silver nitrate. However, its germicidal effectiveness is also decreased. Pharmacologists have written that "colloidal silver preparations are now in a deserved oblivion."⁵ Duke-Elder expressed the opinion that this mild silver protein solution has "little bactericidal action since few free ions are liberated."⁶ Havener noted that "Argyrol is one of the poorest germicides."⁷ None of these authors cited a controlled study on humans to support their assertions. Despite these negative opinions, almost a quarter of the 214 ophthalmologists surveyed in a large international study (with a 96%-response rate) continue to use this mild silver protein solution in the preoperative chemical preparation of the eye.⁸ This investigation, using detailed bacteriologic analysis, was unable to verify that the application of this mild silver protein solution on the eye in vivo was significantly better than an untreated eye in reducing the number of microorganisms on the conjunctiva.

Another property of this mild silver protein solution contributes to its popularity. This mild silver protein solution has the capability of darkly staining mucus or debris present on the conjunctiva, eyelids, or skin. It therefore serves as a marker for the adequacy of the preoperative surgical preparation of the eye. The surgeon may then irrigate any remaining mucus and debris from the eye. Indeed, in the international survey by Apt and Isenberg,⁸ many respondents

commented that they used it mainly to distinguish mucus and debris in the preparation. However, this positive aspect of the tested mild silver protein solution must be weighed against our recent finding that irrigation itself increases the bacterial flora of the conjunctiva (see p 761).

In the design of this study, it was decided to irrigate the conjunctiva of the eye receiving the mild silver protein solution as is commonly practiced. The control eye received no irrigation in light of our aforementioned findings. Thus, any increased degree of antisepsis obtained by the mild silver protein solution may be offset by the increase in bacterial flora engendered by irrigation.

A frequently cited study of the effectiveness of the tested mild silver protein solution and other agents is that of Thompson et al⁶ published in 1937. Of the ten bactericidal agents they studied, our tested mild silver protein solution (Argyrol) had the second highest percentage of surviving organisms after one and ten minutes of exposure. Although the investigation by Thompson et al was performed on the conjunctiva of rabbits, doubts about the effectiveness of our tested mild silver protein solution should have been raised at that time. On the human conjunctiva, our study did not find a significant bactericidal effect of this mild silver protein solution when investigated in a masked fashion.

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Chemical Preparation of Skin and Eye in Ophthalmic Surgery: An International Survey

Leonard Apt, M.D.
Sherwin Isenberg, M.D.

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SUMMARY

We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

Since the studies of Carl Eberth in 1875, surgeons have known that bacteria are found in hair follicles, sweat glands, and in both the superficial and deeper layers of the skin.¹ Joseph Lister's carbolic acid in spray form, or soaked in gauze and laid on the skin, was the first attempt at preoperative antisepsis. Subsequently, other techniques for achieving preoperative asepsis of the operative field have evolved.

Today, in the course of training in ophthalmic surgery, or when visiting different institutions, one often sees different techniques in preoperative chemical preparation of the eye. The main reasons given for using a certain regimen are tradition and the impression of effectiveness. A scientific rationale rarely is mentioned. To learn the preferences of many ophthalmologists throughout the world, and to determine whether a consensus on a specific regimen exists, we undertook a survey. This information is not found in the ophthalmic literature. The survey was not intended to answer questions definitively about the best method and choice of agents.

MATERIALS AND METHODS

Questionnaires were mailed to 221 ophthalmologists of which 214 were answered and returned. This return rate is

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96.8%. In order to obtain a representative sample, about half of the questionnaires were sent to well-known ophthalmic surgeons at academic institutions and half to prominent private practitioners of ophthalmology. Ten percent of the questionnaires were answered by well-known ophthalmic surgeons from such foreign countries as Mexico, Belgium, Japan, Argentina, Canada, Germany, Great Britain, and Switzerland.

The first series of questions asked concerned the sequence of solutions applied to the skin, the duration of application, and the area of the face receiving the application. The second series of questions dealt with solutions intentionally placed on the conjunctiva, duration of application, and what was used as the rinsing agent. The third question asked what proportion of the preparation was done by a physician, nurse, or other nonphysician. Finally, additional comments were requested.

RESULTS

There was considerable disparity in the types and sequence of agents placed on the skin (Table 1). However, 67.5% of the respondents used povidone-iodine products (as Betadine, Isodine, Prepodyne, Septodyne) somewhere in the preparation, while hexachlorophene (pHisoHex) was used by 16.5%, and aqueous iodine solution was used by 12.6% somewhere in the preparation. The most frequent regimen of all, used by a third of the respondents, was povidone-iodine solution on the skin followed by a rinse with alcohol. The term "rinse" includes saline, sterile water, lactated Ringer solution, balanced salt solution, or similar product (Figure 1). Half of the respondents used a single

TABLE 1
ROUTINE OF CHEMICAL AGENTS
USED FOR SKIN PREPARATION
 (n=196)

Multiple Agents	Percent
Povidone-iodine soap - rinse* - Povidone-iodine solution ± alcohol	15.0
Soap + rinse - Povidone-iodine solution ± rinse or alcohol	7.3
Hexachlorophene ± alcohol or rinse - Povidone-iodine ± alcohol or rinse	7.3
Soap ± rinse ± alcohol ± rinse	4.0
Soap ± rinse ± Iodine ± alcohol	3.9
Hexachlorophene + rinse - Iodine ± alcohol	2.4
Hexachlorophene + rinse - merthiolate	1.5
Povidone-iodine - rinse - Iodine	1.0
Alcohol - Povidone-iodine	1.0
Single Agents - Rinse or Alcohol	
Povidone-iodine	32.5
Iodine 1%	4.8
Hexachlorophene	4.3
Zephiran	2.9
Iorhexidene 1%	2.4
Merfen	1.0
Merthiolate	1.0
Alcohol	1.0
Don't know	1.0

*Rinse = saline solution, sterile water, lactated Ringer solution, balanced salt solution, or similar product.

TABLE 2
CHEMICAL AGENTS INTENTIONALLY PLACED
ON THE CONJUNCTIVA
 (n=206)

Chemical Agent	Percent
Normal Saline	34.5
Nothing	26.7
Argyrol ± rinse	22.3
Balanced salt solution	5.3
Betadine solution (diluted)	2.4
Neosporin ± rinse	2.0
Ringer solution	1.5
Chlorhexidine	1.0
Sterile water	1.0
Chloramphenicol	1.0
Mercury bichloride	1.0
Gentamycin	0.5
1/2 Gentamycin mix	0.5
Don't know	0.5

8 deferred or did not answer.

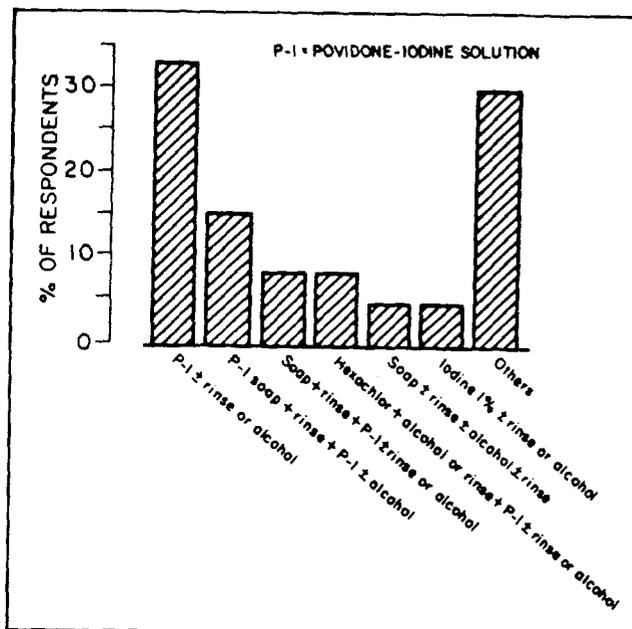


FIGURE 1. (Apt and Isenberg). Percentage of respondents using a particular chemical agent on the skin as part of the preoperative preparation.

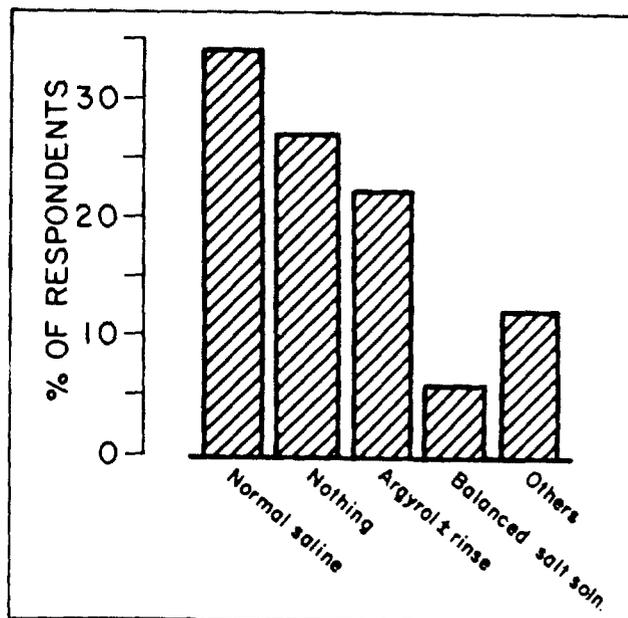


FIGURE 2. (Apt and Isenberg). Percentage of respondents using a particular chemical agent on the conjunctiva as part of the preoperative preparation.

primary agent (such as aqueous iodine, hexachlorophene, or a povidone-iodine product) followed by a rinse or alcohol, while half used a combination of primary agents (Table 1).

The amount of time that these agents were applied to the skin varied from one second to several minutes. So much variation in the length of time was reported as to make

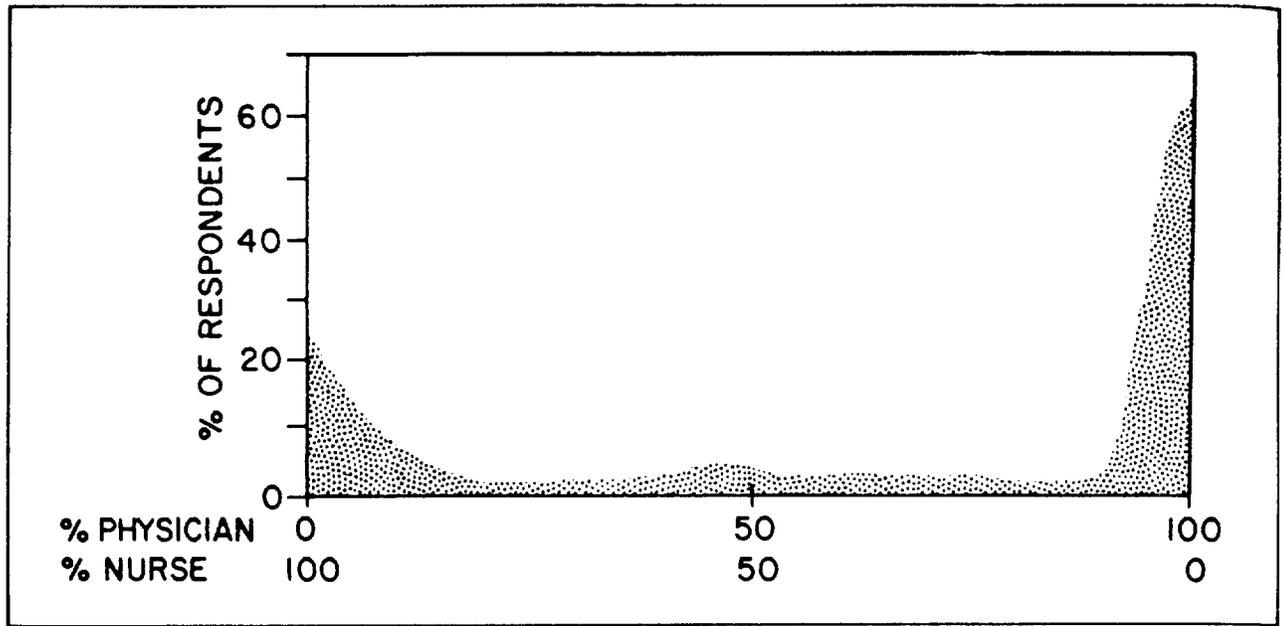


FIGURE 3: (Apt and Isenberg). Relative proportion of physicians compared with nurses performing preoperative preparation of the eye.

TABLE 3
HOW MUCH IS DONE BY PHYSICIAN
RELATIVE TO NURSE
(n=205)

Physician/Nurse	Percent
100%/ 0	62.0
98%/ 2%	0.5
90%/ 10%	0.5
80%/ 20%	1.0
75%/ 25%	1.0
50%/ 50%	2.9
25%/ 75%	1.5
20%/ 80%	0.5
15%/ 85%	0.5
10%/ 90%	4.4
0 100%	29.4
Not known	0.5

9 deferred or did not answer.

preoperative preparation. Sixty-two percent of the respondents indicated that the physician does the entire preparation, while 29% reported that the nurse does the entire preparation. The rest of the respondents answered that the physician and nurse each do part of the preparation (Table 3 and Figure 3).

COMMENT

The validity of this survey was enhanced by the broad spectrum of ophthalmologists contacted, including subspecialists and general ophthalmologists, academicians and nonacademicians, Americans and foreigners, and younger and senior ophthalmologists. The highly satisfactory rate of returned questionnaires (96.8%) also attests to the validity of this survey.

While all ophthalmologists use a form of chemical preparation for the eye prior to surgery, there has been little recent mention or study of this subject in the ophthalmic literature. A lack of interest in this subject was exhibited by some ophthalmologists who replied that they did not know what agents were used in preparation of the operative field. To answer this survey, these surgeons had to obtain the information from others, usually the surgical nurse. The great disparity found in this study in the chemical agents chosen also indicates a lack of recent scientific interest in this topic. In 1951, Maumenee and Michler compared five different techniques for sterilizing the operative field that were then popular.² These five techniques were soap and saline, either alone or followed by merthiolate or aqueous iodine, and hexachlorophene and saline followed by either benzalkonium chloride or aqueous iodine and alcohol. In our survey, about 11% of the respondents still used one of these techniques. The advent of povidone-iodine, first experimentally in the 1960s and then clinically in the early

conclusions difficult. The facial areas treated were almost universally the forehead, both eyelids, the cheeks, and the nose.

Some ophthalmic surgeons intentionally place solutions on the conjunctiva while others do not (Table 2). About a quarter of the respondents place nothing on the conjunctiva. Forty-two percent simply rinse the conjunctiva with saline solution, balanced salt solution, Ringer solution, or sterile water. Only 31% use a solution bearing any antimicrobial properties. Of the latter, mild silver protein (Argyrol) is by far the most frequently used (Figure 2).

In general, more physicians than nurses perform the

1970s, changed the techniques of many ophthalmologists.³⁻⁴ In fact, this survey showed that povidone-iodine is currently the single most popular agent for use in chemical preparation of the skin prior to ophthalmic surgery in this country.

Povidone (polyvinylpyrrolidone) is a polymer with surfactant properties that combines easily with iodine. About two thirds of the iodine remains in the elemental state and is slowly released for antibiotic activity. Aqueous solutions of iodine can cause toxicity to the skin and corneal epithelium, and inflammatory changes in the conjunctiva. But if iodine is combined with povidone these problems are less common and of lesser magnitude. Povidone-iodine has been shown to be bactericidal and virucidal in dilute solutions within minutes *in vitro*.⁵ Given the proper concentration and enough contact time, it is effective even against fungi and spores.

There is more consensus among ophthalmologists in regard to the immediate preoperative preparation of the conjunctiva. More than two thirds of the respondents either ignore the conjunctiva or merely irrigate it. Irrigation presumably would remove mucus or other debris, but would not bear any significant antimicrobial action. Only 31% of the reports indicated the use of an antimicrobial agent on the conjunctiva just prior to surgery. However, some ophthalmologists may have used topical antibiotics on the conjunctiva in the days preceding surgery. Whether better practice truly sterilizes the conjunctiva, or permits active growth of resistant bacteria or regrowth of the original bacteria if a bacteriostatic drug is used, is controversial.⁶ Argylol was the agent most commonly used on the conjunctiva by those who used antimicrobial agents at the time of surgery. Some individuals commented that Argylol was used because it stains the mucus and other debris, which then can be specifically removed by irrigation, and not necessarily because of its antimicrobial properties.

In reviewing the different combinations of chemicals used to sterilize the skin, some comments of practical importance are indicated. If a soap or scrub is used, either as povidone-iodine, another antimicrobial agent, or simple soap, one should be careful to avoid inadvertent entry of these chemicals onto the conjunctiva. Vascular dilation, hyperemia, and possible corneal damage could result from soap or detergent instillation. Potentially this could lead to more hemorrhage if the conjunctiva is incised. One could place a vasoconstrictor on the conjunctiva before and after the preparation to minimize this problem. Some vasoconstrictors such as phenylephrine will dilate the pupil, while others such as naphazoline will not.

Hexachlorophene is bacteriostatic and is more effective against gram-positive than gram-negative bacteria. It is important to know that a single application of hexachlorophene, as used by some surgeons, has little antimicrobial activity. To be maximally effective, hexachlorophene should be applied at least daily beginning five to seven days prior to

surgery. The film of hexachlorophene then produced enhances its antimicrobial effects. Alcohol should not be used to remove the hexachlorophene. Care should be taken to prevent hexachlorophene from entering the palpebral fissure because it is injurious to the corneal epithelium.⁷

It has been noted that benzylkonium chloride is incompatible with iodine and therefore should not be placed in direct contact with it, even on skin.⁸ In addition, benzylkonium chloride is inactivated by blood, other organic material, soap, and cotton material which often is used in its application. Ophthalmologists who use multiple agents should reconsider their individual activity with regard to effectiveness, spectrum, and duration of action to avoid overlap.

Some doubt exists as to the efficacy of any preoperative chemical preparation of the eye. Lincoff and coworkers found in one study that an extensive preoperative ophthalmic preparation, including three preoperative soap scrubs, povidone-iodine preparation, saline lavage, and bathing and lavaging implants with chloramphenicol, did not significantly alter their rate of infected scleral implants.⁹ In a later study, Hahn, Lincoff, Lincoff, and Kreissig determined that the same organism found on routine intraoperative conjunctival culture was usually the infecting agent in infected scleral implants.¹⁰ They felt that the source of infection was contamination at the site of the buckle operation. Perhaps more emphasis should be placed on sterilization of the conjunctiva. Sterilization of the conjunctiva ultimately might decrease the incidence of infectious endophthalmitis.

REFERENCES

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- 2 Maumenee AE, Michler RC: Sterility of the operative field after ocular surgery. *Trans Pacific Coast Ophthalmol Soc* 1951, 32:172-179.
- 3 Kiffney GT Jr, Hattaway AC: Povidone-iodine as an ophthalmic antiseptic. *Surg Forum* 1966; 17:434-436.
- 4 Chase RC, Ellis PP: Iodophosphors and skin asepsis. *Ann Ophthalmol* 1970, 12:312-317.
- 5 Siggers BA, Stewart GT: Polyvinylpyrrolidone-iodine: an assessment of anti-bacterial activity. *J Hyg (Camb)* 1964, 62:509-518.
- 6 Fahmy JA: Bacterial flora in relation to cataract extraction. V. Effects of topical antibiotics on the preoperative conjunctival flora. *Acta Ophthalmol* 1980, 58:567-575.
- 7 Browning CW, Lippas J: pHisoHex keratitis. *Arch Ophthalmol* 1955, 53:817-824.
- 8 *Physician's Desk Reference*, ed 7. Oradell, Medical Economics Co., 1980, p 1859.
- 9 Lincoff H, Nadel A, O'Connor P: The changing character of the infected scleral implant. *Arch Ophthalmol* 1970, 84:421-426.
- 10 Hahn YS, Lincoff A, Lincoff H, et al: Infection after sponge implantation for scleral buckling. *Am J Ophthalmol* 1979, 87:180-185.

A. INGREDIENT NAME:

THYMOL IODIDE

B. Chemical Name:

Dithymol Diiodide, Iodothymol

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specifications)</i>	<i>(Results)</i>
Assay:	43.0% min.	44.08%

E. Information about how the ingredient is supplied:

Reddish-brown, tasteless powder

F. Information about recognition of the substance in foreign pharmacopeias:

Port. and Swiss.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

It has been used in dusting powders and ointments, and in dental root filling.

I. Information about strength:

J. Information about route of administration:

K. Stability data:

Stable

Loses iodine on prolonged exposure to light.

Gives off purple iodine vapors when heated above 100°

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1240
47716

PRODUCT: THYMOL IODIDE
RELEASE #: 102161

POWDER.
LOT # :B60244A02

GRADE: PURIFIED
CODE:MT15545

SPECIFICATIONS

RESULT

1. DESCRIPTION	REDDISH BROWN POWDER	CONFORMS
2. Identification	To pass test	Passes test
3. Alkalinity	To pass test	Passes test
4. Soluble Halides	1.5% max.	0.9%
5. Assay <i>D</i>	<u>43.0% min.</u>	<u>44.08%</u>
6. Solubility	To pass tests	Passes tests
7. Loss on drying (4 hrs./sulfuric acid)	3% max.	0.2%

ATTENTION: TONY HATCHETT

Date :02/13/97

Prepared by: J.PATEL



QUALITY CONTROL REPORT

CHEMICAL NAME.: THYMOL IODIDE PURIFIED _____

MANUFACTURE LOT NO.: B62871M05

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/NF ___/MERCK ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

REDDISH-BROWN OR REDDISH-YELLOW, BULKY POWDER; SLIGHT AROMATIC
ODOR; LOSES IODINE ON PROLONGED EXPOSURE TO LIGHT. K

2) SOLUBILITY.:

INSOLUBLE IN WATER, GLYCEROL, ALKALINE SOLUTIONS; READILY SOLUBLE
IN CHLOROFORM, ETHER, COLLODION, FIXED AND VOLATILE OILS,
USUALLY LEAVING A SLIGHT RESIDUE; SLIGHTLY SOLUBLE IN ALCOHOL.

3) MELTING POINT.:

K GIVES OFF PURPLE IODINE VAPORS WHEN HEATED ABOVE 100 DEGREES.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

----- IDENTIFICATION -----

PRODUCT #: T2763 NAME: THYMOL IODIDE
CAS #: 552-22-7

----- TOXICITY HAZARDS -----

DATA NOT AVAILABLE

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.
MAY CAUSE IRRITATION.
THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY
INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS
CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,
CALL A PHYSICIAN.

IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

----- PHYSICAL DATA -----

APPEARANCE AND ODOR

POWDER

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING
TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

----- REACTIVITY DATA -----

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

CARBON MONOXIDE, CARBON DIOXIDE

HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR PROTECTIVE EQUIPMENT.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS
COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN
IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR,
CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.

CAUTION:

AVOID CONTACT AND INHALATION.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT
PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL
NOT BE

HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM
CONTACT WITH THE

ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR
ADDITIONAL

TERMS AND CONDITIONS OF SALE

of fungous skin infections.

Thymol (0.01%) is added as an antioxidant to halothane, trichloroethylene, and tetrachloroethylene. Thymol, 10% in isopropyl alcohol, has been used to preserve urine.

Thymol had only a low solubility in water and was a poor bactericide. Its use as a disinfectant even for clinical thermometers was not recommended.—Report by the Public Health Laboratory Service Committee on the Testing and Evaluation of Disinfectants, *Br. med. J.*, 1965, *1*, 408.

Herpes. Fifteen patients with herpes of the genitalia were treated topically with thymol (as Listerine) twice daily. Symptomatic relief was obtained in 14 days with gradual healing of the lesions. There had been one recurrence in 8 months.—H. M. Radman, *Md. St. med. J.*, 1978, *27*, 49. See also V. Knight and M. W. Noall (letter), *New Engl. J. Med.*, 1976, *294*, 337.

Use in food. The Food Additives and Contaminants Committee recommended that, on the grounds of safety, thymol could continue to be used as a stabiliser for solvents used in food.—*Report on the Review of Solvents in Food*, FAC/REP/25, Ministry of Agriculture, Fisheries and Food, London, HM Stationery Office, 1973.

Preparations

Compound Thymol Glycerin (B.P.). Glycerinum Thymolis Compositum. Thymol 50 mg, sodium bicarbonate 1 g, borax 2 g, sodium benzoate 800 mg, sodium salicylate 520 mg, menthol 30 mg, cineole 0.13 ml, pumilio pine oil 0.05 ml, methyl salicylate 0.03 ml, alcohol (90%) (or industrial methylated spirit, suitably diluted) 2.5 ml, glycerol 10 ml, sodium metabisulphite 35 mg, carmine, food grade of commerce, 30 mg, dilute ammonia solution 0.075 ml, water to 100 ml, pH 7.1 to 7.6. To be diluted with about 3 times its vol. of warm water before use; diluted solutions should be prepared immediately before use.

Modified formula. Fading and discoloration of Compound Thymol Glycerin during storage could be minimised by increasing the sodium metabisulphite to 50 mg per 100 ml and by protecting from light.—Pharm. Soc. Lab. Rep. No. P/69/33, 1969.

Reports of contamination of Compound Thymol Glycerin.—M. H. Hughes (letter), *Lancet*, 1972, *1*, 210; T. A. Rees (letter), *ibid.*, 532.

A study suggesting that phenol might be worth investigating as a potential preservative of Compound Thymol Glycerin.—Pharm. Soc. Lab. Rep. P/78/9, 1978. Confirmation that phenol 0.5% was physically compatible with Compound Thymol Glycerin. Initial studies also suggested that cinnamon oil and citral appeared worthy of further investigation as preservatives.—Pharm. Soc. Lab. Rep. P/80/3, 1980.

Compound Thymol Mouth-wash (B.P.C. 1949). Collut. Thymol. Co. Thymol 30 mg, liquefied phenol 0.52 ml, potassium hydroxide solution 0.52 ml, methyl salicylate 0.01 ml, peppermint oil 0.01 ml, bordeaux B solution 1.04 ml, water to 100 ml. To be diluted with 3 times its vol. of warm water before use.

Amended formula. Thymol 30 mg, liquefied phenol 0.52 ml, potassium hydroxide solution 0.52 ml, methyl salicylate 0.01 ml, peppermint oil 0.01 ml, amaranth solution 1 ml, water to 100 ml.—*Compendium of Past Formulae 1933 to 1966*, London, The National Pharmaceutical Union, 1969.

Compound Thymol Solution-tablets (B.P.C. 1963). Solv. Thymol. Co. Each contains thymol 3.24 mg, sodium bicarbonate 324 mg, borax 324 mg, phenol 32.4 mg, and amaranth 650 µg. One solution-tablet to be dissolved in 60 ml of warm water.

Thymol Mouth-wash Compound (A.P.F.). Collut. Thymol. Alb.; Liq. Thymol. Co. Thymol 150 mg, menthol 10 mg, benzoic acid 800 mg, methyl salicylate 0.05 ml, cineole 0.05 ml, glycerol 2 ml, alcohol (90%) 20 ml, water to 100 ml. Dilute with 7 vol. of water for use as a gargle or mouth-wash.

2292-1

Dithymol Di-iodide. 4,4'-Bis(iodo-oxy)-5,5'-di-isopropyl-2,2'-dimethyl-1,1'-biphenyl.
 $C_{20}H_{24}I_2O_2 = 550.2$.

CAS — 552-22-7

2283-e

Thymol Iodide (B.P.C. 1949), Dithymol Diiodide, Iodothymol, Timol Ioduro. A mixture of iodine derivatives of thymol, chiefly dithymol di-iodide, containing not less than 43% of iodine.

NOTE. The name iodothymol is also applied to an antihelmintic compound (see p.94).

Pharmacopoeias. In *Port.* and *Swiss*.

A reddish-brown or buff-coloured, almost tasteless, bulky, amorphous powder with a slight aromatic odour. Practically insoluble in water, glycerol, and sodium hydroxide solution; slightly soluble in alcohol; soluble in chloroform, ether, soft paraffin, and fixed and volatile oils, usually leaving a slight residue. Incompatible with alkalis, mercuric chloride, and metallic oxides. Protect from light.

Thymol iodide is insoluble and has little or no antiseptic action but acts as an absorbent and protective. It has been used in dusting-powders and ointments, and in dental root filling preparations.

2284-1

Tribromometacresol. 2,4,6-Tribromo-*m*-cresol;

2,4,6-Tribromo-3-methylphenol.

$C_7H_5Br_3O = 344.8$.

CAS — 4619-74-3.

Tribromometacresol is an antifungal agent used in the treatment of dermatomycoses. It is applied topically as an aerosol spray containing 2%. It should be applied with caution to suppurating mycoses; it should not be applied near the eyes or mucous membranes.

Proprietary Names

Triphysan (*Dumex. Denm.*); Tri-Physol (*Sigma. Austral.*).

2285-y

Triclobisonium Chloride. Hexamethylenebis[*d*-methyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]ammonium chloride].

$C_{36}H_{74}Cl_2N_2 = 605.9$.

CAS — 7187-64-6 (*triclobisonium*); 79-90-3 (*chloride*).

A white or nearly white, almost odourless, crystalline powder. M.p. about 243°. Freely soluble in water, alcohol, and chloroform; practically insoluble in ether. Protect from light.

Triclobisonium chloride is a quaternary ammonium compound with properties and uses similar to those of other cationic surfactants as described under Cetrimide, p.551. It has been reported to have activity against *Candida albicans* and *Trichomonas vaginalis*. It has been applied topically as a 0.1% ointment or cream in the treatment of skin infections and as a 0.1% cream or pessaries in the treatment of vaginitis.

2286-j

Triclocarban. 3,4,4'-Trichlorocarbanilide. 1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea.

$C_{13}H_9Cl_3N_2O = 315.6$.

CAS — 101-20-2.

A fine white odourless powder. M.p. 250° to 256°. Practically insoluble in water; soluble 1 in 25 of acetone, 1 in 100 of propylene glycol, and 1 in 100 of dimethyl phthalate; soluble 1 in 10 to 1 in 4 of macrogols.

Macrogol 400 monolaurate increased the solubility of triclocarban, resulting in increased bactericidal activity.—A. E. Elkhouly and R. C. S. Woodroffe, *J. appl. Bact.*, 1973, *36*, 387.

Adverse Effects and Precautions. When subjected to prolonged high temperatures triclocarban can decompose to form toxic chloroanilines, which can be absorbed through the skin. Mild photosensitivity has been seen in patch testing.

An outbreak of methaemoglobinaemia in 18 infants (12 premature) in a nursery in a 5-week period ceased when the laundry process applied to clothing and napkins was revised. The process had involved washing in detergent, bluing, a chemical rinse containing triclocarban 2%, neutralising, drying and autoclaving.—R. O. Fisch *et al.*, *J. Am. med. Ass.*, 1963, *185*, 760.

Eight patients developed methaemoglobinaemia after receiving an enema prepared from soap containing about 2% of triclocarban. Three days prior to the incident the procedure for preparing the soap gel had been changed to include heating near to boiling-point for several hours. Laboratory tests showed that boiling reduced the triclocarban content of the soap gel (pH 9.5) and led to the formation of primary amines.—R. R. Johnson *et al.*, *Pediatrics*, 1963, *31*, 222.

Cutaneous and mucosal lesions.—H. Barrière, *Therapeutique*, 1973, *49*, 685.

Uses. Triclocarban is a non-phenolic disinfectant. It is bacteriostatic against Gram-positive organisms in high dilutions but is less effective against Gram-negative organisms and some fungi. It is used in soaps, usually in a concentration of 2%, for similar purposes to hexachlorophane, and has been applied in solutions, powders, and ointments for the control of skin infections.

A review of antimicrobial agents, including triclocarban, used in cosmetics.—I. R. Gucklhorn, *Mfg Chem.*, 1970, *41* (Feb.), 30.

Proprietary Preparations

Cutisan (Martindale Pharmaceuticals, UK; Farillon, UK). Triclocarban, available as Ointment containing 2%; as Powder containing 1%; and as Solution containing 1%. For infected skin conditions, leg ulcers, and burns. (Also available as Cutisan in *Fr.*)

TCC (Monsanto, UK). A brand of triclocarban.

Other Proprietary Names

Arg.—Ungel; *Belg.*—Solubacter; *Fr.*—Nobacter, Septivon-Lavril, Solubacter.

A preparation containing triclocarban was also formerly marketed in Great Britain under the proprietary name Crinagen (*Pharmax*).

2287-z

Triclosan. Cloxifenol; CH 3565. 5-Chloro-2-(2,4-dichlorophenoxy)phenol.

$C_{12}H_7Cl_3O_2 = 289.5$.

CAS — 3380-34-5.

A white to off-white crystalline powder or soft agglomerates with a slightly aromatic odour. M.p. 55° to 57°. Practically insoluble in water; very soluble in most organic solvents; soluble 1 in 3 of 4% sodium hydroxide solution. Protect from light.

Adverse Effects. Contact dermatitis has occasionally been reported.

From studies on the percutaneous absorption of triclosan in rats, it was calculated that the absorbed dose from a shampoo preparation (0.05% triclosan) in a woman would be about 4.8 µg per kg body-weight and from an aerosol (0.1% triclosan) 24.9 µg per kg. These doses were considered to have no effect in humans.—J. G. Black and D. Howes, *J. Soc. cosmet. Chem.*, 1975, *26*, 205.

Uses. Triclosan is bacteriostatic against Gram-positive and most Gram-negative organisms. It has little activity against *Pseudomonas* spp., yeasts, or fungi. It is used in surgical scrubs, soaps, and deodorants in concentrations of 0.05 to 2%.

Review of properties and microbiological activity.—T. E. Funa and A. G. Schenkel, *Soap chem Spec.*, 1968, *44* (Jan.), 47.

Handwashing for 2 minutes with soap containing triclosan 0.75% was less effective in removing skin bacteria than washing with soap containing hexachlorophane 2%.

rotatory, but the angle of rotation in a
 yme Oil is not less than 1.4950 and not
 yme Oil with 10 ml. of hot water, and
 moistened filter: not even a transient
 te upon the addition of 1 drop of ferric

Oil into a cassia flask, add 75 ml. of
 tightly, shake the mixture thoroughly,
 cient potassium hydroxide T.S. to raise
 e graduated portion of the neck of the
 me clear, adjust it to the temperature
 volume of the residual liquid. This
 e presence of not less than 40 per cent,

in tight, light-resistant containers.

y 1½ minims).

OL

H



Mol. wt. 150.22

tals, often large, or as a white, crystal-
 like odor and a pungent taste. It is
 nsity than water, but when liquefied by
 ol solution is neutral to litmus.

about 1000 ml. of water, in 1 ml. of
 f ether, and in about 2 ml. of olive oil.
 d or volatile oils.

l weight of camphor or menthol: the

d in 1 ml. of glacial acetic acid, and add
 of nitric acid: the liquid shows a deep
 flected light.

tube in a water bath with 5 ml. of a 10
 : a clear, colorless, or pale red solution
 n standing, without the separation of
 few drops of chloroform to this solution
 t color is produced.

nd 51°, but when melted remains liquid
 391.

Non-volatile residue—Volatilize about 2 Gm. of Thymol, accurately weighed, on a
 water bath, and dry at 100° to constant weight: not more than 0.05 per cent of
 residue remains.

Packaging and storage—Preserve Thymol in tight, light-resistant containers.

CATEGORY—Antifungal; antibacterial; anthelmintic.

USUAL DOSE—Anthelmintic, 2 Gm. (approximately 30 grains) divided
 into three doses.

Thymol Iodide

THYMOL IODIDE

Thymol Iodide is a mixture of iodine derivatives of thymol, princi-
 pally dithymol diiodide $[\text{C}_9\text{H}_7(\text{CH}_3)(\text{OI})(\text{C}_9\text{H}_7)-1,3,4]_2$, containing,
 when dried over sulfuric acid for 4 hours, not less than 43 per cent of I.

Description—Thymol Iodide occurs as a reddish brown or reddish yellow, bulky
 powder, with a very slight, aromatic odor. It is affected by light.

Solubility—Thymol Iodide is freely soluble in chloroform, in ether, in collodion,
 and in fixed and volatile oils, usually leaving a slight residue. It is slightly soluble
 in alcohol. Thymol Iodide is insoluble in water and in glycerin, and in cold and
 in hot solutions of the fixed alkali hydroxides.

Identification—Heat about 100 mg. of Thymol Iodide with 2 ml. of sulfuric acid: it
 decomposes with the separation of iodine.

Loss on drying—Dry Thymol Iodide over sulfuric acid for 4 hours: it loses not more
 than 2 per cent of its weight, page 690.

Residue on ignition—Thymol Iodide yields not more than 1.5 per cent of residue on
 ignition, page 711.

Soluble halides—Digest 100 mg. of Thymol Iodide with 50 ml. of warm water for
 10 minutes, filter, cool, and add 5 drops of diluted nitric acid and 1 ml. of silver
 nitrate T.S.: any turbidity produced is not greater than that in a control test
 containing 2 mg. of potassium iodide.

Alkalinity—Shake 500 mg. of Thymol Iodide with 10 ml. of water, and filter the mix-
 ture: the filtrate is not alkaline to litmus.

Iodine—Shake 500 mg. of Thymol Iodide with 10 ml. of water, filter the mixture, and
 add a few drops of starch T.S.: no blue color is produced.

Assay—Mix thoroughly about 250 mg. of Thymol Iodide, previously dried over sul-
 furic acid for 4 hours and accurately weighed, with about 3 Gm. of anhydrous
 potassium carbonate. Place the mixture in a platinum crucible, cover with about
 1 Gm. of anhydrous potassium carbonate, and heat moderately, gradually in-
 creasing the heat but not exceeding a dull redness, until the mass is completely
 carbonized. Extract the residue with boiling water until the last washing, after
 acidification with diluted nitric acid, produces no opalescence with silver nitrate
 T.S. Heat the combined washings, which measure about 150 ml., on a water
 bath, and add a solution of potassium permanganate (1 in 20) in small portions,
 until the hot liquid remains pink. Add just enough alcohol to remove the pink
 tint, cool to room temperature, dilute to exactly 200 ml., mix well, and filter
 through a dry filter, rejecting the first 50 ml. of filtrate. To exactly 100 ml. of the
 subsequent clear filtrate, add about 1 Gm. of potassium iodide (free from iodate)
 and an excess of diluted sulfuric acid, and titrate the liberated iodine with 0.1 N
 sodium thiosulfate, adding starch T.S. near the end of the titration. Each ml.
 of 0.1 N sodium thiosulfate is equivalent to 2.115 mg. of I.

Packaging and storage—Preserve Thymol Iodide in tight, light-resistant containers.

CATEGORY—Antifungal; anti-infective.

MSDS Material Safety Data Sheet
Professional Compounding Centers of America
9901 South Wilcrest, Houston Texas 77099 1-800-331-2498

24 Hour Chemtrec Phone 1-800-424-9300

----- IDENTIFICATION -----
PRODUCT #: 30-1240 NAME: THYMOL IODIDE
CAS #: 552-22-7

----- TOXICITY HAZARDS -----
DATA NOT AVAILABLE

----- HEALTH HAZARD DATA -----
ACUTE EFFECTS
MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.
MAY CAUSE IRRITATION.
THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY
INVESTIGATED.

FIRST AID
IF SWALLOWED, WASH OUT MOUTH WITH WATER
PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER
FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND
SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,
CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER
FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING
THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

----- PHYSICAL DATA -----
APPEARANCE AND ODOR: POWDER

----- FIRE AND EXPLOSION HAZARD DATA -----
EXTINGUISHING MEDIA
WATER SPRAY.
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

----- REACTIVITY DATA -----
STABILITY
STABLE. K

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
CARBON MONOXIDE, CARBON DIOXIDE

HAZARDOUS POLYMERIZATION WILL NOT OCCUR.

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR PROTECTIVE EQUIPMENT.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.

CAUTION:

AVOID CONTACT AND INHALATION.

THE ABOVE INFORMATION ON THIS MSDS WAS OBTAINED FROM CURRENT AND REPUTABLE SOURCES. HOWEVER THE DATA IS PROVIDED WITHOUT WARRANTY, EXPRESSED OR IMPLIED, REGARDLESS OF ITS CORRECTNESS OR ACCURACY. IT IS THE USER'S RESPONSIBILITY BOTH TO DETERMINE SAFE CONDITIONS FOR USE OF THIS PRODUCT AND TO ASSUME LIABILITY FOR LOSS, INJURY, DAMAGE OR EXPENSE RESULTING FROM IMPROPER USE OF THIS PRODUCT.

A. INGREDIENT NAME:

TINIDAZOLE

B. Chemical Name:

1-(2-ethylsulphonylethyl)-2-methyl-5-nitroimidazole

C. Common Name:

Fasigin

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.36% dry basis

E. Information about how the ingredient is supplied:

An almost white or pale yellow, crystalline powder, odorless.

F. Information about recognition of the substance in foreign pharmacopeias:

British Pharmacopeia 1993

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Ripa, T. The plasma half-life was about 13 hours. *Chemotheraapy, Basle*, 1977; 14: 1084.

Jokipii, A. M. M Concentrations in the CSF. *J antimicrob. Chemother.*, 1977; 3: 239.

Sawyer, P. R. A review of tinidazole in the treatment of trichomoniasis, amoebiasis, and giardiasis. *Drugs*, 1976; 11: 423.

Wüst, J. Figures achieved with metronidazole and ornidazole. *Antimicrob, Ag Chemother.* 1977; 11: 631.

Wise, R. The median minimum inhibitory concentration of tinidazole against *Bacteroides*. *Chemotherapy, Basle*, 1977; 23: 19.

Klustersky, J. The activities of clindamycin, tinidazole, an doxycycline in vitro. *Antimicrob. Ag. Chemother.*, 1977; 12: 563.

Bakshi, J. S. Amoebiasis. *Drugs*, 1978; 15(Suppl): 1, 33.

Apte, V. V. and Packard, R. S. Excellent response was achieved in patients with trichomonal vaginitis. *Drugs*, 1978; 15(Suppl 1): 43.

Welch, J. S. A single dose of tinidazole was as effective as the longer regimen. *Med J Aust.*, 1978; 1: 469.

Levi, G. C. A cure-rate in patients with giardiasis treated with tinidazole. *Am J trop Med. Hyg.* 1977; 26: 564.

Anjaneyulu, R. Trichomoniasis. *J int. med Res.*, 1977; 5: 438.

H. Information about dosage forms used:

Capsules

I. Information about strength:

150mg twice a day

J. Information about route of administration:

Orally

K. Stability data:

Manufacture Date: June 1997

Expiration Date: June 2002

Store in a well-closed container, protected from light.

L. Formulations:

M. Miscellaneous Information:

ANALYSIS CERTIFICATE No. 3203

30-2391
54235

Your Ord. No. - 8th October 1997

Our Ref. No. 2905

MATERIAL	Quantity	Batch
TINIDAZOLE JP 12 1-(2-(ethylsulfonyl)-ethyl)-2-methyl-5-nitroimidazole	Kg. 10.-	75179

Empirical formula $C_8H_{13}N_2O_4S$

Specific rotation

Molecular weight 247.28

Aspect crystalline powder

Light absorption

Color creamish

Odor characteristic odour

Loss on drying 0.2565%

Taste

Residue on ignition 0.046%

Melting point 126.1°C

Chloride

Boiling range

Sulfate

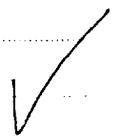
Solubility conforms

Heavy metals max. 10 ppm

Identification: positive.

pH

Titer (Assay) 99.36% dry basis



Other requirements, notes Related substances by TLC : passes.

Bulk density : 0.6502 gm/u

MANUF. DATE : JUNE 1997
EXPIRY DATE : JUNE 2002

The Analyst

11/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: TINIDAZOLE

MANUFACTURE LOT NO.: 77405

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

E 1) DESCRIPTION.:

PALE YELLOW FINE CRYSTALLINE POWDER; ODORLESS.

2) SOLUBILITY.:

SPARINGLY SOLUBLE IN WATER AND IN ALCOHOL; SOLUBLE IN DILUTE ACIDS.

3) MELTING POINT.:

MELTS AT ABOUT 126-127 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) COMPLIES (A) AS PER IR SPECTRUM CO. SPECS.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

----- IDENTIFICATION -----

PRODUCT #: T3021 NAME: TINIDAZOLE

CAS #: 19387-91-8

MF: C8H13N3O4S1

SYNONYMS

BIOSHIK * CP 12574 * 1-(2-(ETHYLSULFONYL)-ETHYL)-2-METHYL-5-NITROIMIDAZOLE * FASIGIN * FASIGYN * 1H-IMIDAZOLE, 1-(2-(ETHYLSULFONYL)ETHYL)-2-METHYL-5-NITRO- * PLETIL * SIMPLOTAN * SORQUETAN * TINIDAZOL * TINIDAZOLE * TRICOLAM * TRIMONASE *

----- TOXICITY HAZARDS -----

RTECS NO: NI6255000

IMIDAZOLE, 1-(2-(ETHYLSULFONYL)ETHYL)-2-METHYL-5-NITRO-

TOXICITY DATA

ORL-RAT LD50:2710 MG/KG	IYKEDH 11,811,80
IPR-RAT LD50:2720 MG/KG	IYKEDH 11,811,80
SCU-RAT LD50:3000 MG/KG	IYKEDH 11,811,80
IVN-RAT LD50:>250 MG/KG	YKYUA6 32,204,81
ORL-MUS LD50:3200 MG/KG	JMCMAR 21,781,78
IPR-MUS LD50:2730 MG/KG	IYKEDH 11,811,80
SCU-MUS LD50:3940 MG/KG	IYKEDH 11,811,80
IVN-MUS LD50:>250 MG/KG	YKYUA6 32,204,81

TARGET ORGAN DATA

BEHAVIORAL (SOMNOLENCE)

BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)

LUNGS, THORAX OR RESPIRATION (CYANOSIS)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES
(RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

EXPOSURE CAN CAUSE:

GASTROINTESTINAL DISTURBANCES

NAUSEA, HEADACHE AND VOMITING

URTICARIA, FLUSHING, PRURITUS, DYSURIA, CYSTITIS, DRYNESS OF THE MOUTH,

DIZZINESS, VERTIGO, AND VERY RARELY, INCOORDINATION AND ATAXIA,

A METALLIC, SHARP, UNPLEASANT TASTE, FURRY TONGUE, GLOSSITIS, AND STOMATITIS.

EXPOSURE TO AND/OR CONSUMPTION OF ALCOHOL

MAY INCREASE TOXIC EFFECTS.

CHRONIC EFFECTS

POSSIBLE CARCINOGEN.

POSSIBLE MUTAGEN.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.

IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

----- PHYSICAL DATA -----

MELTING PT: 127-128°C

SOLUBILITY: CHLOROFORM-SOLUBLE

APPEARANCE AND ODOR

SOLID.

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO

PREVENT CONTACT WITH SKIN AND EYES.

----- REACTIVITY DATA -----

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

THERMAL DECOMPOSITION MAY PRODUCE CARBON MONOXIDE, CARBON DIOXIDE,

AND NITROGEN OXIDES.

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

NIOSH/MSHA-APPROVED RESPIRATOR.

USE ONLY IN A CHEMICAL FUME HOOD.

COMPATIBLE CHEMICAL-RESISTANT GLOVES.

CHEMICAL SAFETY GOGGLES.

HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

POSSIBLE RISK OF IRREVERSIBLE EFFECTS.

WEAR SUITABLE PROTECTIVE CLOTHING.

DO NOT BREATHE DUST.

POSSIBLE CARCINOGEN.

POSSIBLE MUTAGEN.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE

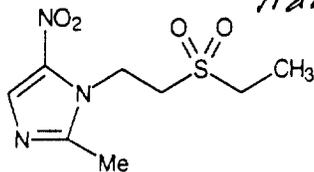
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE

ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL

TERMS AND CONDITIONS OF SALE

Tinidazole ☆

ACBP 1993
Addendum
1996



$C_8H_{13}N_3O_4S$ 247.3 19387-91-8

Definition Tinidazole contains not less than 98.0% and not more than 101.0% of 1-(2-ethylsulphonyl)-2-methyl-5-nitroimidazole, $C_8H_{13}N_3O_4S$, calculated with reference to the dried substance.

Characteristics An almost white or pale yellow, crystalline powder; practically insoluble in water; soluble in acetone and in dichloromethane; sparingly soluble in methanol.

Identification Identification test C may be omitted if identification tests A, B, D and E are carried out. Identification tests B, D and E may be omitted if identification tests A and C are carried out.

A. Melting point, 125° to 128°, Appendix V A, Method I.
B. Dissolve 10 mg in methanol and dilute to 100 ml with the same solvent. Dilute 1 ml of the solution to 10 ml with methanol. Examined between 220 nm and 350 nm, Appendix II B, the solution shows an absorption maximum at 310 nm. The specific absorbance at the maximum is 340 to 360.

C. Examine by infrared absorption spectrophotometry, Appendix II A. The absorption maxima in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the spectrum obtained with tinidazole EPCRS. Examine the substances prepared as discs.

D. Examine the chromatograms obtained in the test for Related substances. The principal spot in the chromatogram obtained with solution (2) is similar in position and size to the principal spot in the chromatogram obtained with solution (3).

E. To about 10 mg add about 10 mg of zinc powder, 0.3 ml of hydrochloric acid and 1 ml of water. Heat in a water bath for 5 minutes and cool. The solution yields the reaction characteristic of primary aromatic amines, Appendix VI.

Appearance of solution Dissolve 1.0 g in acetone and dilute to 20 ml with the same solvent. The solution is clear, Appendix IV A, and not more intensely coloured than reference solution Y₅, Appendix IV B, Method II.

Related substances Examine by thin-layer chromatography, Appendix III A, using silica gel GF₂₅₄ as the coating substance.

Solution (1) Dissolve 0.20 g of the substance being examined in methanol with the aid of ultrasound and dilute to 10 ml with the same solvent.

Solution (2) Dilute 1 ml of solution (1) to 10 ml with methanol.

Solution (3) Dissolve 20 mg of tinidazole EPCRS in methanol and dilute to 10 ml with the same solvent.

Solution (4) Dilute 1 ml of solution (2) to 20 ml with methanol.

Solution (5) Dilute 4 ml of solution (4) to 10 ml with methanol.

Solution (6) Dissolve 10 mg of 2-methyl-5-nitroimidazole (tinidazole impurity A) in methanol and dilute to 100 ml with the same solvent.

Solution (7) Dissolve 10 mg of tinidazole impurity B EPCRS in methanol and dilute to 100 ml with the same solvent.

Heat the plate at 110° for 1 hour and allow to cool.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using a mixture of 25 volumes of butan-1-ol and 75 volumes of ethyl acetate. Allow the plate to dry in air and examine in ultraviolet light (254 nm).

Any spots corresponding to tinidazole impurity A and to tinidazole impurity B in the chromatogram obtained with solution (1) are not more intense than the corresponding spots in the chromatogram obtained with solutions (6) and (7), respectively (0.5%).

Any other secondary spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%) and at most one such spot is more intense than the spot in the chromatogram obtained with solution (5) (0.2%).

Heavy metals 1.0 g complies with limit test D for heavy metals, Appendix VII (20 ppm). Prepare the standard using 2 ml of lead standard solution (10 ppm Pb).

Loss on drying Not more than 0.5%, determined on 1 g by drying in an oven at 100° to 105°, Appendix IX D.

Sulphated ash Not more than 0.1% determined on 1 g, Appendix IX A, Method II.

Assay Dissolve 0.15 g in 25 ml of anhydrous acetic acid. Titrate with 0.1M perchloric acid VS, determining the end point potentiometrically, Appendix VIII B. Each ml of 0.1M perchloric acid VS is equivalent to 24.73 mg of $C_8H_{13}N_3O_4S$.

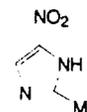
Storage Store in a well-closed container, protected from light.

Action and use Antiprotozoan; antibacterial.

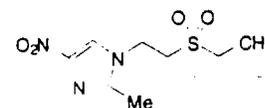
1/96

The impurities limited by the requirements of this monograph include:

2-methyl-5-nitro-1H-imidazole
(tinidazole impurity A)



1-(2-ethylsulphonyl)-
2-methyl-4-nitroimidazole
(tinidazole impurity B)



suramin had differing toxicity. Storage in the tropics probably also affected the potency.— E. Nnochi, *Trans. R. Soc. Trop. Med. Hyg.*, 1964, 58, 413.

Adverse Effects. Suramin may cause nausea, vomiting, abdominal pain, diarrhoea, urticaria, collapse, paraesthesia, hyperaesthesia of the hands and soles of the feet, peripheral neuritis, fever, skin rash, dermatitis, photophobia, lachrymation, amblyopia, and uveitis. A serious effect is albuminuria, with the passage of casts and blood cells. Agranulocytosis and haemolytic anaemia are rare.

When used in onchocerciasis some of the effects may represent an allergic reaction to the killed filariae.

References: Second Report of a WHO Expert Committee on Onchocerciasis, *Tech. Rep. Ser. Wild Hlth Org. No. 335*, 1966.

Pregnancy and the neonate. Suramin had teratogenic effects in mice.— H. Tuchmann-Duplessis and L. Mercier-Parot, *C. r. Séanc. Soc. Biol.*, 1973, 167, 1717, per *Trop. Dis. Bull.*, 1974, 71, 1107. A woman with advanced trypanosomiasis was successfully treated with suramin and melarsoprol, in addition to supportive therapy, from the 20th week of pregnancy; she gave birth to an apparently normal child.— M. N. Lowenthal, *Med. J. Zambia*, 1971, 5, 175, per *Trop. Dis. Bull.*, 1972, 69, 495.

Precautions. It should not be used in the presence of renal disease or adrenal insufficiency.

Absorption and Fate. Following intravenous injection, suramin becomes bound to plasma proteins and a low concentration in plasma is maintained for up to 3 months.

Uses. Suramin is used in the treatment of the early stages of African trypanosomiasis, especially *Trypanosoma rhodesiense* infections, but as it does not reach the cerebrospinal fluid it is ineffective in the advanced disease when the central nervous system is affected.

Suramin is administered by intravenous injection. To test the patient's tolerance, it is advisable to begin treatment with an injection of 200 mg followed, if well tolerated after 24 to 48 hours by a dose of 20 mg per kg body-weight (up to 1 g) on days 1, 3, 8, 15, and 22. The urine should be tested before each dose, and if protein is present the dose should be reduced or administration delayed.

Combined therapy with trypanamide has been used, particularly for late *T. gambiense* infection; 12 injections can be given intravenously at intervals of 5 days, each containing suramin up to 10 mg per kg body-weight (max. of 500 mg) and trypanamide up to 30 mg per kg (max. of 1.5 g), as a 20% solution prepared immediately before use. Two or 3 such courses have been given at intervals of 1 month. Suramin is more commonly used in conjunction with melarsoprol.

Suramin has also been used in the prophylaxis of trypanosomiasis, in a dose of 1 g to provide protection for up to 3 months, but it may mask latent infections. As with pentamidine, it is important to detect more advanced infections and to treat these with melarsoprol.

Suramin is also effective in clearing the adult filariae of onchocerciasis but has only a limited action on microfilariae. The usual dose is 1 g (after an initial test dose) weekly for 5 or 6 weeks. Diethylcarbamazine is active on the microfilariae and the 2 drugs are sometimes used in conjunction.

Onchocerciasis. Less ocular deterioration was observed in a group of patients with onchocerciasis who had been treated 14 to 15 years earlier with a single full course of suramin 4.2 g, than was seen in a similar untreated group.— F. H. Budden, *Trans. R. Soc. Trop. Med. Hyg.*, 1976, 70, 484. The incidence of optic atrophy increased from 1 in 25 to 5 in 25 three years after patients had been treated with suramin 5.2 g (total dose) for ocular onchocerciasis. There was no change in the incidence (1 in 23) in 23 patients not given suramin.— B. Thylefors and A. Rolland, *Bull. Wild Hlth Org.*, 1979, 57, 479.

cf discussions of the treatment of onchocerciasis.—

Br. J. Ophthalmol., 1978, 62, 427; B. Thylefors, *Bull. Wild Hlth Org.*, 1978, 56, 63.

Further references: B. O. L. Duke *et al.*, *Tropenmed. Parasit.*, 1976, 27, 133; J. Anderson *et al.*, *Tropenmed. Parasit.*, 1976, 27, 263; J. Anderson *et al.*, *Tropenmed. Parasit.*, 1976, 27, 279.

Trypanosomiasis. See Report of a Joint WHO Expert Committee and FAO Expert Consultation, *Tech. Rep. Ser. Wild Hlth Org. No. 635*, 1979.

Preparations

Suramin Injection (B.P.C. 1973). A sterile solution of suramin in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in the requisite amount of Water for Injections. Store the sealed container in a cool place. Protect from light.

Proprietary Names

Germanin (Bayer, Ger.); Moranyl (Specia, Fr.).

4798-p

Teclozan. Win 13,146. *NN'-p*-Phenyl-enedimethylenebis(2,2-dichloro-*N*-(2-ethoxyethyl)acetamide).

$C_{20}H_{21}Cl_2N_2O_4 = 502.3$.

CAS — 5560-78-1.

White crystals. M.p. about 142°. Slightly soluble in water.

Adverse Effects. Headache, nausea, vomiting, diarrhoea, and constipation have been reported, but teclozan is generally well tolerated.

Uses. Teclozan is used in the treatment of intestinal amoebiasis. About 20% of a dose is stated to be absorbed and to be rapidly excreted. The usual dose is 100 mg thrice daily for 5 days, or 500 mg daily, in divided doses, for 3 days.

Of 51 patients with chronic intestinal amoebiasis given teclozan 750 mg daily in divided doses after meals for 2 days, 43 were reported to be cured; a further 5 patients responded to a second course of treatment with teclozan. The drug was well tolerated.— D. Huggins, *Anais Esc. nac. Saude públ. Med. trop.*, 1971, 5, 29, per *Trop. Dis. Bull.*, 1972, 69, 399.

Of 30 patients with mild amoebiasis, 25 were reported cured after receiving teclozan 100 mg thrice daily for 5 days; 2 patients required a second course of treatment and 3 remained resistant to teclozan. Two patients developed diarrhoea during treatment which was otherwise well tolerated.— A. Arcilla-Latonio *et al.*, *J. Philipp. med. Ass.*, 1972, 48, 137, per *Trop. Dis. Bull.*, 1973, 70, 345.

A cure-rate of 92.8% (at 4 weeks) was achieved in 28 boys with chronic amoebiasis given teclozan 100 mg thrice daily for 5 days.— A. Z. El-Abdin *et al.*, *J. Egypt. med. Ass.*, 1973, 56, 174, per *Trop. Dis. Bull.*, 1974, 71, 1028.

Cure in 56 of 60 patients with intestinal amoebiasis after treatment with teclozan 1.5 g in 3 divided doses in 24 hours.— P. Fernandes *et al.*, *Folha med.*, 1974, 69, 293.

Cure in 26 of 27 children, aged 1 to 5 years, with amoebiasis (usually chronic) after treatment with teclozan 750 mg in 3 divided doses in 24 hours.— H. F. Bezerra *et al.*, *Rev. bras. Med.*, 1977, 34, Suppl. (Aug.), 50.

Proprietary Names

Falmonox (Winthrop, Arg.; Winthrop, USA).

4799-s

Tinidazole. CP 12574. 1-[2-(Ethylsulphonyl)ethyl]-2-methyl-5-nitroimidazole. $C_8H_{13}N_3O_2S = 247.3$.

CAS — 19387-91-8.

Colourless crystals. M.p. about 127°.

Adverse Effects and Precautions. As for Metronidazole, p.968.

Absorption and Fate. Tinidazole is absorbed from the gastro-intestinal tract.

Pharmacokinetics of tinidazole and metronidazole in man and in mice.— J. A. Taylor *et al.*, *Antimicrob. Ag. Chemother.*, 1969, 267.

The biological half-life of tinidazole was 12.7 hours after administration of 150 mg as a single dose and when administered twice daily for 7 days to 7 volunteers. The maximum serum concentration was 8.91 µg per ml.— P. G. Welling and A. M. Monro, *Arzneimittel-Forsch.*, 1972, 22, 2128. See also B. A. Wood and A. M. Monro, *Br. J. vener. Dis.*, 1975, 51, 51, per *Abstr. Hyg.*, 1975, 50, 382.

The peak serum concentrations of tinidazole in 4 volunteers 6 to 11 hours after a single dose of 2 g were between 20 and 40 µg per ml, and 48 hours after ingestion the serum concentration was still above the minima. trichomonacidal concentration for most of the 8 strains of *Trichomonas vaginalis* examined.— A. Forsgren and J. Wallin, *Br. J. vener. Dis.*, 1974, 50, 146 and 148, per *Abstr. Hyg.*, 1974, 49, 593.

In 6 gynaecological patients given a single dose of tinidazole 2 g peak serum concentrations were 32 to 52 µg per ml 3 to 6 hours after the dose, and 18 to 35 µg per ml 8.5 to 15 hours after the dose. Concentrations in saliva, vaginal secretions, peritoneal fluid, and various tissue homogenates were broadly comparable with those in serum. The plasma half-life was about 13 hours.— T. Ripa *et al.*, *Chemotherapy, Basle*, 1977, 23, 227, per *Int. pharm. Abstr.*, 1977, 14, 1084.

In 4 healthy subjects given tinidazole 2 g concentrations in the CSF 90 minutes later (17 to 39 µg per ml) were 88% of those in serum.— A. M. M. Jokipii *et al.*, *J. antimicrob. Chemother.*, 1977, 3, 239.

Uses. Tinidazole which is a nitroimidazole like metronidazole has antiprotozoal activity and is effective against *Trichomonas vaginalis*, *Entamoeba histolytica*, and *Giardia lamblia*. It is also active against anaerobic bacteria.

In trichomoniasis it is given by mouth in a dose of 150 mg twice daily for 7 days or as a single dose of 2 g to both men and women. It has been given in similar doses in the treatment of giardiasis.

In amoebiasis doses of 2 g once daily for 3 days are commonly used.

A review of tinidazole in the treatment of trichomoniasis, amoebiasis, and giardiasis.— P. R. Sawyer *et al.*, *Drugs*, 1976, 11, 423.

Proceedings of a symposium on the use of tinidazole in the treatment of amoebiasis, giardiasis, and trichomoniasis.— *Drugs*, 1978, 15, Suppl. 1, 1-60.

The following anaerobic bacteria were inhibited by 3.1 µg per ml of tinidazole and killed by 6.3 µg per ml: *Bacteroides fragilis* and *melaninogenicus*, *Clostridium perfringens* and other species of clostridia, *Eubacterium fusobacterium*, *Peptococcus*, *Peptostreptococcus*, and *Veillonella* spp. *Propionibacterium acnes* was relatively resistant. The same figures were achieved with metronidazole and ornidazole.— J. Wüst, *Antimicrob. Ag. Chemother.*, 1977, 11, 631.

The median minimum inhibitory concentration of tinidazole against *Bacteroides* spp. was 0.12 µg per ml, compared with 0.25 µg per ml for metronidazole or nimorazole.— R. Wise *et al.*, *Chemotherapy, Basle*, 1977, 23, 19.

The activities of clindamycin, tinidazole, and doxycycline *in vitro* were compared against 376 anaerobic bacteria. Clindamycin and tinidazole had MICs of 0.5 and 3 µg per ml respectively against 90% of 200 strains of *Bacteroides fragilis*. Tinidazole had an MIC of 12 µg per ml against 72 strains of the *Clostridium* spp. but benzylpenicillin and ampicillin were more active. Tinidazole was generally less active than benzylpenicillin, ampicillin, cephalothin, carbenicillin, erythromycin, chloramphenicol, tetracycline, and doxycycline against: 20 strains of *Bacteroides melaninogenicus*, 54 of the *Fusobacterium* spp., and 30 strains of anaerobic Gram-positive cocci.— J. Klasterky *et al.*, *Antimicrob. Ag. Chemother.*, 1977, 12, 563.

Amoebiasis. In a series of controlled studies 436 patients with intestinal amoebiasis were treated with tinidazole 600 mg twice daily for 5 days or 2 g once daily for 3 days, or metronidazole 400 mg thrice daily for 5 days or 2 g once daily for 3 days. Cure-rates for tinidazole were 97.2% and 88.3% respectively in patients passing trophozoites and 87.5% and 93.4% in those passing cysts, compared with 87.5% and 73.3%, and 84.2% and 47.3% for metronidazole. A cure-rate of 96% was achieved in 50 patients with hepatic amoebiasis given tinidazole 2 g once daily for 2 days, compared with 75.5% in 49 given metronidazole. A cure-rate of 88.3% was achieved in 92 patients with giardiasis given tinidazole in a mean dose of 61.8 mg per kg as a single dose, compared with 46.7% in 92 given metronidazole 56 mg per kg.— J. S. Bakshi *et al.*, *Drugs*, 1978, 15, Suppl. 1, 33.

In a multicentre study in 8 countries a cure-rate of 95% was achieved in 502 patients with amoebiasis given tinidazole 2 g once daily (50 mg per kg body-weight for children) for 2 or 3 days. An excellent response was achieved in 60, and a good response in 17, of 82 with hepatic amoebiasis. A cure-rate of 88% was achieved in 1 children with giardiasis given a single dose of about 0.0 mg per kg. A cure-rate of 95.2% was achieved in 859 patients with trichomonal vaginitis given a single dose of 2 g.— V. V. Apte and R. S. Packard, *Drugs*, 1978, 15, Suppl. 1, 43.

Of 88 aboriginal children infected with *Giardia lamblia* or *Entamoeba histolytica* 23 received a single dose of tinidazole 1 to 1.5 g, 23 tinidazole 1 to 1.5 g daily for 3 days, 23 metronidazole 200 mg twice daily for 5 days, and 19 were left untreated. Both metronidazole and tinidazole successfully cleared the majority of *G. lamblia* infections but *E. histolytica* infections were more effectively treated with tinidazole. (A single dose of tinidazole was as effective as the longer regimen. No adverse reactions occurred with either drug.— J. S. Welch et al., *Med. J. Aust.*, 1978, 1, 469.

Further references: N. Islam and M. Hasan, *Curr. ther. Res.*, 1975, 17, 161; J. N. Scragg et al., *Archs Dis Childh.*, 1976, 51, 385.

Liver abscess. Tinidazole 57 mg per kg body-weight daily for 5 days or 50 mg per kg daily for 3 days was effective in the treatment of amoebic liver abscess in 23 of 25 children aged 3 months to 6 years.— J. N. Scragg and E. M. Proctor, *Archs Dis Childh.*, 1977, 52, 408.

Of 16 patients with hepatic amoebiasis 15 were cured after treatment with tinidazole 2 g as a single dose daily for 3 to 6 days, compared with 12 of 15 given metronidazole in the same dosage regimen for 4 to 10 days.— N. Islam and K. Hasan, *Drugs*, 1978, 15, Suppl. 1, 26.

Further references:— H. A. Meyer, *E. Afr. med. J.*, 1974, 51, 923, per *Trop. Dis. Bull.*, 1975, 72, 720; S. N. Mathur et al., *J. int. med. Res.*, 1977, 5, 429; M. A. Quaderi et al., *J. trop. Med. Hyg.*, 1978, 81, 16.

Giardiasis. Cure in 35 of 38 children with giardiasis after a single dose of tinidazole; 2 others were cured after a second dose. Doses were: under 1 year, 500 mg; 7 years, 1 g; 12 years, 1.5 g.— S. Danzig and W. L. F. Hatchuel (letter), *S. Afr. med. J.*, 1977, 52, 708, per *Trop. Dis. Bull.*, 1978, 75, 783.

Cure-rate of 96.7% in patients with giardiasis treated with tinidazole 150 mg twice daily for 7 days.— G. C. Yi et al., *Am. J. trop. Med. Hyg.*, 1977, 26, 564, per *Trop. Dis. Bull.*, 1978, 75, 648. See also S. Y. Salih and R. E. Abdalla, *J. trop. Med. Hyg.*, 1977, 80, 11, per *Trop. Dis. Bull.*, 1977, 74, 731.

Cure of 53 of 55 patients with giardiasis given tinidazole 2 g as a single dose.— N. A. El Masry et al., *Am. J. trop. Med. Hyg.*, 1978, 27, 201, per *Trop. Dis. Bull.*, 1978, 75, 544.

See also under Amoebiasis, above.

Further references: L. Jokipii and A. M. M. Jokipii, *J. infect. Dis.*, 1979, 140, 984; M. B. Tadros, *J. Egypt. Soc. Parasit.*, 1979, 9, 467, per *Trop. Dis. Bull.*, 1980, 77, 125; A. Sabchareon et al., *S.E. Asian J. trop. med. publ. Hlth.*, 1980, 11, 280, per *Trop. Dis. Bull.*, 1981, 78, 161.

Prophylaxis in surgery. In a prospective, randomised, double-blind study of 6 months' duration involving 71 patients 2 g of tinidazole given before surgery prevented wound infection after elective colonic surgery in 37 of 40 patients in comparison with 28 of 31 patients treated with placebo.— P. S. Hunt et al., *Med. J. Aust.*, 1979, 1, 107.

Postoperative infections occurred in 6 of 50 patients who received 2 g of tinidazole 12 to 18 hours before undergoing elective abdominal hysterectomy and 2 g 48 hours postoperatively; infections occurred in 28 of 50 similar control patients.— P. C. Appelbaum et al., *Chemotherapy, Basle*, 1980, 26, 145.

Further references: J. Adno and R. Cassel, *S. Afr. med. J.*, 1979, 56, 565 (gynaecological surgery); M. Karhunen et al., *Br. J. Obstet. Gynaec.*, 1980, 87, 70 (hysterectomy).

Trichomoniasis. Tinidazole 2 g as a single dose produced parasitological cure in 47 of 50 patients with trichomoniasis, compared with 32 of 50 given metronidazole.— R. Anjaneyulu et al., *J. int. med. Res.*, 1977, 5, 438.

Further reports of the successful use of 2-g doses of tinidazole in women.— H. T. M. Rao and D. R. Sheenoy, *J. int. med. Res.*, 1978, 6, 46; J. P. Ward, *Med. J. Aust.*, 1976, 2, 651; R. Jones and P. Enders, *ibid.*, 1977, 2, 679; M. Massa et al., *Boln chil. Parasit.*, 1976, 31, 46, per *Trop. Dis. Bull.*, 1977, 74, 291.

Successful use in men of single 1-g doses of tinidazole.— N. Kawamura, *Br. J. vener. Dis.*, 1978, 54, 81, per *Abstr. Hyg.*, 1978, 53, 465.

See also under Amoebiasis, above.

Vaginitis. Administration of a single dose of tinidazole 2 g to 35 women with *Gardnerella vaginalis* (*Haemophilus vaginalis*) infection led to disappearance of the bacteria in 33; of the other 2 women the count was reduced in one and a repeat treatment was successful in the second. Two women relapsed after 15 to 20 days and repeat treatment was successful. All the patients' partners were given the same dose of tinidazole, and abstinence from sexual intercourse was recommended for at least 24 hours.— M. Bardi et al. (letter), *Lancet*, 1980, 1, 1029.

See also under Trichomoniasis, above.

Proprietary Names

Fasigin (Pfizer, Ital.); Fasigyn (Pfizer, Arg.; Pfizer, Austral.); Roerig, Belg.; Pfizer, Denm.; Pfizer, Neeth.; Pfizer, Norw.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer,

Switz.; Fasigyne (Pfizer, Fr.); Simplotan (Pfizer, Ger.); Trichogin (Chiesi, Ital.); Tricolam (Pfizer, Spain).

6000-c

Tryparsamide (B.P. 1968). Tryparsam.; Tryparsamidum; Glyphenarsine; Tryparson. Sodium hydrogen 4-(carbamoylmethylamino)phenylarsonate hemihydrate. $C_8H_{10}AsN_2NaO_4 \cdot \frac{1}{2}H_2O = 305.1$.

CAS — 554-72-3 (anhydrous); 6159-29-1 (hemihydrate). *Pharmacopoeias*. In Ind., Int., It., Mex., and Turk.

A colourless, odourless, crystalline powder which is slowly affected by light.

Soluble 1 in 1.5 of water, forming a neutral solution; soluble 1 in 3500 of alcohol; practically insoluble in chloroform and ether. A 4.62% solution is iso-osmotic with serum. Aqueous solutions deteriorate on storage and should be used immediately after preparation; solutions for injection are prepared aseptically. Store in a cool place in small airtight containers. Protect from light.

Adverse Effects. Side-effects include dizziness, tinnitus, nausea, vomiting, headache, fever, exfoliative dermatitis, allergic reactions, and bradycardia immediately after an injection. Liver damage may also occur.

The most serious toxic effect is upon the optic nerve. Treatment should be discontinued immediately if visual defects appear; though blindness may occur suddenly, especially if optic injury is already present, visual defects may not become apparent until a few weeks after a course of treatment has been completed.

Uses. Tryparsamide is trypanocidal. Because it penetrates the cerebrospinal fluid it has been used in the treatment of African trypanosomiasis with central nervous system involvement particularly in *Trypanosoma gambiense* infections. It has been given in doses of 30 to 60 mg per kg body-weight (up to maximum of 2 g) intravenously each week for 12 to 14 weeks. The trypanosomes may become resistant to tryparsamide. Because of the risk of blindness, melarsoprol is now preferred. For the use of tryparsamide in conjunction with suramin, see p.984.

Preparations

Tryparsamide Injection (B.P. 1968). Tryparsam. Inj. A sterile solution in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in the requisite amount of Water for Injections.

Database: Medline <1995 to February 1998>

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Unique Identifier

96415043

Authors

Salo JP. Salomies H.

Title

High performance thin layer chromatographic analysis of hydrolyzed tinidazole solutions. II. Hydrolysis kinetics of tinidazole.

Source

Journal of Pharmaceutical & Biomedical Analysis.

14(8-10):1267-70, 1996 Jun.

Abstract

In a citrate-borate-phosphate buffer, 5 mM tinidazole solutions exhibited maximum stability around pH 4.0-5.0. The hydrolysis of tinidazole was mostly a first-order reaction. At pH 10.0 and 60-80 degrees C, tinidazole had an activation energy of 122 kJ mol⁻¹ for hydrolysis. It was postulated that tinidazole decomposes by different mechanisms under basic and neutral/acidic conditions.

<2>

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Authors

Salo JP. Salomies H.

Title

High performance thin layer chromatographic analysis of hydrolyzed tinidazole solutions. I. Development and validation method.

Source

Journal of Pharmaceutical & Biomedical Analysis.

14(8-10):1261-6, 1996 Jun.

Abstract

A stability-indicating high performance thin layer chromatography method for analyzing hydrolyzed tinidazole solutions using silica gel plates was developed and validated. The mobile phase used was methanol-diethyl ether-chloroform (1:9:3, v/v/v) allowing small changes in its composition. Detection was at 314 nm. Rf values being 0.1-0.4, baseline resolution was achieved for tinidazole and the hydrolysis products. The analytes were stable on the sorbent and could be precisely and accurately measured

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Treatment of non-invasive amoebiasis. A comparison between tinidazole alone and in combination with diloxanide furoate

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Summary

Tinidazole (40 mg/kg body-weight in one daily dose for five days) and tinidazole (same dose) plus diloxanide furoate (20 mg/kg body-weight divided into three daily doses for 10 days) were compared as treatments for amoebiasis. The parasitic cure rates were 44 and 91% respectively. We cannot, therefore, recommend tinidazole alone in this dosage as a treatment for non-invasive amoebiasis.

Introduction

Tinidazole (Fasigyn) has recently been widely used as an alternative to metronidazole for the treatment of infections with *Entamoeba histolytica*. In a previous study (PEHRSON, 1982), tinidazole was given to a series of patients with chronic intestinal or asymptomatic amoebiasis. When checked by at least three stool specimens taken on different days, one month after treatment, we found a parasitic cure rate (p.c.r.) of 0% (0/14). This should be compared with the results obtained in other studies, showing a cure rate of 77 to 96% (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKSHI *et al.*, 1978), using the same dosage schedule but mainly in cases of acute intestinal amoebiasis.

To investigate the reasons for the unsatisfactory response we obtained, which could be due to too low a dose or to a low efficiency of tinidazole in the gut lumen, we carried out a new trial with a higher daily dose of tinidazole and compared the effect of this higher dose with that following treatment with tinidazole and diloxanide furoate (Furamide) in combination. This latter was found to be an effective intraluminal amoebicide (WOODRUFF & BELL, 1960, 1967; WOLFE, 1973), whose mode of action upon the amoeba is unknown. We omitted Furamide as a single regimen, because it is considered to be ineffective against invasive amoebiasis and there is always a risk of developing an invasive form of the disease if zymodeme differentiation of strains of *Entamoeba histolytica* is not performed routinely (SARGEANT & WILLIAMS, 1978; SARGEANT *et al.*, 1982).

Materials and Methods

During the period of the study, 41 patients were diagnosed as suffering from amoebiasis. All of them were supposed to have contracted their infections abroad, as amoebiasis is not considered to be endemic in Sweden. No cases of acute, dysenteric amoebiasis or diagnosed or suspected cases of liver abscess were included. The patients had not received any anti-amoebic drug during the previous year. Nine of the patients had a concomitant infection with *Giardia lamblia*, two with *Shigella flexneri*, two with *Campylobacter jejuni*, one with *Salmonella paratyphi A*, one with *Hymenolepis nana*, one with *Ascaris lumbricoides* and one with *Trichuris trichiura*.

In a predetermined, random order, the patients were allocated to two groups, 18 being treated with tinidazole alone and 23 with the combination. All were hospital in-patients and kept under supervision during treatment.

Dosage schedules

- (1) tinidazole 40 mg/kg body-weight in one daily dose for five days;
- (2) tinidazole as above plus diloxanide furoate 20 mg/kg body-weight divided into three daily doses for 10 days.

Approximately one month after the treatment was completed, checks were made, including the examination of at least three stool specimens taken on different days. One of these was examined by direct microscopy of freshly passed, loose faeces induced by a 50% magnesium sulphate purgative and the other normally passed specimens were examined by the formol-ether-concentration technique described by RIDLEY & HAWGOOD (1956). Failure was defined as the persistence of amoebic trophozoites or cysts in any of these specimens.

Those in whom the treatment with tinidazole failed were later treated with the combination of tinidazole and diloxanide furoate and those in whom the combination failed were treated with metronidazole 40 mg/kg body-weight daily for 10 days.

Results

Data on the participants and the results of the checks one month after treatment are shown in Table I. In no case were the side effects severe enough to cause cessation of treatment. Statistical analysis was made, using the chi-square test, and showed a significant difference between the two groups on the 1%-level (two-tailed test) and in favour of the combination. No differences could be found between the response of Swedes and that of the immigrants, or between those infected on different continents (Asia, Africa, South America). The presence of other parasites did not seem to affect the outcome of the treatment.

Discussion

Our results with tinidazole alone (44% p.c.r.), in treating non-dysenteric amoebiasis, are unsatisfactory and differ very much from those obtained in previously published studies by different authors, using the same dosage schedules (77 to 96% p.c.r.) (ISLAM & HASAN, 1975; APTE & PACKARD, 1978) or lower (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKSHI *et al.*, 1978). The patients in these studies were, however, mainly cases of acute amoebic dysentery, a factor which may have influenced the results.

A weak amoebicidal effect of the nitroimidazoles on the cyst stage of *E. histolytica* was observed by

Table I—Some characteristics and treatment results of 41 patients with non-invasive amoebiasis

Treatment	No.	Median age (age range) years	Patients with symptoms v. asymptomatics	Swedes v. other nationalities	Parasite-free at check	Parasite cure rate
Tinidazole 40 mg/kg × 1 + V	18	28 (9-68)	11:7	8:10	8	44%
Tinidazole 40 mg/kg × 1 × V + diloxanide furoate 500 mg × 3 × X	23	26 (6-68)	15:8	11:12	21	92%

SPILLMAN *et al.* (1976), but this report was contradicted by BAKSHI *et al.* (1978). Our drug trial was carried out in a country in which amoebiasis is not endemic, making reinfection during follow-up very unlikely, and confirming that the low p.c.r. was caused by "true" treatment failures.

We therefore believe that our poor results with tinidazole alone are due to its ineffectiveness in eradicating cysts in the lumen of the gut, either because of too effective absorption (MONRO, 1974) or inactivation by aerobic organisms as shown by RALPH & CLARKE (1978).

When tinidazole was combined with diloxanide furoate, we obtained a cure rate of 91%, which may be compared with studies by WOODRUFF & BELL (1967), in which they reported a cure rate of 95% in amoebic cyst-passers treated with diloxanide furoate alone for 10 days and WOLFE (1973), who found a cure rate of 83% using the same schedule. It is also noteworthy that all our failures with tinidazole alone have proved to be freed from their infection after treatment with the combination.

Acknowledgements

We wish to thank Mrs. Inger Pontén, the head nurse in the tropical ward and Birgit Lindberg, the chief technician at the laboratory of tropical diseases, for their devoted work with the patients.

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