DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

APR - 4 2000

Date

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From Chief, Dietary Supplements Branch, Division of Compliance & Enforcement, Office of Nutritional Products, Labeling, and Dietary Supplements, HFS-811

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	Vincamine
Firm:	General Nutrition Corporation
Date Received by FDA:	January 20, 2000
90-day Date:	April 18, 2000

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after April 18, 2000.

Robert J. Moore, Ph.D.

95S-0316

RPT62

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Washington, DC 20204

APR - 3 2000 0107 '00 APR -5 P1:23

Susan Trimbo, Ph.D.
Vice President, Scientific Affairs
General Nutrition Corporation
300 Sixth Avenue
Pittsburgh, Pennsylvania 15222

Dear Dr. Trimbo:

This letter is in response to your letter to the Food and Drug Administration (FDA) dated January 12, 2000, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act). Your letter notified FDA of your intent to market a product containing a new dietary ingredient named vincamine. Your submission was received by FDA on January 20, 2000. Your submission will be kept confidential for 90 days from the date of receipt, and after April 18, 2000, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

The submission contained five papers that reported the results of studies conducted in human patients with cerebrovascular insufficiency to test the therapeutic effects of vincamine. The studies in this submission, when considered along with the information in your previous submission, appear to provide an adequate basis that a dietary supplement containing vincamine will reasonably be expected to be safe in healthy adults who would consume dietary supplements that provide up to 20 milligrams of vincamine per day for up to 6 months. However, the studies do not appear to be sufficient to establish that a dietary supplement containing vincamine, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe for children.

Moreover, the information you submitted does not address the safety of chronic, long-term use (that is, use in excess of 6 months, the longest study duration reported in the information you provided). Therefore, a dietary supplement containing vincamine that is labeled for use by children or for periods in excess of 6 months may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Please contact us if you have questions concerning this matter.

Sincerely,

John B. Foret

John B. Foret
Director
Division of Compliance and Enforcement
Office of Nutritional Products, Labeling,
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

GNC LiveWell.

Susan Trimbo, Ph.D.
Vice President
Scientific Affairs

RECEIVED
JAN 20 2000

January 12, 2000

Lynn A. Larsen Ph.D.
Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C. Street (HFS-450)
Washington, D.C. 20204

Re: Vincamine

Dear Dr. Larsen;

This letter is in response to your September 13 letter to GNC, which expresses concerns about the safety of vincamine. We have carefully reviewed your correspondence and wish to provide a response to your comments and submit additional information for your consideration.

Vincamine has been used extensively in an oral dosage form since 1969. A number of scientific publications, including clinical trials of varying design, appear in the literature dating back to the mid 1970s. We submit three published clinical trials which monitored both the clinical tolerance of vincamine (or time-released version) as well as serum chemistry values as part of the overall safety evaluation. These studies are summarized in the attached table and full copies (plus translations) are provided for your review. The findings are representative of those reported in other publications. All of the studies provided evaluated vincamine given orally at a dose of 60 mg per day. (GNC has an interest in marketing a 30-mg tablet which would be taken once per day.) Collectively, these studies establish that the side effects of oral vincamine use (when taken for up to 12 weeks) are generally not classified as serious and primarily affect the gastrointestinal tract.

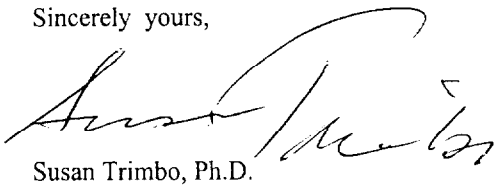
In addition to the trials cited above, we have included two open trials involving large numbers of subjects treated for up to 6 months. These trials report tolerance data that are consistent with those reported in the double-blind, placebo-controlled trials summarized in the attached table. Overall the percentage of individuals reporting side-effects is within the range reported in controlled trials for other dietary supplements such as ginkgo biloba extract.

General Nutrition Corporation, 300 Sixth Avenue, Pittsburgh, PA 15222
Tel: (412) 338-8844 Fax: (412) 338-8954

With regard to the toxicological data provided in our June 28, 1999 submission, additional explanation of the findings is necessary. A number of the publications examined the effects of intravenous administration of vincamine. It should be noted that the side-effects (type, severity and incidence) associated with vincamine use in these studies is linked to the route of infusion, infusion rate and dose. The enclosed study by Pirani et al (1978) provides data in support of this point. Furthermore, a number of the intravenous studies examined the effects of dosages up to 60mg . One would expect effects of the compound to be more pronounced compared to orally administered vincamine at the same dose due to the higher bio availability of an intravenously administered compounds. Together these findings, along with the other safety data submitted, establish that this dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement is reasonably expected to be safe.

We respectfully request that you reconsider the safety information provided herein. General Nutrition Corporation remains interested in marketing Vincamine as a dietary supplement as provided for under Section 8 of the Dietary Supplement Health and Education Act of 1994. An original and two copies of this correspondence and supporting documentation are provided.

Sincerely yours,



Susan Trimbo, Ph.D.
Vice President, Scientific Affairs

ST/tf
Enclosures
Cc: Ron Thompson

Vincamine Studies

Double-Blind, Placebo-Controlled

Author	Study Design/ Population	Dose of Administration Form of Administation Route of Adminsitration	Treatment Duration	Safety/Tolerance Findings
Mikus				
Arzneimittelforschung 1978 28(11): 2165-2168	• Double-blind, placebo-controlled. • 26 subjects (16 men: 10 women) cerebrovascular insufficiency. • Age range 46-76 years	• 60mg/day • vincamine cromesilate • oral	4 weeks	• No change in body weight, blood pressure, EKG, liver or renal function. • Low rate of side-effects. • No change in most lab values: Reduction in serum cholesterol (within normal range) • 2 reports of fatigue, 1 report of itching, 1 report of dry mouth.
Schenker				
Praxis 1979 68: 1005-1011	• Double blind-placebo-controlled • 50 patients cerebrovascular insufficiency. • Age range 55-89 years	• 60mg/day • vincamine (time release) • oral	4 weeks	• mild, transitory gastrointestinal complaints in 4 subjects.
Fischoff et al				
Neuropsychobiology 1996 34; 29-35	• Multicenter, double blind, placebo controlled • 152 patients cerebrovascular insufficiency (71 patients completed each treatment.) • Age range 50-85 years	• 60mg/day • vincamine(time realease) • oral	12 weeks	• no effect on blood pressure or lab values • triglycerides declined more in vincamine group • 19 patients reported AEs (12 vincamine treated)- diarrhea, insomnia, vertigo, hypotension, nervousness, vomiting, and nausea.

Open Studies

Peritti et al				
ClinTer 1981 97(2) 137-145	• Multicenter, open 1854 outpatients with cerebrovascular insufficiency completed protocol (791 Men, 1063 woman) • Age range 51-96 years	• 60 mg/day vincamine • vincamine HCI • oral	6 months	• 27 subjects out of 2440 discontinued due to side effects (gastrointestinal) • Mild transient side-effects in 135 of 1854 patients • Excellent tolerance
Alescio e tal				
Minerva Med 1978 69(31):2095-2113	• Multicenter, open-label • 828 patients (399 men; 429 woman) cerebrovascular insufficiency • Age range 45-87 years	• 60mg/day • vincamine • oral	Up to 60 days	• good tolerance • 5 discontinued treatment due to GI complaints or allergic skin reactions. • No significant effect on blood chemistry. • Normalizationof blood pressure. • EKG abnormal in 1 subject

99-10-29

German/Translation

CLINICAL, PSYCHOLOGICAL AND NEUROPHYSIOLOGICAL RESULTS OF A DOUBLE-BLIND STUDY ON VINCAMINE-CROMESILATE IN PATIENTS WITH CEREBRO-VASCULAR INSUFFICIENCY

By: P. Mikus

Von Bodelschwinghschen Anstalte, Bethel

From: Arzneimittelforschung 1978; 28(11): 2165-8

ABSTRACT

In a long-term double-blind cross-over design 16 patients with amnestic syndrome due to cerebro-vascular insufficiency were submitted to vincamine-cromesilate (Vincaryl®) and placebo treatment. The efficiency of vincamine was proved by mildly ameliorated psychometric patterns, biochemically by decreased cholesterol level and ophthalmodynamographically by slight increase of pulsation capacity). By means of EMG, ECG and EEG clinic side effects were excluded.

1. Introduction

Continuing and supplementing an earlier report of experience with vincamine [15], vincamine cromesilate (Vincaryl®) [Manufacturer Synthilabo, Paris (France)], a newly developed derivative of this substance which has a delayed action onset time compared to vincamine but a significantly longer duration of effect, was subjected to a clinical test. In more recent studies vincamine cromesilate was found to have good tolerance and vasoactive effects in cases of retinal edema [4] and in neuropsychiatric disorders [16] such as volatile hemiparesis, hemiparesis caused by cerebromalacia, vertebralis-basilaris insufficiency, vascularly related coma, cerebral arteriosclerosis and senile cerebrovascular insufficiency. In this study we have attempted by compar-

ing experimental psychological, laboratory chemical, clinical and neurophysiological findings to contribute to the explanation of the action mechanism.

2. Methodology

2.1. Patients examined

Corresponding to the indication of the preparation, 26 patients (16 male, 10 female) ranging from 46 to 76 years of age (median age 61.5 years) with the clinical symptoms of chronic cerebrovascular insufficiency were examined. The patients had been long-term residents of the von Bodelschwinghsche Anstalte. Epileptics were not included in the study, because, according to experimental findings on animals [19], a convulsion-provoking effect by vincamine appeared possible.

The criteria of selection for inclusion in the study series was a reduced memory capacity in the numerical response of the Hamburg-Wechsler intelligence test below the age-related average of eight correctly reproduced numbers [24]. This selection criterion is based on a study by Hass [8] who found an average value of 6±1.6 correctly reproduced numbers for mild and moderately severe amnestic psychosyndromes such as are characteristics of cerebrovascular insufficiency.

2.2. Time schedule

At first for four weeks all vasoactive preparations were discontinued, and after this the first series of tests was performed in order to obtain reference values (A). Then for the 16 male subjects for 4 weeks the test drug C (Vincaryl) was administered in a dose of 3 x 1 capsule 20 mg, for the female subjects

preparation B (placebo) was begun. Then the preparations were switched.

The alternating sequence was supposed to balance out any memory residues during the repetition of the test (despite parallel tests). The study was performed from January to March 1975 in the von Bodelschwinghsche Anstalte.

2.3. Parameters

In order to conform to the purpose of the study and to register the broadest possible spectrum of objectivizable effects the following parameters were studied:

I. The basic documentation contained all of the data necessary concerning the patients according to the testing standards [3].

II. Psychometric findings (see Table):

1. Learning addresses: 5 addresses were supposed be learned within 3 min. and were supposed to be recalled immediately upon being given the key word and also after the completion of the other tests (memory, see under 6 and Table 1).

2. Modified Benton test: Instead of the well known paper-pencil form the graphic reproduction of the figure seen was not requested but rather an optical recognition of 12 geometric figures from a number of 45.

3. Number response from the Hamburg-Wechsler Intelligence test (according to [24]).

4. Recounting of stories: a story consisting of 2 sentence fragments was supposed to be reproduced after reading through twice word for word.

Of even greater significance than the effects of the preparation on the EKG appeared to be, according to the results of Jacquy [11], the possible effect on the encephalorheogram. Following the lead technique for the cranial rheogram described by Schimert and Simon [20] it was attempted to register the area supplied by the a. carotis or a. vertebralis with a bitemporal or bioccipital electrode position. A standardized rheography instrument according to Schufried [21] was used for an extremital lead. Under this lead condition in each case (bitemporally, biocipitally) we measured:

a) the amplitude height of the highest deflection;

b) the angle of increase of the tan a:

c) the area integral under the curve determined in mm^2 planimetrically.

V. Laboratory chemistry (see Table 1): Using the generally registered urine and blood picture data as well as the kidney and liver function tests registered in comparable preliminary studies on vincamine [4,15,16] now also a differential blood picture was registered -- both hemoglobin, thrombocytes and BSR. Besides this with respect to the conjectured cerebral metabolic effects of vincamine cromesilate of particular interest were the triglycerides and the cholesterol as well as the total protein, blood sugar and enzyme activities (GOT, GPT, CPK, alkaline phosphatase, □-amylase).

VI. Neurophysiology: Assuming that a vasoactive effect on the perfusion in addition to encephalorheography is best objectivized by measuring the pressure ratio and the pulsation volume of the

a. opthalmica, the opthalmodynamography (ODG see Table 1) according to Hager [9] is included in this study because it had proven itself elsewhere also as a test method for pharmacological studies [26].

The pulsation volumes obtained in the prone position follow a normal distribution with a mean value of 72.7 ml and a point spread of ±19.2 [6].

Conforming to the other results of the study which pertained to theophylline preparations [14], an isolated increase in the opthalmica blood pressure values and/or an increase in the pulsation volume can be assumed which Finke (cited in [6]) increasingly found around 53 % with Rheomacrodex.

The EMG (see Table 1) was recorded in order to exclude possible harmful side effects such as were described by Gibbels [7] for Vinca-major alkaloids. Hypothetically in such cases normal nerve conduction speeds would have to drop below the pathological limit in advance.

The limiting values which differed somewhat depending on author and lead conditions [5,12] are reported along with the results.

VII. EEG: In our earlier investigation [15] a significant improvement could be found in the sense of an acceleration of the basic rhythm while on vincamine. According to Friedlander [6] and Verdeaux [23] in old age a general tendency for the □-rhythm to slow down, the □-index to be reduced and the slower elements up to the □ region to increase are characteristic -- especially after the 60th year.

Table 1. Statistically significant changes on Vincaryl (C) compared to the initial value (A) and/or placebo (B).

Parameters			Initial value	Vincaryl	Placebo	Significance level (%)
II	Benton	right	6	5	6	5
		wrong	3	4	4	5
	ZN	total	7	8		5
	History		5	9	7	1
	Wiendieck	general. LZ	6	7		5
		total LZ	9	10		10
	Address, memory		3	3	5	10
IV	Heart frequency		76	71		5
	QT duration %			110	104	10
V	Monocytes		6	5		1
	Cholesterol		237	209		5
	GOT		12	9		5
	GPT			9	12	5
	CPK		32	21		10
VI ODG	RR_4		149	143	137	10
	RR_1	brach.	89	85		10
	RR_m	brach.	114	110		5
	RR_m	opthal.		144	134	5
	RR_m	average	114	110	104	10
		pressure	54	56		5
	Pulsation volume					
EMG	NLG mot.					
	N. uln.			62	65	1
	N. mod.			61	64	5
	N. tib.			49	51	5

At the Paris Symposium of December 1973 on cerebral perfusion and cerebral metabolism at that time several hypothetical attempts at explanation were reported [17].

In this study now as opposed to the previous ones a possible dependence of the base frequency on the vincamine cromesilate medication was to be verified.

Since an automatic frequency analysis was found to be too costly in the preliminary studies and was of relatively low validity, compared to a visual frequency analysis, the latter was used for the evaluation as described by Pechstein and Dolonsky [18].

3. Results

The reports delivered at the international introductory symposium confirmed the delayed action onset with prolonged action duration of vincamine cromesilate compared to vincamine. This was still unknown when the tests were planned, so that it is entirely possible that the effect of the drug was sufficient still in the -- relatively brief -- placebo phase. To estimate the effect of the preparation therefore a comparison with the initial value makes sense. In Table 1 the significant variations of the three series of measured values determined in the t-test with the significance level in each case are compared.

Subjectively a certain euphorizing effect could be demonstrated which manifested itself in increasing vivacity as far as could be registered by a questionnaire of this type. As a limitation, however, it must be remarked that a discrepancy exists between the subjective impression verdict of the patients and that of the examining doctor as regards the effect of the preparation, see Table 2.

Table 2. Judgment of impression

	Sex	Improved	Unchanged	Worsened	Total
Patient	m w	9 0	7 10	0 0	16 10
Total		9	17	0	26
Doctor	m w	2 0	14 10	0 0	16 10
Total		2	24	0	26

On the whole, therefore we find a significant change in the status picture according to the impression verdict of the examining doctors. The evaluation of the patients also reveals sex-

specific evaluation stereotypes in that the male patients tend rather toward a positive evaluation tendency. This was most probably psychologically motivated due to the higher receptivity of this patient group because of the greater amount of attention experienced as a result of the trial (so called Hawthorne effect).

3.1. Side effects

Weight and blood pressure remained unchanged under the different drug conditions.

The rate of side effects is extremely low and also nonspecific. On 4 occasions side effects were related to the preparation (fatigue twice, itching once, oral dryness once) compared to 52 side effects for which the concurrent medication (usually neuroleptics) was held responsible.

3.2. Internalistic findings

Corresponding to the relatively small pathological initial values in the EKG, in this parameter no significant change was noted. All modal values characterize physiological conditions.

The evaluation of the rheography findings offered the greatest measurement-technical difficulties. The angle of increase and the peak height were found to be unreliable parameters because of the too great point spread. For the final evaluation therefore the planimetrically determined area integrals of the bitemporal and bioccipital lead curves were used which, however, did not reveal any significant changes.

3.3. Laboratory chemistry

Except for the clinically interesting -- although in the normal range -- cholesterol reduction all of the other laboratory values studied did not change under the conditions of the medication.

3.4. Neurophysiology

In the EMG the nerve conduction speeds of the fastest motor fibers of the above mentioned nerves were measured. Based on these findings one finds -- under these measurement conditions -- no change in the nerve conduction speed so that it may be concluded from this that vincamine cromesilate in the total dose given here of 1.9 g manifests no neurotoxic effects. The sensory latencies also displayed no change.

3.5. EEG

Compared to our earlier study in this patient group scarcely any pathological EEG initial conditions were demonstrated, especially since convulsion-inducing diseases of an organic brain character were intentionally bracketed out.

In the case of the □ base rhythm which was totally age-conforming for all the initial findings therefore no positive changes were expected. Negative changes in the sense of a slowing of the base activity toward the slower frequencies from the □ range did not occur.

Pathological graphic elements could not be observed -- even during the routinely performed convulsion provocation by hyperventilation and photostimulation.

4. Summary and discussion

As a supplement to our earlier investigation of vincamine 26 patients with the symptoms of cerbrovacular insufficiency from the von Bodelschwinghschen Anstalte were included in a double blind experiment. The criteria for selection was a mild to moderate amnestic psychosyndrome.

The basic documentation corresponded to the ministerial guidelines for testing drugs.

In the impression verdict of the patients concerning the effect vincamine sex-specific differences became clear in the sense of a Hawthorne effect among the male patients.

In the psychometrically registered memory performance such as number recollection and the figure-background differentiation positive changes could be demonstrated. Likewise after four weeks of medication a more stable affective mood was noted (satisfaction with life).

Clinically the weight, EKG, blood picture, urine status, liver and kidney function remained unchanged on vincamine.

The side effects are slight at 8 % and nonspecific (fatigue, itching, oral dryness).

Of the perfusion parameters studied, an increase was found in the pulsation volume of the a. opthalmica which, however, still remained in the physiological normal range while the bioccipital and bitemporal rheographic findings remained unchanged. As a bloodless analogue to the Xenon clearance, however, this method is of interest and should be expanded further, i.e. the lead conditions and the evaluation should be modified,

e.g. according to Jacquy. Presently we have found the planometrically determined area integral to be optimal.

The EMG and EKG remained unchanged during the four week oral vincamine cromesilate medication so that -- as set forth individually -- neurotoxic side effects are improbable.

This merits particular intention to the extent that in animal experimental studies [19] with rats with an elevated convulsion tendency on pervincamine with an additional O_2 deficiency a hypersynchronization in the EEG was observed which in these animals must be regarded as a precursor to convulsive activity. This convulsive tendency -- to be sure performed under extreme conditions -- cannot be confirmed clinically in human experiments.

A contraindication to pervincamine cromesilate in convulsive diseases therefore need not be assumed according to the results of these investigations.

Furthermore future studies should concentrate on the fat metabolism since the laboratory chemically found reduction in cholesterol indicates a metabolic action mechanism which may lead to improved cerebral perfusion, but at the least is significant prophylactically, since cholesterol, among others, contributes to constricting the vessel lumina and therefore may cause reduced perfusion. Conversely, a lowering in the long term leads to improved cerebral perfusion.

The improved cerebral perfusion -- despite high grade age related degradation as was apparent from the initial values -- leads to an objectivizable improvement in the acoustic short-term

memory (CN, history, recounting) and the long-term memory (address reproduction from memory) on the assumption of a preparation effect which persists in the placebo phase.

5. References

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4. Diskussion

Die Ergebnisse unserer Untersuchungen lassen erkennen, daß 30 mg Ipratropiumbromid (p.o.) eine signifikant hemmende Wirkung auf die nicht stimulierte HCl-Sekretion in dem Zeitabschnitt 11—12 h nach der Einnahme aufweisen. Bereits früher durchgeführte Untersuchungen hatten ergeben, daß Dosen von 15 mg Ipratropiumbromid die Basalsekretion 1—2 h nach der Einnahme hemmen (Wagner 1973; Otto 1973; Kutz et al. 1976).

Die systemische Resorption von Ipratropiumbromid hat sich bei Studien mit radioaktiv markiertem Material am Menschen als relativ gering erwiesen (Adlung et al. 1976). Ein maximales Plasmaniveau wurde bei oraler Gabe von 30 mg nach 3 h gemessen. Auch nach 12 h lagen die Plasmakonzentrationen noch im meßbaren Bereich. Unsere Untersuchungen, bei denen sämtliche Patienten eine geringere Basalsekretion unter Ipratropiumbromid als unter Plazebo aufwiesen, zeigen, daß 30 mg Ipratropiumbromid eine therapeutisch ausreichende Dosis darstellen.

Die fehlende Wirkung nach Pentagastrin kann durch das lange Intervall zwischen Einnahme der Versuchssubstanz und Durchführung der Untersuchungen erklärt werden. Möglicherweise weist Ipratropiumbromid eine Wirkungsdauer von 11—12 h auf, so daß bei einem längeren Zeitintervall keine Wirkung mehr zu erwarten ist. Unter Berücksichtigung pharmakokinetischer Studien ist es jedoch wahrscheinlicher, daß die zugeführte Pentagastrin-Dosis (6 µg/kg), die eine maximale HCl-Sekretion bewirkt, zu hoch war, so daß die nur noch geringgradige Verminderung der Empfindlichkeit der Parietalzellen, die 12—13 h nach Gabe von Ipratropiumbromid noch vorhanden war, nicht mehr nachgewiesen werden konnte.

Da 30 mg Ipratropiumbromid eine sichere Wirkungsdauer von 11—12 h haben, ist es bei der therapeutischen Anwendung mit hoher Wahrscheinlichkeit ausreichend, das Präparat in dieser Dosis 2mal täglich anzuwenden, um eine genügend konstante Hemmung der Magensekretion zu erzielen. Es dürfte dabei wichtig sein, das Präparat möglichst auf leeren Magen einzunehmen (morgens vor dem Frühstück, abends vor der Nachtruhe), da die Resorption durch den Füllungszustand des Magens beeinflußt werden dürfte.

5. Literatur

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Klinische, psychologische und neurophysiologische Ergebnisse einer Doppelblindstudie mit Vincamin-cromesilat bei Patienten mit cerebraler Durchblutungsinsuffizienz*)

Von P. Mikus

Zusammenfassung: *20 Patienten mit einem leichten bis mittelschweren amnestischen Psychosyndrom infolge zerebrovaskulärer Insuffizienz wurden in einem Doppelblind-Überkreuz-Versuch je 4 Wochen lang mit Vincamin-cromesilat (Vincaryl®) und Plazebo behandelt.*

Bei fehlenden neurotoxischen (EEG und EMG) und klinisch-internistischen Nebenwirkungen konnte die Wirksamkeit des Präparates mit Hilfe psychometrischer Tests, Laborchemie und im Ophthalmodynamogramm objektiviert werden.

Summary: *Clinical, Psychological and Neurophysiological Results of Double-blind Study on Vincamine-cromesilate in Patients with Cerebro-vascular Insufficiency*

In a long-term double-blind cross-over design 26 patients with amnestic syndrome due to cerebro-vascular insufficiency were submitted to vincamine-cromesilate (Vincaryl®) and placebo treatment. The efficiency of vincamine was proved by mildly ameliorated psychometric patterns, biochemically by decreased cholesterol level and ophthalmodynamographically by slight increase of pulsation capacity). By means of EMG, ECG and EEG clinic side effects were excluded.

*) Gekürzte Fassung eines Referates, gehalten in Garmisch-Partenkirchen (März 1976) und Athen (April 1976) anläßlich der Internationalen Einführung des Pervincamin® durch die Firma Synthélabo, Paris.

1. Einleitung

In Fortsetzung und Ergänzung eines früheren Erfahrungsberichtes mit Vincamin [15] wurde Vincamin-cromesilat (Vincaryl®*)), ein neu entwickeltes Derivat dieser Substanz, das gegenüber Vincamin einen verzögerten Wirkungseintritt, aber eine wesentlich längere Wirkungsdauer hat, der klinischen Prüfung unterzogen. In neueren Arbeiten wurde die gute Verträglichkeit und die vasoaktive Wirkung des Vincamin-cromesilat bei Retina-Ödemen [4] und neuropsychiatrischen Erkrankungen [16], wie flüchtigen Hemiparesen, Hemiparesen durch Hirnerweichung, Vertebralis-Basilaris-Insuffizienz, vaskulär bedingtem Koma, Hirnarteriosklerose und seniler Hirnmangeldurchblutung, nachgewiesen.

In dieser Arbeit sollte versucht werden, durch die Gegenüberstellung experimentalpsychologischer, laborchemischer, klinischer und neurophysiologischer Befunde zur Klärung des Wirkungsmechanismus beizutragen.

2. Methodik

2.1. Untersuchte Patienten

Entsprechend der Indikation des Präparates wurden 26 Patienten (16 männliche, 10 weibliche) im Alter zwischen 46 und 76 Jahren (Durchschnittsalter 61,5 Jahre) mit den klinischen Symptomen einer chronischen cerebrovaskulären Insuffizienz untersucht. Die Patienten waren langjährige in den v. Bodelschwinghschen Anstalten untergebracht. Epileptiker wurden nicht in die Untersuchung einbezogen, da aufgrund tierexperimenteller Befunde [19] eine krampfprovozierende Wirkung des Vincamin möglich schien.

Auswahlkriterien für die Aufnahme in die Untersuchungsreihe war eine verminderte Gedächtnisleistung im Zahlennachsprechen des Hamburg-Wechsler-Intelligenztests unter dem altersüblichen Durchschnitt von 8 richtig reproduzierten Zahlen [24]. Dieses Auswahlkriterium basiert auf einer Untersuchung Haases [8], der für leichte bis mittelschwere amnestische Psychosyndrome, wie sie für die zerebrale Durchblutungsinsuffizienz charakteristisch sind, einen Durchschnittswert von 6 ± 1,6 richtig reproduzierten Ziffern fand.

2.2. Zeitplan

Es wurden zunächst 4 Wochen lang alle gefäßaktiven Präparate abgesetzt und danach die erste Untersuchungsserie durchgeführt, um Ausgangswerte (A) zu erhalten. Danach wurde bei den 16 männlichen Versuchspersonen 4 Wochen lang das Prüfpräparat C (Vincaryl) in der Dosierung von 3mal einer Kapsel à 20 mg gegeben, bei den weiblichen Versuchspersonen wurde mit Präparat B (Plazebo) begonnen. Danach wurden die Präparate ausgetauscht.

Die alternierende Reihenfolge sollte etwaige Erinnerungsreste bei der Testwiederholung (trotz Paralleltests) ausbalancieren.

Die Untersuchung wurde von Januar bis März 1975 in den v. Bodelschwinghschen Anstalten durchgeführt.

2.3. Parameter

Um der obigen Fragestellung gerecht zu werden und ein möglichst breites Spektrum objektivierbarer Wirkungen zu erfassen, wurden folgende Parameter untersucht:

I. Die **Basisdokumentation** enthielt alle nach den Prüfnormen [3] erforderlichene Daten über den Patienten.

II. Psychometrische Befunde (s. Tab.):

1. Adressen Lernen: 5 Adressen sollten in 3 min gelernt werden und wurden unter Vorgabe eines Reizwortes sofort abgefragt sowie nach Beendigung der übrigen Tests (Erinnerung, s. u. 6 u. Tab. 1).
2. Modifizierter Benton-Test: Statt der bekannten Paper-Pencil-Form wurde nicht die graphische Reproduktion der gesehenen Figuren gefordert, sondern ein optisches Wiedererkennen von 12 geometrischen Figuren aus einer Anzahl von 45.
3. Zahlennachsprechen aus dem Hamburg-Wechsler-Intelligenztest (nach [24]).
4. Geschichten nacherzählen: eine aus 2 Satzfragmenten bestehende Geschichte sollte nach 2maligem Vorlesen wörtlich wiedergegeben werden.
5. Wiendieck-Skala: In einer speziell für die Gerontopsychiatrie entwickelten Skala [25] wurde die allgemeine, relative und gesamte Lebenszufriedenheit psychometrisch zu erfassen versucht.
6. Adressen: Wiedergabe aus der Erinnerung (s. o. 1 u. Tab. 1).
7. Bergener-Skala [2]: körperliche Gebrechlichkeit, allgemeine Verwirrtheit, aggressiv-gereiztes Verhalten, Aktivität auf der Station und eingeschränkte Sinnestätigkeit wurden gemeinsam mit dem Pflegepersonal zu den verschiedenen Untersuchungszeitpunkten in einer „rating-scale" festgehalten.

Sämtliche psychometrischen Tests genügten hinsichtlich Reliabilität und Validität den geforderten testtheoretischen Gütekriterien [13].

III. Der **Beurteilungsbogen über klinische Wirkungen und Nebenwirkungen** enthielt alle Beurteilungskategorien, die sich in der vorgenannten Untersuchung [15] aufgrund des AMP-Bogens (somatischer Befund) als relevant erwiesen hatten, erweitert um solche, die bei vergleichbaren Präparaten als Nebenwirkungen genannt wurden, wobei differenziert wurde zwischen

1 = fehlende Nebenwirkungen;
2 = vermutlich präparat-spezifische Nebenwirkungen;
3 = vermutlich auf Begleitmedikation zurückführende Nebenwirkungen;
9 = keine Angaben.

IV. Der **EKG-Befundbogen** (s. Tab. 1) enthielt sämtliche für die EKG-Auswertung relevanten Parameter in skalierter Form. Es wurden die Extremitäten-Standardableitungen durchgeführt.

Von noch größerer Bedeutung als die Auswirkungen des Präparates auf das EKG erschien nach den Ergebnissen von Jacquy [11] die mögliche Beeinflussung des Enzephalorheogramms. In Anlehnung an eine bei Schimert und Simon [20] beschriebene Ableitungstechnik des Schädelrheogramms wurde bei bitemporaler bzw. bioccipitaler Elektrodenlage das Versorgungsgebiet der A. carotis bzw. A. vertebralis zu erfassen versucht. Benutzt wurde ein für Extremitätenableitung standardisiertes Rheographiegerät nach Schuhfried [21]. Ausgemessen wurden bei der jeweiligen Ableitebedingung (bitemporal, bioccipital):

a) die Amplitudenhöhe des höchstens Ausschlags;
b) der Anstiegswinkel des tg α;
c) das planimetrisch in mm^2 ermittelte Flächenintegral unter der Kurve.

V. Laborchemie (s. Tab. 1): Über die in vergleichbaren Voruntersuchungen über Vincamin [4, 15, 16] global erfaßten Urin- und Blutbildstaten sowie Nieren- und Leberfunktionsprüfungen wurde jetzt auch ein Differentialblutbild erfaßt — sowie Hämoglobin, Thrombozyten und BSG. Darüber hinaus galt im Hinblick auf die vermuteten zerebralmetabolischen Wirkungen des Vincamin-cromesilat besonderes Interesse den Triglyceriden und dem Cholesterin sowie dem Gesamteiweiß, Blutzucker und den Fermentaktivitäten (GOT, GPT, CPK, alkalische Phosphatase, α-Amylase).

VI. Neurophysiologie: Unter der Vorstellung, daß eine gefäßaktive Wirkung auf die Durchblutung neben der Enzephalorheographie am ehesten durch Messung der Druckverhältnisse und des Pulsationsvolumens der A. ophthalmica zu objektivieren sei, wurde die Ophthalmodynamographie (ODG s. Tab. 1) nach Hager [9] in diese Untersuchung einbezogen, da sie sich als Testmethode bei Arzneimittelprüfungen auch anderweitig [26] bewährt hat.

Die im Liegen gewonnenen Pulsationsvolumina folgen einer Normalverteilung mit einem Mittelwert von 72,7 ml und einer Streuung von ± 19,2 [6].

Analog zu anderen Untersuchungsergebnissen, die sich auf Theophyllinpräparate bezogen [14], kann ein isolierter Anstieg der Ophthalmica-Blutdruckwerte und/oder eine Zunahme des Pulsationsvolumens angenommen werden, das Finke (Zit. nach [6]) bei Rheomacrodex um 53 % zunehmend fand.

Das EMG (s. Tab. 1) wurde abgeleitet zum Ausschluß möglicher schädlicher Nebenwirkungen, wie sie von Gibbels [7] für Vinca-maior-Alkaloide beschrieben werden. Hypothetisch müßten dabei vorher normale Nervenleitgeschwindigkeiten unter den pathologischen Grenzwert absinken.

Die je nach Autor und Ableitebedingungen [5, 12] etwas unterschiedlichen Grenzwerte sind bei den Ergebnissen angegeben.

VII. EEG: In unserer früheren Untersuchung [15] konnte eine signifikante Verbesserung im Sinne einer Beschleunigung des Grundrhythmus unter Vincamin gefunden werden. Nach Friedländer [6] und Verdeaux [23] ist im Alter eine allgemeine Tendenz zur Verlangsamung des α-Rhythmus, eine Verringerung des α-Index sowie eine Zunahme der langsameren Elemente bis

*) Hersteller: Synthélabo, Paris (Frankreich).

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Tab. 1: Statistisch signifikante Veränderungen unter Vincaryl (C) gegenüber Ausgangswert (A) und/oder Plazebo (B).

Parameter			Ausgangswert	Vincaryl	Plazebo	Signifikanz-Niveau (%)
II	Benton	richtig	6	5	6	5
		falsch	3	4	4	5
	ZN	gesamt	7	8		5
	Geschichte		5	9	7	1
	Wiendieck, allg. LZ		6	7		5
		gesamte LZ	9	10		10
	Adresse, Erinnerung		3	3	5	10
IV	Herzfrequenz		76	71		5
	QT-Dauer %			110	104	10
V	Monozyten		6	5		1
	Cholesterin		237	209		5
	GOT		12	9		5
	GPT			9	12	5
	CPK		32	21		10
VI ODG	RR_s		149	143	137	10
	RR_d	brach.	89	85		10
	RR_m	brach.	114	110		5
	RR_s	ophthal.		144	134	5
	RR_m	Mitteldruck	112	110	104	10
	Pulsationsvolumen		54	56		5
EMG	NLG mot.					
	N. uln.			62	65	1
	N. med.			61	64	5
	N. tib.			49	51	5

hin zum ϑ-Bereich — besonders nach dem 60. Lebensjahr — charakteristisch.

Im Pariser Symposium vom Dezember 1973 über Hirndurchblutung und Hirnmetabolismus wurden dabei einige hypothetische Erklärungsversuche referiert [17].

In dieser Untersuchung sollte nun differenzierter als in der vorangegangenen eine mögliche Abhängigkeit der Grundfrequenz von der Vincamin-cromesilat-Medikation überprüft werden.

Da sich in Voruntersuchungen eine automatische Frequenzanalyse als zu aufwendig und im Vergleich nicht aussagekräftiger gezeigt hatte zu einer visuellen Frequenzanalyse, wurde die letztere zur Auswertung herangezogen, wie von Pechstein u. Dolansky [18] beschrieben.

3. Ergebnisse

Die auf dem internationalen Einführungssymposium gehaltenen Referate bestätigten den verzögerten Wirkungseintritt bei verlängerter Wirkungsdauer des Vincamin-cromesilat gegenüber dem Vincamin. Dies war bei der Versuchsplanung noch nicht bekannt, insofern ist es gut möglich, daß der Präparateffekt noch in die — relativ zu kurz gewählte — Plazebophase hineinreicht. Zur Abschätzung der Präparatwirkung ist daher der Vergleich mit dem Ausgangswert sinnvoll. In Tab. 1 sind die aufgrund des t-Tests ermittelten statistisch signifikanten Veränderungen der 3 Meßwertreihen mit dem jeweiligen Signifikanzniveau zusammengestellt.

Subjektiv konnte eine gewisse euphorisierende Wirkung nachgewiesen werden, die sich in zunehmender Lebensfreude äußert, soweit über einen solchen Fragebogen erfaßbar. Einschränkend muß jedoch angemerkt werden, daß eine Diskrepanz besteht zwischen dem subjektiven Eindrucksurteil der Patienten und dem der Prüfärzte hinsichtlich der Präparatwirkung, wie Tab. 2 zeigt.

Tab. 2: Eindrucksurteil.

	Geschlecht	Gebessert	Unverändert	Verschlechtert	Gesamt
Patient	m	9	7	0	16
	w	0	10	0	10
Gesamt		9	17	0	26
Arzt	m	2	14	0	16
	w	0	10	0	10
Gesamt		2	24	0	26

Insgesamt ergibt sich somit keine wesentliche Änderung des Zustandsbildes nach dem Eindrucksurteil der Prüfärzte. Die Beurteilung der Patienten läßt zudem geschlechtsspezifische Beurteilungsstereotypien erkennen, indem die männlichen Patienten eher zu einer positiven Beurteilungstendenz neigen. Dies dürfte am ehesten psychologisch zu begründen sein durch eine größere Empfänglichkeit dieser Patientengruppe auf die durch den Versuch erfahrene größere Zuwendung (sog. Hawthorne-Effekt).

3.1. Nebenwirkungen

Gewicht und Blutdruck blieben unter den verschiedenen Präparatbedingungen unverändert.

Die Nebenwirkungsrate ist äußerst gering und zudem unspezifisch. 4mal wurden Nebenwirkungen auf das Präparat bezogen (2mal Müdigkeit, einmal Juckreiz, einmal Mundtrockenheit) gegenüber 52 Nebenwirkungen, für die die Begleitmedikation (meist Neuroleptika) verantwortlich gemacht wird.

3.2. Internistische Befunde

Entsprechend den relativ geringen pathologischen Ausgangswerten im EKG zeichnete sich in diesem Parameter keine signifikante Änderung ab. Alle Modalwerte kennzeichnen physiologische Bedingungen.

Die Beurteilung der Rheographiebefunde bereitete die größten meßtechnischen Schwierigkeiten. Anstiegswinkel und Gipfelhöhe haben sich infolge zu großer Streubreite als unreliable Parameter erwiesen. Für die abschließende Beurteilung wurden daher die planimetrisch ermittelten Flächenintegrale der bitemporal und bioccipital abgeleiteten Kurven herangezogen, die jedoch keine signifikanten Veränderungen ergaben.

3.3. Laborchemie

Bis auf die klinisch interessante — wenn auch im Normbereich liegende — Cholesterinsenkung haben sich sämtliche sonst überprüften Laborwerte unter den Präparatbedingungen nicht verändert.

3.4. Neurophysiologie

Im EMG wurden die Nervenleitgeschwindigkeiten der schnellsten motorischen Fasern der obengenannten Nerven gemessen. Anhand dieser Befunde ergibt sich — unter diesen Meßbedingungen — keine Änderung der Nervenleitgeschwindigkeit, so daß daraus gefolgert werden kann, daß Vincamin-cromesilat in der hier gegebenen Gesamtdosis von 1,8 g keine neurotoxische Wirkung entfaltet. Auch die sensiblen Latenzen zeigten keinerlei Änderung.

3.5. EEG

Im Vergleich zu unserer früheren Untersuchung waren bei diesem Patientenkollektiv kaum pathologische EEG-Ausgangsbedingungen nachzuweisen, zumal hirnorganische Anfallserkrankungen bewußt ausgeklammert waren.

Bei dem durchweg altersentsprechenden α-Grundrhythmus aller Ausgangsbefunde war daher nicht mit positiven Veränderungen zu rechnen. Negative Veränderungen im Sinne einer Verlangsamung der Grundaktivität zu langsameren Frequenzen aus dem ϑ-Bereich sind nicht aufgetreten.

Pathologische Graphoelemente konnten — auch unter der routinemäßig durchgeführten Krampfprovokation durch Hyperventilation und Photostimulation — nicht beobachtet werden.

4. Zusammenfassung und Diskussion

In Ergänzung einer früheren Untersuchung über Vincamin wurden 26 Patienten mit den Symptomen einer zerebralen Druchblutungsinsuffizienz der von Bodelschwinghschen Anstalten in einen Doppelblindversuch einbezogen. Auswahlkriterium war ein leichtes bis mittelschweres amnestisches Psychosyndrom.

Die Basisdokumentation entsprach den ministeriellen Richtlinien für die Prüfung von Arzneimitteln.

Im Eindrucksurteil der Patienten über die Wirkung des Vincamin wurden geschlechtsspezifische Unterschiede im Sinne eines Hawthorne-Effektes bei den männlichen Patienten deutlich.

In den psychometrisch erfaßten Gedächtnisleistungen wie Zahlennachsprechen und in der Figur-Grund-Differenzierung konnten positive Veränderungen nachgewiesen werden. Ebenso zeigte sich nach 4wöchiger Medikation eine stabilere affektive Stimmungslage (Lebenszufriedenheit).

Klinisch blieben Gewicht, EKG, Blutbild, Urinstatus, Leber- und Nierenfunktion unter Vincamin unverändert.

Die Nebenwirkungen sind mit 8 % gering und unspezifisch (Müdigkeit, Juckreiz, Mundtrockenheit).

Von den untersuchten Durchblutungsparametern ergab sich ein Anstieg des Pulsationsvolumens der A. ophthalmica, das allerdings noch im physiologischen Normbereich liegt, während die bioccipitalen und bitemporalen Rheographiebefunde unverändert blieben. Als unblutiges Analogon zur Xenon-Clearance ist diese Methode jedoch von Interesse und sollte weiter ausgebaut werden, d. h., die Ableitebedingungen und die Auswertung sollten modifiziert werden, z. B. nach Jacquy. Uns haben sich die planimetrisch ermittelten Flächenintegrale als derzeit optimal erwiesen.

EMG und EKG blieben unter 4wöchiger oraler Vincamincromesilat-Medikation unverändert, so daß — wie im einzelnen dargelegt — neurotoxische Nebenwirkungen unwahrscheinlich sind.

Dies verdient insofern besondere Beachtung, als bei tierexperimentellen Untersuchungen [19] mit Ratten mit erhöhter Krampfneigung unter Pervincamin und zusätzlichem O_2-Mangel eine Hypersynchrosisation im EEG beobachtet werden konnte, die bei diesen Tieren als Vorstufe zu einer Krampfaktivität angesehen werden muß. Diese — allerdings unter Extrembedingungen durchgeführte — Krampfbereitschaft läßt sich klinisch im Humanversuch nicht bestätigen.

Eine Kontraindikation des Pervincamin-cromesilat bei Anfallserkrankungen ist nach dem Ergebnis dieser Untersuchungen somit nicht anzunehmen.

Weiterhin sollten sich zukünftige Untersuchungen auf der Fettstoffwechsel konzentrieren, da die laborchemisch gefundene Senkung des Cholesterins auf einen metabolischen Wirkmechanismus hinweist, der zur verbesserten cerebralen Durchblutung führen dürfte, zumindest jedoch prophylaktisch bedeutsam ist, da das Cholesterin unter anderem dazu beiträgt, die Gefäßlumina zu verengen und damit einer Minderdurchblutung Vorschub zu leisten. Umgekehrt führt eine Senkung auf längere Sicht zu einer verbesserten Hirndurchblutung.

Die verbesserte Hirndurchblutung führt auch — trotz hochgradigem Altersabbau, wie aus den Ausgangswerten ersichtlich — zu einer objektivierbaren Verbesserung des akustischen Kurzzeitgedächtnisses (ZN, Geschichte nacherzählen) und des Langzeitgedächtnisses (Adressen-Wiedergabe aus der Erinnerung) unter der Annahme einer noch in der Plazebophase nachklingenden Präparatwirkung.

5. Literatur

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99-10-30

German/Translation

THERAPEUTIC INFLUENCE OF VINCAMINE ON IMPAIRMENT OF CEREBRAL PERFORMANCE IN ELDERLY PATIENTS. RESULTS OF A DOUBLE-BLIND STUDY

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ABSTRACT:

The results of a placebo controlled double blind study with Cetal®retard with 50 hospitalized patients are reported. All patients showed symptoms of cerebrovascular insufficiency. For evaluation psychometric and psychopathometric test methods (d2 Brickenkamp-Test and Show Syndrome test by Ertigkeit) were applied.

Further evaluation of the patients symptoms was carried out by the investigator, by the patients using a special rating scale and by the attending staff.

Cetal®retard proved to be effective in all criteria studied. The differences were in part of high statistical significance as well within group A = Verum (day 1/day 28) as in between group A and B. The drug was well tolerated, gastrointrestinal side-effects were slight and transient.

It has been shown that Cetal®retard is a suitable and effective drug in the therapy of the symptoms of cerebrovascular insufficiency.

The relative and absolute increase in the number of elderly persons has become more significant from year to year and confronts us with numerous problems to be solved not only of a sociolopolitical but also a medical nature [1]. The life expectancy can be expected to increase except significantly further not only in western industrial countries but also in the third world by the end of the millennium.

The satisfaction of the increasing needs in the sector of medical care of the elderly is of concern to the practicing physician as well as to the clinician.

In the treatment of the diseases of the elderly a pessimistic attitude still prevails. It would be unreasonable to arouse exaggerated hopes, especially as regards the truly ground breaking control of the somatic factors underlying cerebral diseases of the elderly.

But in the treatment of the individual symptoms great progress has been made, and to the extent that this falls within the scope of drug prophylaxis and therapy, it involves maintaining or reactivating the age-related decrease in cerebral activity so that the years gained are actually a gain. The calendar age today is no longer a contraindication for therapeutic measures of all types [2]. Above all, new possibilities of treatment exist which should simulate the doctor to maintain a more positive attitude in geriatric medicine also.

As the organic basis of cerebral age-related disorders on the one hand primarily degenerative processes and on the other hemodynamic and metabolic factors with the clinical symptoms of general cerebrovascular insufficiency come into consideration.

In the clinical picture of diffuse cerebrovascular insufficiency, which is often also called cerebral sclerosis or in the case of severe arterial hypertension also hypertensive encephalopathy, for the most part one finds mental disturbances as the key syndrome. However, they may but need not be linked with neurological disorders. These include functional psychoses

[3,4], i.e. with manifestation forms of somatogenic or organic psychological disturbances, the organic psychosyndrome according to Bleuler or the acute exogenous reaction types according to Bonhöffer.

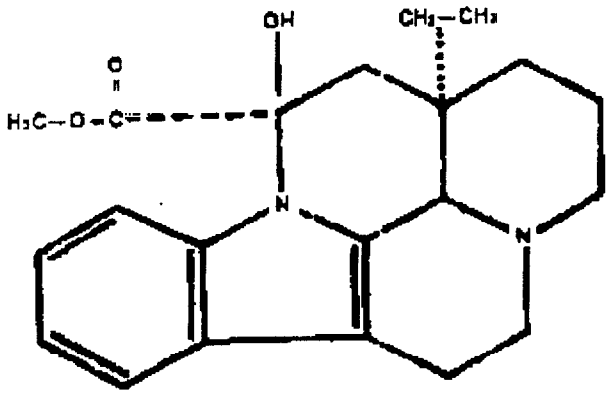
Functional psychoses manifest themselves in numerous forms, e.g. as a slowing down and increasing difficulty in the thought processes and in the processes of perception. As disturbances of memory and orientation and of states of confusion. In the milder stages the functional reduction is manifested in patterns of complaints which are expressed as a depressive mood or as a pseudoneurasthenic symptom complex.

General hypoxidosis of the brain caused by cerebroarterial sclerosis with mental symptomatology is very common especially in elderly patients and therefore represents one of the most important geriatric problems.

The therapy requires on the one hand a basic treatment of the possible cardiac decompensation as well as a specific therapy of the concurrent and secondary diseases in the case of polymorbidity of elderly patients.

Depending on the individual clinical picture, above all, on the neurological defect syndromes, activating therapeutic measures are necessary in the form of physical therapy and ergo therapy.

In the drug treatment above all of the mental symptoms of cerebral insufficiency manifestations which are susceptible to therapy and reversible, in recent times vincamine an alkaloid of *Vinca minor*, has aroused some attention (Fig. 1).



Vincamine

This substance was available for our studies in the galenic form of timed-release capsules. The timed-release capsules assure for this depot drug form, compared to vincamine pure substance, a clearly recognizable retardation of the effect characterized by a plasma level persisting more than 10 hours [15]. Vincamine has been attributed an effect on the cerebral metabolism [5,6] and a hemodynamic effect with improvement of the microcirculation, predominantly in the less perfused areas [7,8,9].

As an antihypoxidotic agent with neuroanabolic and neurotrophic properties it alters, among others, the flow properties of the blood by improving the flexibility of the erythrocytes and thrombocytes and the cellular respiration, thereby causing a distinct improvement in the cerebral metabolic relationships [19,20].

In clinical studies reference has been made to the regression of behavioral disturbances [12] and to the increase in intellectual capacity [13,14]. The substance promotes learning and memory processes, relieves functional cerebral capacity reductions of the aging person and favorably influences the

deficiency syndrome in cerebral-atrophic processes and in the transition syndrome [*Durchgangssyndrom*] [12,14].

It is therefore obvious that a clinical study should be performed with vincamine for the purpose of determining the efficacy on the patient group of an old-age nursing home. For this purpose a randomized placebo-controlled double-blind study was chosen.

The test criteria were matched to the symptoms of this group of patients with diminishing cerebral performance capacity, and the problem was approached from different aspects in order to arrive at the best founded evaluation.

Methodology

50 resident patients with uniform sex distribution ranging from 55 to 89 years of age with an average age of 73 years were included in the study for whom it could be safely assumed that their problems were traceable to cerebrovascular insufficiency. The patients came from a mixed rural and urban population of all social strata.

In all patients the cerebrovascular efficiency had caused personality changes of an organic brain nature to varying degrees. 27 suffered from mild and 23 from a serious organic psychosyndrome, 13 had transient ischemic attacks and 6 had suffered ischemic insults. 12 patients displayed discrete neurological disturbances such as hemihypesthesia and disturbed reflexes. Those patients were excluded who because of a serve form of functional psychosis or psychomotor disorders, aphasia and other handicaps were unable to participate in the envisioned

testing programs. The presence of a cerebral tumor, epilepsy or alcoholism were other criteria for exclusion.

Other geriatric disorders included 11 with cardiac insufficiency, 5 with peripheral arteriosclerosis, 9 with essential hypertension, 5 with diabetes mellitus, 3 with coronary heart disease. These patients were preliminarily treated with cardiac glycosides, antihypertensives or diabetes therapy. This therapy as well as the activating therapy methods of ergo therapy and physical therapy were continued during the test period. All other drugs, especially vasoactive substances and vasoactive metabolic geriatric agents were discontinued 14 days before the beginning of the test.

The patients were randomly assigned to two groups of equal size with 25 patients each. The medication was administered in a strictly random manner. The patients received identically appearing capsules containing either 30 mg of vincamine (Group A) or placebo (Group B). The medication schedule of 2 x 1 capsule daily was the same in both groups.

The test medication was taken regularly by all patients during the test period of 4 weeks. The observation time of 4 weeks was considered sufficient on the basis of earlier clinical tests [14], because the success of the therapy occurs after 2 to 3 weeks and after 3 weeks no significant increase can be expected any longer.

The choice of the test criteria was matched especially carefully to the clinical picture and the age group. Basically therefore we were interested primarily in those mental and

intellectual disturbances caused by cerebrovascular insufficiency which were susceptible to clinical testing and from which we could expect results relevant for practice. The first group of questions concerned the registration of disturbances of attentiveness and memory. For this purpose on the one hand before beginning therapy and after 28 days an attention-load test (d2-Brickenkamp) was performed. This test covers the ability of the person to distinguish quickly and reliably similar single visual stimuli. The corresponding capacity, the "visual attention tension" makes up a considerable part of the ability to concentrate and is essentially dependent on the intelligence.

In addition the test arrangement included subtests with the syndrome short test according to Erzigkeit [16].

The theoretical principle of the syndrome short test was the concept of functional psychosis according to Wieck [3,4]. According to this concept, functional psychoses are basically capable of regression and are based on general cerebral disorders such as can be triggered, for example, by cerebral hypoxidosis.

The syndrome short test in whose scoring the age and IQ of the patient are included permits a quantification of mild functional psychoses.

The next question to be investigated was the symptomatology. Here certain target symptoms such as vertigo, attentiveness and memory disorder, adaptation and contact disturbances, disorientation, concentration capacity, depression, confusion, sleep disturbances and non-urological or gynecological bladder disturbances and tinnitus, therefore capacity losses and personality

changes were selected which are typical for the clinical picture. The evaluation was performed as an outsider evaluation by the doctor before the treatment and after 28 days was classified according to degrees of severity as mild, moderate or severe.

Observation by the nursing personnel was another test criterion which was also formed as an outsider evaluation. For this purpose the nursing personnel were given a question form with questions regarding behavior to be answered on a graduated scale. The following groups of problems were covered by this: fitting into the daily routine, cooperation, contact behavior with nursing personnel and fellow patients, modes of behavior such as aggression, forgetfulness, reaction rate, personnel cleanliness or neglect of external appearance, various circles of interest from the immediate surroundings, reading or correspondence, interest in and taste for eating and drinking.

The patients were also asked to make a self-evaluation on the first and on the 28th day by giving them a list of complaints (according to V. Zerssen, modified with 39 questions) [17].

The questions listed here pertain to the degree of pathological disturbances of well-being of the patient. The sum of positive answers, according to V. Zerssen, also correlates with the status of the mental disease for brain-organic patients. The controlled application provides indices for changes in the sense of well-being that are independent of the opinion of the doctor, and therefore also of the efficacy of certain therapeutic measures.

The testing of the patients, the questioning regarding symptoms, the self-evaluation and the clinical examinations were performed on the day before the beginning of the test and after 4 weeks. In the case of the short syndrome test in each case intermediate results were obtained after one week.

Results

The results of the criteria tested, Brickenkamp test, target symptoms, sister [nurse] questionnaires and patient complaint list were subjected to a statistical study[1] and are listed below:

d2-Brickenkamp test

The data obtained from the index, total capacity (= C Z-F) of the Brickenkamp test were studied statistically, because it is precisely this index which has been found to be extremely informative and valid in multivariant evaluations (Fig. 2).

The available data on Group A = verum and Group B = placebo in each case were tested for standard distribution before and after treatment as well as for differences before and after treatment in both groups. In this case an approximately normal distribution was always found. For this reason it was possible to use for testing the t test for linked measurements within the group before and after treatment, for the test between the two Groups (A:B) the t-test for unlinked measurements.

In the latter case the differences (before/after) of the two groups were tested. The course difference between the two groups A and B is confirmed at the $P > 0.00001$ level (Table 1), a

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[1] The evaluation was performed by Data Service, the planning and evaluation of the statistical studies by E. Hönig, Rorbach-Ulm.

distinct superiority of Group A being found in the comparison of the two groups.

Short syndrome test according to Erzigkeit

During the course of the test some of the patients were unable to participate regularly in the weekly testing and in the subtests for various reasons. Therefore only the scores of some subtests of a reduced number of patients were available for the evaluation. From the scores of the subtests that were available summary scores were formed f rom the first and the last study and evaluated as a paired measurement (matched pair)[2].

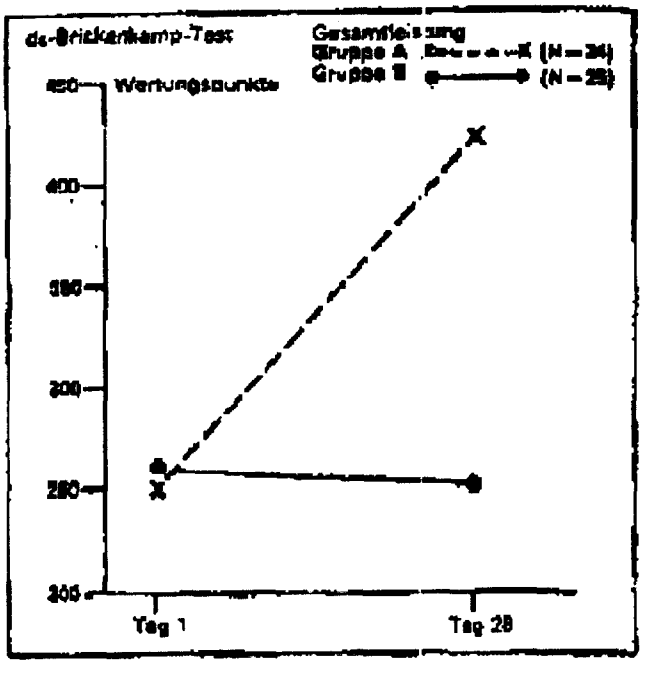

Figure 2. Score points of the results of the overall performance of the d_2-Brickenkamp test on the first and 28th day for Group A (= vincamine) and Group B (= placebo), N = number of patients.
Upper right: Total performance
Group A
Group B
Ordinate: Score points
Abscissa: Day 1 - Day 28

[2] These test results were evaluated by the Neurological University Clinic of Erlangen.

Table 1. Mean values of the results of the overall performance of the d_2-Brickenkamp test in Group A (= vincamine) and in Group B (placebo) on the 1st and 28th day of testing.

	Day 1	Day 2
Group A	251.17	425.04
Group B	258.32	251.96

According to their initial values (first examination) a parallelism was created in the random samples A and B as follows:

1. For each patient of random sample B one patient of random sample A was found with the same initial score.
2. In the case of several patients with the same initial scores those were parallelized who came first in the order of the protocols.
3. In a second step patient scores from random sample A were also admitted for pair formation whose initial value was higher by the absolute amount 1 from that of the other patients of random sample B.

Between the patients of the two random samples the differences of the initial and final values were compared.

In 10 of the matched pairs Patient A and in 4 Patient B displayed stronger improvement.

Despite the small number of patients, as a result of the highly valid test with pairing the positive result is to be considered reliable for the vincamine group.

Target symptoms

Patients with cerebrovascular insufficiency have a quite definite set of target symptoms which are registered by the

treating doctor and classified according to degree of severity (none, mild, moderate, severe).

For the evaluation they were divided into steps of improvement or deterioration. If a patient on the first day had a symptom which was classified as moderately severe and which no longer existed on the 28th day, he was given two improvement steps. If the symptom still persisted but was mild, one improvement step was reported.

The evaluation of the registered improvement or deterioration steps in stages from -2 to +3 were performed according to the Mantel-Haenszel test [18].

Because of the large number of symptoms tested here we made certain that an especially strict scale had to be used for the evaluation.

The significance found, usually below the 1°/∞ level, however, clearly demonstrated the superiority of the A Group.

Vertigo P=0.0034800, tinnitus P=0.0370000, attentiveness P=0.0044600, concentration P=0.0000025, adaptation P=0.0000110, depression P=0.0018800, disorientation P=0.0001390, confusion P=0.0000152, sleep disorders P=0.0101900, bladder disorders P=0.0221000.

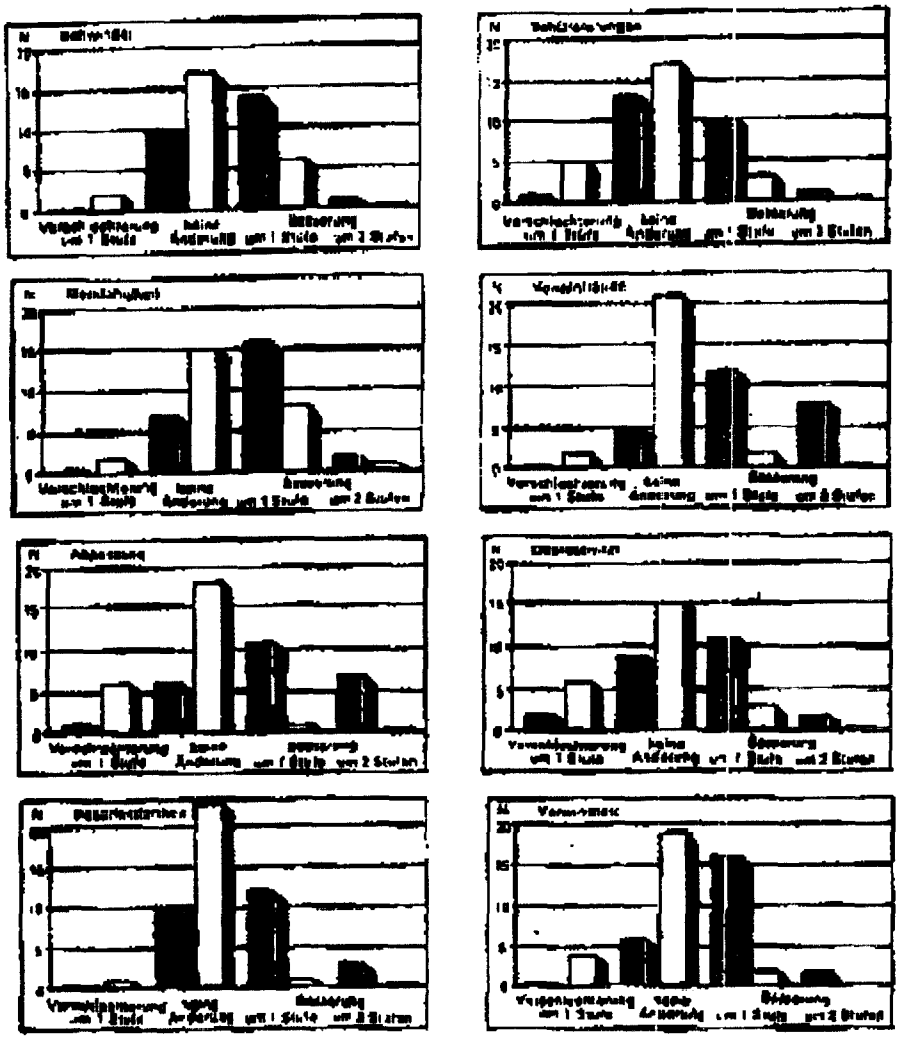

Figure 3. Bar graph of the improvement or deterioration steps of target symptoms on the 1st and 28th day of testing. Black columns=vincamine, white columns=placebo, N=number of patients.
Left side down
Vertigo, attentiveness, adaptation, disorientation
Right down
Sleep disorders, concentration, depression, confusion
Bottom all figures, left to right:
deterioration by one step; no change; improvement by one step, by two steps

In Figure 3 in the form of bar graphs on the one hand the patient numbers of the two groups A (vincamine) are shown as black columns, B (placebo) as white columns for whom the symptom deteriorated or remained unchanged.

In addition the patient numbers of the two groups are plotted in in whom an improvement in the symptoms listed was noted.

Evaluation by the nursing personnel

The question of how the nuns and nurses who had routine contact with the patients evaluated their behavior has some importance. The results of the outsider evaluation performed here, however, show that it is not easy for this group of personnel to evaluate the findings and to classify them accordingly. Although in the general evaluation by the nursing personnel it was preferentially testified that patients of Group A had become less forgetful, more interested and more active during the treatment, in the statistical evaluation of the improvement steps according to Mantel-Haenszel no significant difference could be found between the two groups.

Patient complaint list

The data which were obtained from the sum of the complaints for each of the patients of the two Groups A and B in each case before and after the treatment were evaluated.

An approximately normal distribution was present for the data of Groups A and B both before and also after the treatment but not for the differences (before/after) of Group A. Here the data differed significantly from normally distributed. A logarithmic transformation of the data also yielded no better results. For this reason, for the tests between the two groups the "Wilcoxon Rank Sum Test" was used. The course difference between the two Groups A and B is secured at the P-0.05 level.

In Figure 4 for each of the patients of Group A and Group B the sums of 'yes' answers on the 1st and 28th day in each case are plotted. From this it is apparent that the improvements in the general complaints in the vincamine group predominate.

Tolerance and side effects

In 4 patients mild gastrointestinal disturbances appeared in the sense of irritation of the gastrointestinal tract which, however, were transitory and did not necessitate discontinuation of the medication. Other cases of intolerance or side effects could not be found. Cardiocirculatory check-ups also showed no abnormal changes.

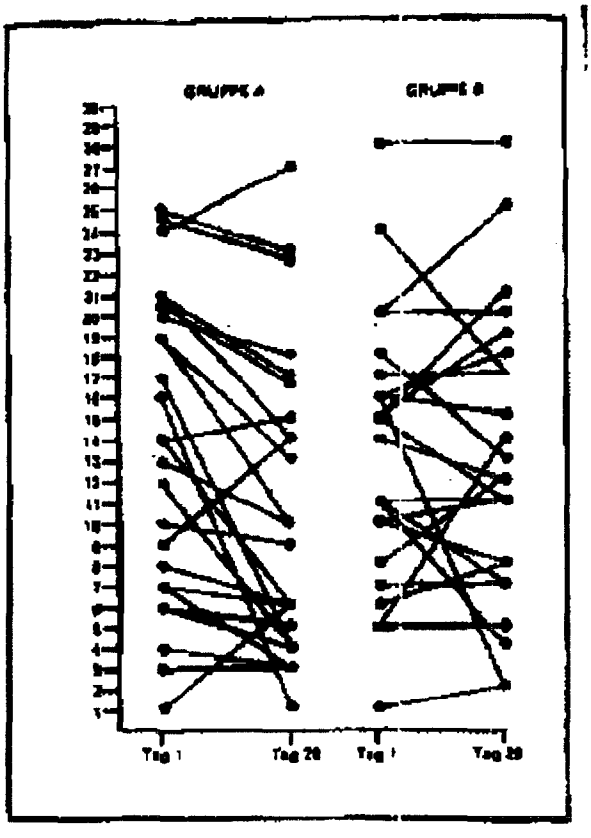

Figure 4. Sum of the 'yes' answers of the patient complaint list of group A (vincamine) and group B (placebo) on the first and 28th day of testing. Tag=day

Discussion

In the present randomized double-blind study the therapeutic efficacy of vincamine, a new active principle for the treatment of cerebrovascular insufficiency, was tested against a placebo. No essential adverse side effects could be found. The choice the test criteria was matched especially carefully to the clinical picture and the age group in order to obtain the broadest possible pronouncement.

Psychometric and psychopathometric test methods served as objective criteria with observation by the doctor and nursing personnel involved as an outsider evaluation. On the basis of a list of complaints the patient himself was able to provide information subjectively concerning the changes in his sense of well-being.

The group of active principles displayed a statistically significant improvement in the symptoms tested in the objective test methods and in the self-evaluation of the patient based on the list of symptoms. This was also the case for the evaluation of the target symptoms by the doctor, while in the evaluation by the nursing personnel although the impression of an improvement in memory, contact behavior and basic activities was present, here to be sure in the evaluation of the test forms no significant differences between the two groups could be found.

Based on the results of the study it may be stated that vincamine is a suitable agent for treatment of the intellectual and mental disorders caused by cerebrovascular insufficiency.

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Die medikamentöse Beeinflussung zerebraler Leistungsstörungen mit Vincamin bei alten Menschen

Ergebnisse einer Doppelblindstudie

Therapeutic Influence of Vincamine on Impairment of Cerebral Performance in Elderly Patients. Results of a Double-Blind-Study

H. Schenker

Zusammenfassung

Es wird über die Ergebnisse einer plazebokontrollierten Doppelblindstudie mit Vincamin[1] an 50 stationären Patienten berichtet. Alle Patienten zeigten Symptome einer zerebrovaskulären Insuffizienz. Zur Beurteilung wurden psychometrische bzw. psychopathometrische Testverfahren (d2 Brickenkamp-Test und Kurzsyndromtest nach Erzigkeit) herangezogen. Weiter erfolgte eine Beurteilung der Zielsymptome durch den Prüfarzt, ein Selbsteinschätzen des Gesamtbefindens des Patienten anhand einer Beschwerdeliste und eine Beurteilung durch das Pflegepersonal.

In allen geprüften Kriterien zeigte sich die Vincamin-Gruppe überlegen. Zum Teil waren die Unterschiede sowohl im Verlauf innerhalb der Gruppe A = Verum am 1. und 28. Tag als auch zwischen den Gruppen A und B statistisch hochsignifikant. Die klinische und psychometrische Beurteilung führte zu übereinstimmenden Ergebnissen. Unverträglichkeitserscheinungen oder Nebenwirkungen in Form von gastrointestinalen Störungen waren selten und flüchtig.

Vincamin hat sich als geeignetes und wirksames Mittel zur Behandlung der Symptome bei zerebrovaskulärer Insuffizienz gezeigt.

Summary

The results of a placebo controlled double blind study with Cetal®retard with 50 hospitalized patients are reported. All patients showed symptoms of cerebrovascular insufficiency. For evaluation psychometric and psychopathometric test methods (d2 Brickenkamp-Test and Short Syndrome test by Erzigkeit) were applied.

Further evaluation of the patients symptoms was carried out by the investigator, by the patients using a special rating scale and by the attending staff.

Cetal®retard proved to be effective in all criteria studied. The differences were in part of high statistical significance as well within group A = Verum (day 1/day 28) as in between group A and B. The drug was well tolerated, gastrointestinal side-effects were slight and transient.

It has been shown that Cetal®retard is a suitable and effective drug jn the therapy of the symptoms of cerebrovascular insufficiency.

[1] Das Präparat Cetal®retard wurde uns freundlicherweise von der Firma Parke-Davis & Co. zur Verfügung gestellt.

Die relative und absolute Zunahme alternder Menschen wird von Jahr zu Jahr bedeutungsvoller und stellt uns vor zahlreiche zu lösende Aufgaben nicht nur sozialpolitischer, sondern auch medizinischer Art (1). Die Lebenserwartung dürfte nicht nur in den westlichen Industrieländern, sondern auch in der Dritten Welt bis zur Jahrtausendwende noch bedeutend ansteigen.

Die Befriedigung der zunehmenden Bedürfnisse im Bereich der medizinischen Betreuung der Betagten beschäftigt den praktisch tätigen Arzt gleichermassen wie den Kliniker.

Bei der Behandlung der Alterskrankheiten besteht noch immer vielfach eine pessimistische Haltung. Es wäre unsinnig, übertriebene Hoffnungen zu wecken, besonders hinsichtlich einer wirklich durchschlagenden Bekämpfung der somatischen Grundlagen der zerebralen Alterserkrankungen.

Aber die Behandlung einzelner Symptome hat doch Fortschritte erzielt, und soweit dies in das Gebiet der medikamentösen Prophylaxe und Therapie fällt, geht es darum, die altersbedingte Abnahme der Hirntätigkeit aufzuhalten bzw. diese zu reaktivieren, damit die gewonnenen Jahre wirklich ein Gewinn sind. Das kalendarische Alter ist heute keine Kontraindikation mehr gegenüber therapeutischen Massnahmen aller Art (2). Es sind vor allem neue Behandlungsmöglichkeiten, die den Arzt veranlassen sollten, auch in der Altersmedizin eine positivere Haltung einzunehmen.

Als organische Grundlage zerebraler Altersstörungen können einmal primär degenerative Vorgänge, einmal hämodynamische und metabolische Faktoren mit den klinischen Zeichen der allgemeinen zerebrovaskulären Insuffizienz in Frage kommen.

Bei dem Krankheitsbild der diffusen zerebrovaskulären Insuffizienz, oft auch als Zerebralsklerose oder bei starker arterieller Hypertonie als hypertensive Enzephalopathie bezeichnet, finden sich zumeist psychische Störungen als führende Symptome. Sie können, aber müssen nicht mit neurologischen Ausfällen verkoppelt sein. Es handelt sich dabei um Funktionspsychosen (3, 4), das heisst um die Manifestationsformen somatogener oder organischer psychischer Störungen, das organische Psychosyndrom nach *Bleuler* oder die akuten exogenen Reaktionstypen nach *Bonhöffer*.

Funktionspsychosen manifestieren sich in mannigfaltigen Erscheinungsformen z. B. als Verlangsamung und Erschwerung der Denkabläufe und der Wahrnehmungsvorgänge, als Gedächtnis- und Orientierungsstörungen und Verwirrtheitszustände. In den leichteren Stadien äussert sich die Funktionsminderung in Beschwerdebildern, die als depressive Verstimmung oder pseudoneurasthenischer Beschwerdenkomplex zum Ausdruck kommen.

Die durch die Hirnarteriosklerose bedingte allgemeine Hypoxidose des Gehirns mit psychischer Symptomatik ist besonders bei alten Patienten sehr häufig und stellt sich deshalb als eines der wichtigsten geriatrischen Probleme dar.

Die Therapie erfordert einerseits eine Basisbehandlung möglicher kardialer Dekompensation sowie bei der Polymorbidität alter Patienten eine spezifische Therapie von Begleit- und Nebenerkrankungen.

Abhängig vom individuellen Krankheitsbild vor allem von neurologischen Defektsyndromen sind aktivierende Behandlungsmassnahmen in Form von Physiotherapie und Ergotherapie notwendig.

In der medikamentösen Behandlung vor allem der psychischen Symptomatik der zerebralen Insuffizienzerscheinungen, die einer Therapie zugängig und reversibel sind, hat in letzter Zeit das Vincamin, ein Alkaloid der Vinca minor, einige Beachtung gefunden (Abb. 1).

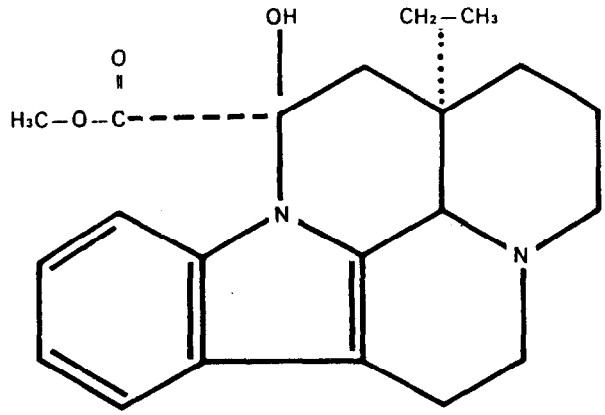

Abb. 1. Vincamin.

Diese Substanz stand uns für unsere Untersuchungen in der galenischen Form der Retardkapseln zur Verfügung. Die Retardkapseln gewährleisten für diese Depotarzneiform im Vergleich zur Vincamin-Reinsubstanz eine deutlich erkennbare Wirkungsverzögerung, gekennzeichnet durch einen über 10 Stunden anhaltenden Plasmaspiegel (15). Dem Vincamin wird eine Wirkung auf den zerebralen Metabolismus (5, 6) und eine hämodynamische Wirkung mit Verbesserung der Mikrozirkulation vorwiegend in minderdurchbluteten Arealen zugesprochen (7, 8, 9).

Als Antihypoxidotikum mit neuroanabolen und neurotrophen Eigenschaften verändert es unter anderem die Fliesseigenschaften des Blutes durch Verbesserung der Flexibilität der Erythrozyten und Thrombozyten und der Zellatmung und bewirkt dadurch eine deutliche Verbesserung der zerebralen Stoffwechselverhältnisse (19, 20).

In klinischen Studien wurde auf die Rückbildung von Verhaltensstörungen (12) und auf die Steigerung der intellektuellen Leistung hingewiesen (13, 14). Die Substanz fördert Lern- und Gedächtnisvorgänge sowie funktionelle zerebrale Leistungsminderungen des alternden Menschen und beeinflusst Defektsyndrome bei hirnatrophischen Prozessen und Durchgangssyndromen günstig (12, 14).

Es war deshalb gegeben, mit Vincamin eine klinische Studie durchzuführen mit dem Ziel, die Wirksamkeit an dem Patientengut eines Alters- und Pflegeheimes z

überprüfen. Hierzu wurde eine randomisierte, plazebokontrollierte Doppelblindstudie ausgewählt.

Die Prüfkriterien wurden auf die Symptomatik dieser Patientengruppe mit Nachlassen zerebraler Leistungsfähigkeit abgestimmt, und, um zu einer möglichst fundierten Beurteilung zu kommen, die Problematik von verschiedenen Gesichtspunkten her eingekreist.

Methodik

In die Untersuchung aufgenommen wurden 50 stationäre Patienten mit gleichmässiger Geschlechtsverteilung im Alter von 55 bis 89 Jahren bei einem Durchschnittsalter von 73 Jahren, bei denen mit Sicherheit angenommen werden konnte, dass ihre Beschwerden auf eine zerebrovaskuläre Insuffizienz zurückzuführen waren. Die Patienten entstammten einer gemischten ländlichen und städtischen Bevölkerung aller sozialer Schichtungen.

Bei allen Patienten hatte die zerebrale Mangeldurchblutung hirnorganische Wesensveränderungen unterschiedlicher Ausprägung zur Folge. 27 litten unter einem leichteren und 23 unter einem schwereren Grad des organischen Psychosyndroms, bei 13 hatten transiente ischämische Attacken und bei 6 ischämische Insulte stattgefunden. 12 Patienten wiesen diskrete neurologische Störungen wie Hemihypästhesie und Reflexstörungen auf. Ausgeschlossen wurden Kranke, die wegen einer schweren Form der Funktionspsychose oder wegen psychomotorischer Störungen, Aphasie und anderweitiger Behinderung nicht an den vorgesehenen Testuntersuchungen teilnehmen konnten. Als weitere Ausschlusskriterien galten das Vorliegen eines zerebralen Tumors, Epilepsie oder Alkoholismus.

Bei der Polypathie alter Patienten litten zudem 11 an einer Herzinsuffizienz, 5 auch unter einer peripheren Arteriosklerose, 9 unter einer essentiellen Hypertonie, 5 an einem Diabetes mellitus, 3 an einer koronaren Herzkrankheit. Diese Patienten waren mit Herzglykosiden, Antihypertonika oder einer Diabetestherapie vorbehandelt. Diese Therapie sowie auch die aktivierenden Behandlungsmethoden der Ergotherapie und Physiotherapie wurden während der Prüfperiode fortgesetzt. Alle anderen Medikamente, insbesondere gefässaktive Substanzen und gefässwirksame, stoffwechselaktive Geriatrika, wurden 14 Tage vor Versuchsbeginn abgesetzt.

Die Patienten wurden randomisiert zwei gleich grossen Gruppen mit je 25 Patienten zugeteilt. Die Zuteilung der Medikation erfolgte streng zufällig. Die Patienten erhielten gleich aussehende Kapseln mit entweder 30 mg Vincamin (Gruppe A) oder Plazebo (Gruppe B). Das Einnahmeschema von 2mal täglich 1 Kapsel war in beiden Gruppen gleich.

Die Testmedikation wurde von allen Patienten während der Versuchsperiode von 4 Wochen regelmässig eingenommen. Die Beobachtungszeit von 4 Wochen wurde aufgrund früherer klinischer Prüfungen als genügend erachtet (14), da sich der Therapieerfolg nach 2 bis 3 Wochen einstellt und nach 3 Wochen keine wesentliche Steigerung mehr zu erwarten war.

Die Auswahl der Prüfkriterien wurde besonders sorgfältig auf das Krankheitsbild und die Altersgruppe abgestimmt. Grundsätzlich interessierten deshalb in erster Linie diejenigen durch die zerebrovaskuläre Insuffizienz hervorgerufenen psychischen und intellektuellen Störungen, die einer klinischen Prüfung zugänglich und von denen praxisrelevante Ergebnisse zu erwarten waren. Der erste Fragenkreis galt der Erfassung von Aufmerksamkeits- und Gedächtnisstörungen. Hierzu wurde einmal vor Therapiebeginn und nach 28 Tagen ein Aufmerksamkeitsbelastungstest (d2-*Brickenkamp*) durchgeführt. Dieser Test erfasst die Fähigkeit des Menschen, ähnliche visuelle Einzelreize rasch und sicher zu unterscheiden. Die dementsprechende Leistung, die «visuelle Aufmerksamkeitsspannung», macht einen beträchtlichen Teil der Konzentrationsfähigkeit aus und ist von der Intelligenz weitgehend unabhängig.

Weiterhin wurden in die Versuchsanordnung mit einbezogen Subtests aus dem Syndromkurztest nach *Erzigkeit* (16).

Als theoretische Grundlage für den Syndromkurztest gilt die Lehre von den Funktionspsychosen nach *Wieck* (3, 4). Nach dieser Lehre sind Funktionspsychosen grundsätzlich rückbildungsfähig und beruhen auf allgemeinen zerebralen Störungen, wie sie beispielsweise durch zerebrale Hypoxidosen ausgelöst werden können.

Der Syndromkurztest, in dessen Bewertung das Alter und der IQ des Patienten mit einbezogen sind, erlaubt eine Quantifizierung leichter Funktionspsychosen.

Die nächste Fragestellung galt der Symptomatik. Hier wurden bestimmte Zielsymptome wie Schwindel, Merkfähigkeits- und Gedächtnisstörungen, Anpassungs- und Kontaktstörungen, Desorientiertheit, Konzentrationsfähigkeit, Depressivität, Verwirrtheit, Schlafstörungen und nicht urologische oder gynäkologische Blasenstörungen und Tinnitus, also Leistungseinbussen und Wesensveränderungen, ausgewählt, die für das Krankheitsbild charakteristisch sind. Die Beurteilung erfolgte als Fremdbeurteilung durch den Arzt vor der Behandlung und nach 28 Tagen gestaffelt nach Schweregraden leicht, mittel oder schwer.

Ein weiteres Prüfungskriterium bildete ebenfalls als Fremdbeurteilung die Beobachtung durch das Pflegepersonal. Hiezu wurde dem Pflegepersonal ein Fragebogen mit einer skalierten Angabe nach verschiedenen Verhaltensweisen vorgelegt. Es wurden dabei folgende Problemkreise erfasst: Eingliederung in das tägliche Leben, Kooperation, Kontaktverhalten mit dem Pflegepersonal und den Mitpatienten, Verhaltensweisen wie Aggressivität, Vergesslichkeit, Reaktionstempo, Beachten der Sauberkeit oder Vernachlässigung der äusseren Erscheinung, verschiedene Interessenkreise der unmittelbaren Umgebung, der Lektüre oder der Korrespondenz, Interesse und Geschmack am Essen und Trinken.

Zur Selbstbeurteilung wurde den Patienten ebenfalls am ersten und am 28. Tag eine Beschwerdeliste (nach *V. Zerssen*, modifiziert mit 39 Fragen) vorgelegt (17).

Die hier angeführten Fragen beziehen sich auf den Grad krankhafter Befindensstörungen des Patienten. Die Summe der Ja-Antworten korreliert nach *V. Zerssen* mit dem Zustand psychischer Erkrankung auch von Hirnorganikern. Die kontrollierte Anwendung liefert vom Ermessen des Arztes unabhängige Indizien für Befindensänderungen und damit auch für die Wirksamkeit bestimmter therapeutischer Massnahmen.

Die Testung der Patienten, die Symptombefragung, die Selbstbeurteilung und klinische Befunderhebung wurde am Tag vor Prüfungsbeginn und nach 4 Wochen durchgeführt. Bei dem Syndromkurztest wurden jeweils nach einer Woche Zwischenergebnisse erhoben.

Ergebnisse

Die Ergebnisse der geprüften Kriterien *Brickenkamp*-Test, Zielsymptome, Schwesternfragebogen und Patientenbeschwerdeliste wurde einer statistischen Untersuchung[1] unterzogen und sind nachstehend aufgeführt:

d2-Brickenkamp-Test

Statistisch untersucht wurden die Daten, die sich aus dem Index, Gesamtleistung (= G Z–F) des *Brickenkamp*-Testes ergaben, denn gerade dieser Index hat sich bei multivariaten Auswertungen als sehr aussagekräftig erwiesen (Abb. 2).

Die vorliegenden Daten der Gruppe A = Verum und Gruppe B = Plazebo wurden jeweils vor und nach der Behandlung auf Normalverteilung hin geprüft, ebenfalls die Differenzen vor und nach der Behandlung beider Gruppen. Dabei wurde jeweils annähernd Normalverteilung gefunden. Aus diesem Grunde konnte zum Test innerhalb der Gruppen vor und nach der Behandlung der t-Test für verbundene Messungen angewendet werden, zum Test zwischen den beiden Gruppen (A:B) der t-Test für unverbundene Messungen.

Im letzteren Fall wurden die Differenzen (vor/nach) beider Gruppen getestet. Der Verlaufsunterschied zwischen den beiden Gruppen A und B ist auf dem $P > 0{,}00001$-Niveau gesichert (Tab. 1), wobei sich beim Vergleich der beiden Gruppen eine deutliche Überlegenheit der Gruppe A ergab.

Syndromkurztest nach Erzigkeit

Während des Versuchsablaufs konnten einige Patienten an der wöchentlichen Testung und an den Subtests aus verschiedenen Gründen nicht regelmässig teilnehmen. Für die Auswertung standen daher nur die Wertpunkte einiger Subtests einer reduzierten Anzahl von Patienten zur Verfügung. Aus den Wertpunkten der zur Verfügung stehenden Subtests wurden Wertpunktsummen für die Erst- und Letztuntersuchung gebildet und als gepaarte Messung (matched pair) ausgewertet[2].

Nach ihren Ausgangswerten (Erstuntersuchung) fand eine Parallelisierung der Stichproben A und B auf folgende Weise statt:

1. Zu jedem Patienten der Stichprobe B wurde ein Patient der Stichprobe A mit dem gleichen Ausgangswert gesucht.
2. Bei mehreren Patienten mit gleichen Ausgangswerten wurden die parallelisiert, die in der Reihenfolge der Protokolle als erste kamen.
3. In einem zweiten Schritt wurden auch Patientenwerte der Stichprobe A zur Paarbildung zugelassen, deren Ausgangswert sich um den Absolutbetrag 1 von den noch übrigen Patienten der Stichprobe B abhob.

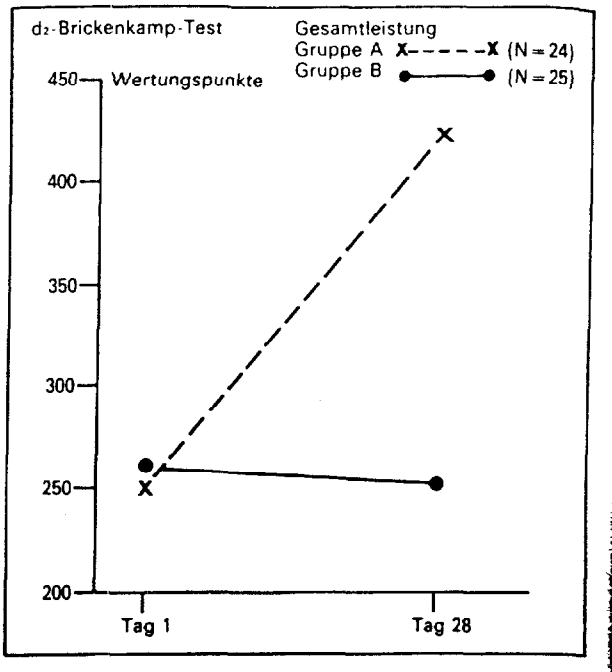

Abb. 2. Wertungspunkte der Ergebnisse der Gesamtleistung des d2-Brickenkamp-Testes am 1. und 28. Tag bei Gruppe A (= Vincamin) und Gruppe B (= Plazebo). N = Anzahl der Patienten.

Tab. 1. Mittelwerte der Ergebnisse der Gesamtleistung des d2-Brickenkamp-Testes in Gruppe A (= Vincamin) und in Gruppe B (= Plazebo) am 1. und 28. Tag der Testung.

	Tag 1	Tag 28
Gruppe A	251.17	425.04
Gruppe B	258.32	251.96

[1] Die Auswertung erfolgte in der Firma Datenservice, Planung und Auswertung statistischer Untersuchungen, E. Hönig, Rorbach-Ilm.

[2] Die Auswertung dieser Testergebnisse wurde in der neurologischen Universitätsklinik Erlangen vorgenommen.

Zwischen den Patienten der beiden Stichproben wurden die Differenzen der Ausgangs- und Endwerte verglichen.

Bei 10 der matched pairs zeigte der Patient A und bei 4 der Patient B stärkere Verbesserungen.

Trotz der geringen Anzahl an Patienten ist durch den sehr aussagekräftigen Test mit Paarbildung das positive Ergebnis für die Vincamin-Gruppe als zuverlässig anzusehen.

Zielsymptome

Patienten mit zerebrovaskulärer Insuffizienz haben eine ganz bestimmte Zielsymptomatik, die durch den behandelnden Arzt erfasst und gestaffelt nach Schweregraden (keine, leicht, mittel, schwer) beurteilt wurde.

Zur Auswertung erfolgte eine Aufgliederung in Besserungs- bzw. Verschlechterungsschritte. Hatte ein Patient am ersten Tag ein Symptom, das als mittelschwer eingestuft wurde und am 28. Tag nicht mehr bestand, wurden zwei Besserungsschritte verzeichnet. Bestand das Symptom nur noch leicht, wurde ein Besserungsschritt angegeben.

Die Beurteilung der aufgezeichneten Besserungs- bzw. Verschlechterungsschritte in Stufen von −2 bis +3 erfolgte nach dem Test von *Mantel Haenszel* (18).

Wegen der Vielzahl der hier getesteten Symptome waren wir uns klar, dass bei der Bewertung ein besonders strenger Massstab angelegt werden musste.

Die gefundenen Signifikanzen zum grossen Teil unter dem 1 ‰-Niveau zeigen jedoch deutlich die Überlegenheit der A-Gruppe.

Schwindel P = 0,0034800, Tinnitus P = 0,0370000, Merkfähigkeit P = 0,0044600, Konzentration P = 0,0000025, Anpassung P = 0,0000110, Depressivität P = 0,0018800, Desorientiertheit P = 0,0001390, Verwirrtheit P = 0,0000152, Schlafstörungen P = 0,0101900, Blasenstörungen P = 0,0221000.

In Abbildung 3 sind in Säulendiagrammen einmal die Patientenzahlen der beiden Gruppen A (Vincamin) als schwarze Säulen, B (Plazebo) als weisse Säulen dar-

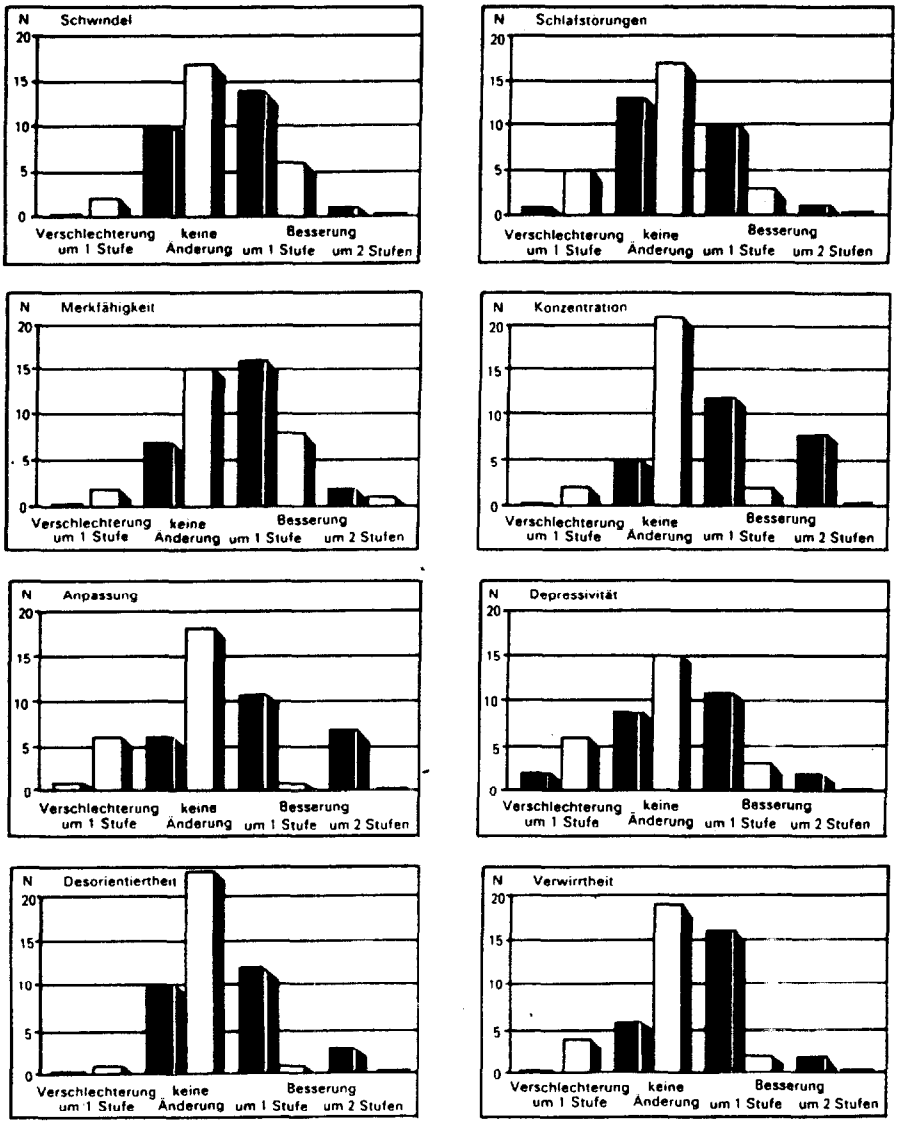

Abb. 3. Säulendiagramme der Besserungs- bzw. Verschlechterungsschritte von Zielsymptomen am 1. und 28. Tag der Testung. Schwarze Säulen = Vincamin. Weisse Säulen = Placebo. N = Zahl der Patienten.

gestellt, bei denen Symptome verschlechtert wurden oder ohne Änderung blieben.

Daneben sind die Patientenzahlen der beiden Gruppen aufgezeichnet, bei denen eine Besserung der angeführten Symptome zu verzeichnen war.

Beurteilung durch das Pflegepersonal

Der Frage, wie Schwestern und Pfleger, die laufend Kontakt mit den Patienten haben, deren Verhalten beurteilen, kommt einige Bedeutung zu. Die Ergebnisse der hier vorgenommenen Fremdbeurteilung zeigen allerdings, dass es diesem Personenkreis offenbar nicht ganz leichtfällt, die Befunde entsprechend zu bewerten und zu rubrizieren. Obgleich in der Allgemeinbeurteilung durch das Pflegepersonal den Patienten der Gruppe A vorzugsweise testiert wurde, dass sie weniger vergesslich, interessierter und aktiver unter der Behandlung geworden sind, konnte bei der statistischen Auswertung der Besserungsschritte nach *Mantel Haenszel* ein signifikanter Unterschied zwischen den beiden Gruppen nicht festgestellt werden.

Patientenbeschwerdeliste

Ausgewertet wurden die Daten, die sich aus der Summe der Beschwerden für jeden der Patienten der beiden Gruppen A und B jeweils vor und nach der Behandlung ergaben.

Annähernde Normalverteilung lag vor für die Daten der Gruppen A und B, sowohl vor als auch nach der Behandlung, nicht aber für die Differenzen (vor/nach) der Gruppe A. Hier unterschieden sich die Daten signifikant zu Normalverteilten. Auch eine logarithmische Transformation der Daten brachte kein besseres Ergebnis. Aus diesem Grunde wurde zum Test zwischen den beiden Gruppen der «Wilcoxon Rank Sum Test» angewandt. Der Verlaufsunterschied zwischen den beiden Gruppen A und B ist auf dem P-0,05-Niveau gesichert.

In Abbildung 4 sind für jeden Patienten der Gruppe A und der Gruppe B die jeweiligen Summen der Ja-Antworten am 1. und 28. Tag aufgezeichnet. Es ist auch hieraus ersichtlich, dass in der Vincamin-Gruppe die Besserungen der Allgemeinbeschwerden überwiegen.

Verträglichkeiten und Nebenwirkungen

Bei 4 Patienten zeigten sich leichte gastrointestinale Störungen im Sinne von Irritationen im Magendarmtrakt, die jedoch flüchtig waren und kein Absetzen der Medikation erforderten. Andere Unverträglichkeiten oder Nebenwirkungen konnten nicht festgestellt werden. Auch Kontrollen des Herzkreislaufs ergaben keine abnormen Veränderungen.

Diskussion

In der vorliegenden randomisierten Doppelblindstudie wurde die therapeutische Wirksamkeit von Vincamin, einem neuen Wirkstoff zur Behandlung der zerebrovaskulären Insuffizienz, gegenüber einem Plazebo untersucht. Wesentliche unerwünschte Nebenwirkungen konnten nicht festgestellt werden. Die Auswahl der Prüfkriterien wurde besonders sorgfältig auf das Krankheitsbild und die Altersgruppe abgestimmt, um eine möglichst breit gefächerte Aussage zu erhalten.

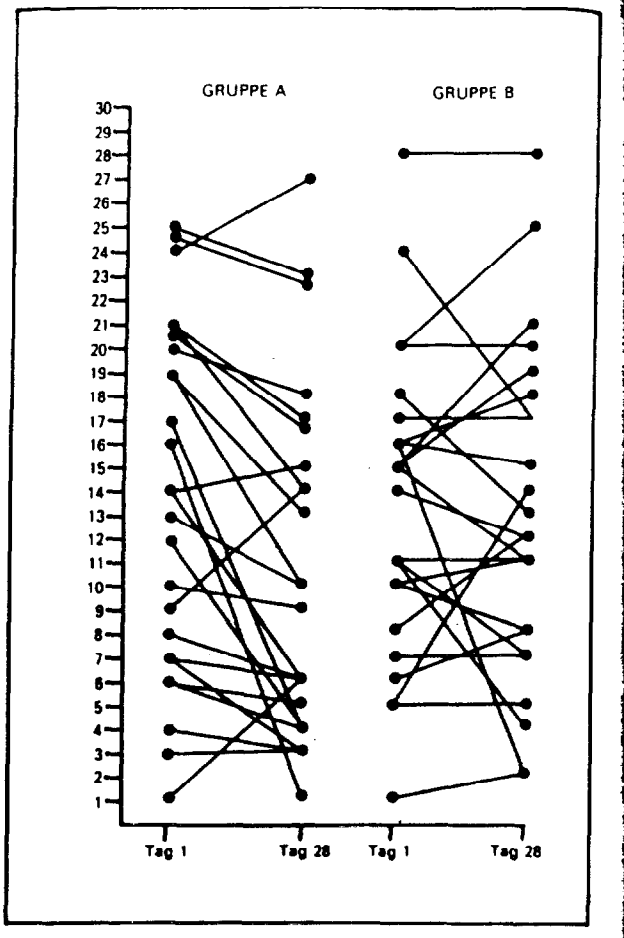

Abb. 4. Summe der Ja-Antworten der Patientenbeschwerdelisten der Gruppe A (= Vincamin) und der Gruppe B (= Placebo) am 1. und 28. Tag der Testung.

Es wurden psychometrische und psychopathometrische Testmethoden als objektive Kriterien und Beobachtung durch den Arzt und das Pflegepersonal als Fremdbeurteilung beigezogen. Anhand einer Beschwerdeliste konnte der Patient selber subjektiv über die Veränderungen seines Befindens Auskunft geben.

Die Wirkstoffgruppe wies bei den objektiven Testmethoden und bei der Selbstbeurteilung des Patienten aufgrund der Beschwerdeliste eine statistisch signifikante Besserung der geprüften Beschwerden auf. Dies war auch bei der Beurteilung der Zielsymptome durch den Arzt der Fall, während bei der Beurteilung durch das Pflegepersonal zwar der Eindruck einer Verbesserung der Gedächtnisleistung, des Kontaktverhaltens und der Grundaktivitäten bestand, bei der Auswertung der Prüfbogen sich allerdings hier keine signifikanten Un-

terschiede zwischen den beiden Gruppen feststellen liessen.

Aufgrund der Untersuchungsergebnisse kann ausgesagt werden, dass Vincamin ein geeignetes Mittel zur Behandlung der durch die zerebrovaskuläre Insuffizienz hervorgerufenen intellektuellen und psychischen Störungen darstellt.

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Therapeutic Efficacy of Vincamine in Dementia

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Abstract

This trial was performed to investigate the therapeutic efficacy of vincamine in the treatment of primary degenerative and vascular dementia. 152 male and female patients aged between 50 and 85 years from two psychogeriatric centers and two nursing homes were initially included in the trial and screened for eligibility. 142 patients completed the trial. Clinical diagnosis was established according to DSM-III-R criteria. Allocation of the patients to the primary degenerative dementia of the Alzheimer type (DAT) group or the multi-infarct dementia (MID) group was based on computed tomography scans, electroencephalographic findings and the Hachinski Ischemic Score. In a 12-week double-blind treatment either 30 mg vincamine or placebo was given twice daily. Confirmatory statistics included item 2 of the Clinical Global Impression (CGI), the total score of the Sandoz Clinical Assessment Geriatric (SCAG) scale, the subscale 'need for help' of the nurse's rating of geriatric patients (Beurteilungsskala für geriatrische Patienten; BGP) and the total score of the Short Cognitive Performance Test (Syndrom-Kurztest; SKT). In addition, data on tolerance and on therapy response were evaluated based on descriptive statistics. The therapeutic efficacy of vincamine was clearly demonstrated by confirmatory analysis as the drug was statistically significantly superior to placebo in all four target variables. The clinical relevance of the outcome was further underlined by the results of the responder analysis of the variables SCAG, BGP and SKT. Based on the results of this trial, it can be accepted that the therapeutic effect of vincamine is superior to placebo in patients with mild to moderate dementia of degenerative and vascular etiologies.

Key Words
Placebo-controlled phase III trials
Antidementia drug
Antihypoxidotics
Nootropics
Vincamine
Dementia of the Alzheimer type
Multi-infarct dementia

Introduction

In recent years, the usefulness of nootropic drugs in the therapy of dementia has been a matter of controversial discussion. One of the major sources of controversy was the lack of methodological standards for the evaluation of therapeutic efficacy. In the meantime, the discussion has resulted in several published recommendations for the methodology of clinical trials with nootropics [1–5]. Though the various guidelines do not fully agree with respect to all methodological details, there is general agreement that a study implemented to prove the efficacy of a nootropic drug should be a prospective, randomized, placebo-controlled trial of at least 3 months duration with

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predefined outcome hypotheses pertaining to target variables measured on different assessment levels. The study population should be carefully defined and the diagnosis of dementia should be made according to internationally recognized criteria, preferably according to DSM-III-R of the American Psychiatric Association [6].

There is no general agreement whether the diagnosis of the dementia syndrome should mandatorily be supplemented by an etiological approach and the recommendations diverge with respect to the number of independent outcome criteria considered necessary to prove efficacy. Finally, the question of clinical relevance of therapeutic effects still seems to be quite controversial and unsettled, although its importance is accepted unequivocally.

The present report aims to demonstrate how a clinical trial can be designed and carried out to fulfill recently published methodological criteria for the proof of efficacy. Furthermore, some problems encountered when drawing conclusions on clinical relevance from therapeutic efficacy will be considered. A placebo-controlled phase III trial using the nootropic drug vincamine serves as an illustration with the primary aim to investigate whether the drug is effective in the treatment of elderly patients suffering from mild to moderate dementia of the Alzheimer type (DAT) or multi-infarct dementia (MID). An additional aim of this trial was to evaluate the tolerability of the test substance in elderly patients.

Material and Methods

Drug

Vincamine is an alkaloid compound isolated from *Vinca rosea*. The substance, which belongs to the group of antihypoxidotics and nootropics, is considered to improve the peripheral and cerebral blood flow by reducing the resistance in the vascular system as well as to activate the cerebral metabolism by increasing oxygen and glucose utilization [7, 8]. Computer-assisted spectral analysis of the EEG shows that the substance increases alpha activity and decreases delta and theta activities, thus improving vigilance [9]. The galenic form used in the present investigation was vincamine retard-ratiopharm®, a sustained-release tablet containing 30 mg vincamine. The tablets were administered twice daily. Since the administered placebos were absolutely identical in appearance, verum and placebo could not be distinguished.

Design

The trial was desigend as a multicenter placebo-controlled randomized double-blind study with a treatment phase of 12 weeks. The treatment phase was preceded by an initial screening procedure, in which patients were clinically diagnosed and allocated to the DAT or MID group and a 4-week placebo run-in phase. A treatment period of 12 weeks was chosen because experience has shown that an improvement in cognitive performance and beneficial effects in daily activities can only be observed after a therapy of at least 2 or 3 months.

Patients

After giving written informed consent, 152 patients (107 women and 45 men) from two psychogeriatric centers of the psychiatric hospital Baumgartner Höhe in Vienna, from the Maimonides nursing home in Vienna and from the municipal nursing home in Ybbs were included in the trial. Of the 152 recruited patients, 3 withdrew prematurely because of supervening illness and 4 died of myocardial infarction during the 12-week treatment phase. Due to belatedly recognized violations of inclusion criteria further 3 patients were excluded from the efficacy analysis before breaking the randomization code.

The assigned patients underwent a careful screening procedure and were considered eligible for the trial if they met the following inclusion criteria:

- Age between 50 and 85 years
- Presence of dementia according to DSM-III-R criteria
- MMSE score ≥ 10 and ≤ 23
- Short Cognitive Performance Test (Syndrom-Kurztest; SKT) score ≥ 9 and ≤ 21
- Etiological allocation to the diagnostic group of either DAT or MID

The clinical diagnosis was made according to DSM-III-R criteria. The Mini-Mental State Examination (MMSE) [10], a test to grade cognitive functions, and the SKT, a test to record disturbances of attention and memory functions [11] were used to quantify the degree of cognitive impairment. In order to include only patients with mild to moderate dementia, a total score between 10 and 23 in the MMSE and a total score between 9 and 21 in the SKT was required. The etiological classification was carried out on the basis of CT scans, EEG findings and the Hachinski Ischemic Score (HIS) [12]. Patients were excluded from the trial in case of meeting any of the following criteria:

Brain diseases

- Severe dementia (MMSE < 10; SKT > 21)
- Disturbances of consciousness
- Dementia resulting from alcoholism or head trauma (including postcontusional residual state)
- Acute organic psychosis, e.g. delirium
- Suspicion of depressive pseudodementia (SDS score > 55, Self-Rating Depression Scale) [13]
- Schizophrenic disorders
- Stroke less than 6 months previously
- Epilepsy
- Dementing processes following expanding lesions, Parkinson's disease, or other neurological diseases

Patients with unstable metabolic conditions

- Congestive heart failure or decompensated circulatory insufficiency
- Severe chronic pulmonary disease which may lead to cerebral hypoxia
- Noncompensated cardiac dysrhythmia
- Decompensated diabetes mellitus
- Renal insufficiency
- Thyroid disease
- Pernicious anemia
- Severe dehydration

Diseases which prevent adequate psychometric testing
- Serious communication problems, e.g., sensorimotor aphasia, apraxia
- Inability to follow test instruction
- Noncompensated sensory disturbances

Causes for changed pharmacokinetic behavior
- Severe gastrointestinal disorders
- Hepatic failure

Risks with regard to side effects of the drug
- Hypotension (RR systolic <100 mm Hg; RR diastolic <60 mm Hg)

Condition which might interfere with the psychometric test results
- Alcohol or drug abuse
- Concomitant treatment with other nootropics
- Concomitant treatment with cerebrovasoactive compounds
- Irregular intake of other psychotropic drugs

Assessments

Assessment instruments to evaluate efficacy were chosen to cover the clinical core symptoms of dementia including cognitive and noncognitive symptoms as well as the patient's need for care. Particular attention was paid to ensure independent observation at different levels of assessment, using different sources of information. Efficacy outcome variables were derived from the following assessment instruments:

- Clinical Global Impression (CGI) [14, 15], which is a rating scale to evaluate therapeutic efficacy of drugs. The rating of the physician of item 2 reflects the global improvement of the patient compared to his/her condition at admission of the trial due to drug effects.
- Sandoz Clinical Assessment Geriatric Scale (SCAG) [14, 16], which is a rating scale to measure impairment of cognition, affectivity, social behavior and physical function. The rating of the clinical psychologist shows changes of clinical symptoms during the course of the trial.
- Nurse's rating of geriatric patients (Beurteilungsskala für geriatrische Patienten; BGP) [14], which is a rating scale to assess functional disorders of geriatric patients. The score of the used subscale 'need for help' reflects the need for help with daily routine activities.
- Short Cognitive Performance Test (SKT) [11], which is a psychometric procedure designed to assess deficits in attention and short-term memory. The total score indicates the extent of cognitive impairment.

Assessments were made at the beginning of the treatment phase (baseline), after 6 weeks and after 12 weeks of treatment by three independent investigators who did not exchange their ratings. The CGI was assessed by a physician, the SCAG and SKT were performed by an experienced clinical psychologist and the BGP subscale 'need for help' was rated by a nurse.

In order to evaluate safety and tolerability, physical, neurological and laboratory examinations including a complete blood chemistry analysis as well as blood pressure measurements were additionally performed at the same point of time. Adverse events occurring during the course of drug treatment were documented with a standardized scale for recording side-effects (DOTES/TWIS) [14].

Statistical Evaluation

The four target variables CGI-item 2, SCAG total, BGP subscale 'need for help' and SKT were subject to confirmatory statistical analysis using the one-sided Mann-Whitney U test; whereby a type I error of $\alpha = 5\%$ was specific [17]. Taking into account an α-adjustment according to Holm-Bonferroni, the null hypothesis could be rejected if at least one of the four target variables showed a difference between the treatment groups in favor of vincamine at the 1.25% level of significance.

The comparisons of the score changes for the four target variables at baseline and after 12 weeks of treatment were designated as primary indicators of therapeutic efficacy. The comparisons of the score changes for the variables at baseline and after 6 weeks of treatment as well as the separate analysis of the diagnostic subgroups DAT and MID were performed on a descriptive basis.

In addition, a responder analysis of the three variables SCAG, BGP subscale 'need for help' and SKT with a response criterion set at 15% was performed to illustrate the therapy response after 12 weeks of treatment.

Ethics

Before the trial commenced, the study was examined for its ethical and scientifical justifiability and was approved by an independent ethics committee. An obligatory insurance coverage was acquired for all patients included in the study.

Results

Of 152 hospitalized male and female patients who were initially included in the trial, 75 were allocated to the diagnostic subgroup DAT and 77 to the diagnostic subgroup MID. Since 10 patients did not complete the whole course of the trial, the data of 142 patients were considered valid for efficacy analysis (n = 71 in each treatment group). The patients in the treatment groups were homogeneous with respect to sex, age, weight and severity of dementia.

Target Variables

The confirmatory statistical analysis revealed significant differences in favor of vincamine in comparison to placebo in each of the four target variables ($p < 0.01$). Figure 1 outlines the change of mean values in item 2 of the CGI between onset and termination of the trial. Figures 2–4 illustrate changes of the mean values of the variables SCAG, BGP subscale 'need for help' and SKT between baseline and termination of treatment after 12 weeks.

The mean values (dotted line in the box) at onset or baseline, after 6 weeks and after 12 weeks of treatment show an almost continuous decline in the vincamine treated group, indicating global improvement of the patient's condition on the CGI, improvement of dementia symptomatology on the SCAG, reduction in need for help on the BGP and improvement of cognitive performance on the SKT. The mean score changes in the placebo-treated group are considerably smaller and were observed

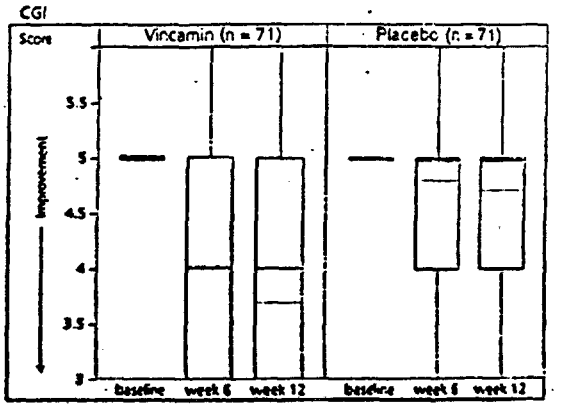

Fig. 1. CGI. Box-whisker plots at baseline and after 6 and 12 weeks of therapy. The dotted line in the box denotes the mean, the solid line, the median. The bounds of the box are the 1st and 3rd quartiles of the distribution. The bars above and below the boxes indicate the range of values within one quartile distance from the 3rd and 1st quartile, respectively.

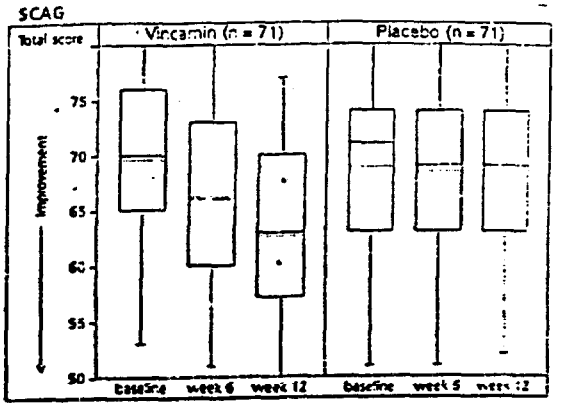

Fig. 2. SCAG – total score. Box-whisker plots at baselines, and after 6 and 12 weeks of therapy See legend of figure 1 for details.

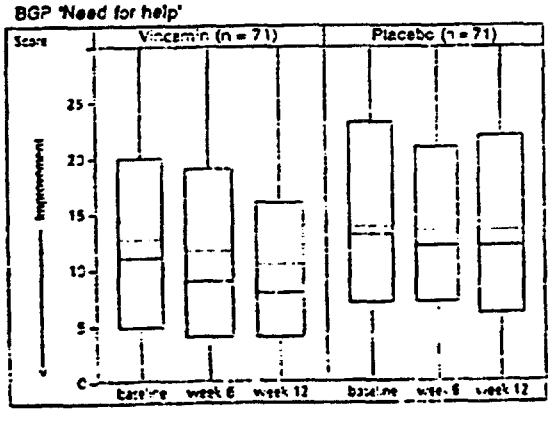

Fig. 3. BGP 'need for help' Box-whisker plots at baseline and after 6 and 12 weeks of therapy See legend of figure 1 for details.

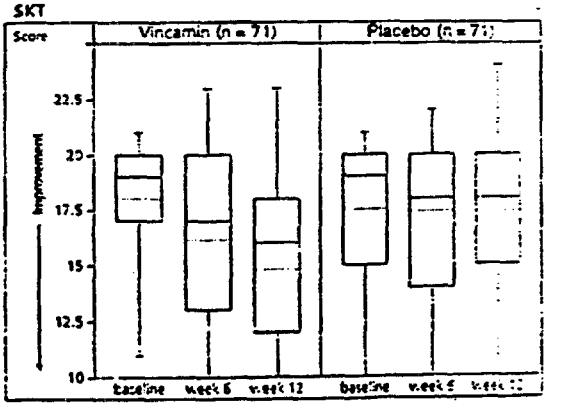

Fig. 4. SKT. Box-whisker plots at baseline and after 6 and 12 weeks of therapy. See legend of figure 1 for details.

only in the first 6 weeks of treatment. Additionally, differences between the vincamine and placebo-treated groups could already be seen after 6 weeks of treatment in CGI, SCAG and SKT score changes ($p < 0.05$).

Table 1 shows the number and the respective percentage of patients who improved or deteriorated after 12 weeks of treatment with vincamine and placebo according to the judgment of the physician. There was a total improvement rate of 72% under vincamine and 25% under placebo. Ten percent of the patients treated with vincamine were rated as 'very much improved', none of the placebo-treated patients fell into this category. Com-

Table 1. CGI: Change of patient's condition after 12 weeks of treatment

Change category	Vincamine		Placebo	
	n	%	n	%
Total improvement	51	72	18	25
Very much improved	7	10	0	0
Much improved	27	38	7	10
Minimally improved	17	24	11	15
No change	18	25	48	68
Worse	2	3	5	7
Total	71	100	69	171

Table 2. Baseline and 12-week treatment scores (mean ± SD) in the diagnostic subgroups DAT and MID

	DAT		MID	
	baseline	week 12	baseline	week 12
CGI				
Vincamine	5.0±0.0	2.8±1.0	5.0±0.2	3.7±1.1
Placebo	5.0±0.3	4.6±0.8	4.9±0.4	4.9±0.7
SCAG total				
Vincamine	68.8±7.2	62.1±8.5	68.3±7.0	63.4±6.7
Placebo	69.0±7.4	67.9±8.0	70.1±6.5	68.1±7.5
BGP ('need for help')				
Vincamine	12.3±8.8	10.4±8.8	12.9±9.1	11.0±8.3
Placebo	15.0±9.1	14.2±9.0	12.5±9.0	12.3±8.7
SKT				
Vincamine	17.8±2.6	14.8±4.4	18.1±2.6	14.8±4.4
Placebo	17.5±3.3	17.5±3.6	17.6±2.8	17.2±3.1

Table 3. Change of at least 15% from baseline score after 12-week therapy

Change category		Data source (measurement level)					
		Psychologist's symptom rating SCAG		Nurse's rating of 'need for help' BGP[1]		Patient's performance SKT	
		n	%	n	%	n	%
Vincamine (n = 71)							
Improved	≥15%	16	23	35	50	38	54
No change	<15%	55	77	33	47	31	44
Worse	≥15%	0	0	2	3	2	3
Placebo (n = 71)							
Improved	≥15%	0	0	12	18	7	10
No change	<15%	69	97	51	75	63	84
Worse	≥15%	2	3	5	7	4	6

[1] The change criterion could not be applied to 1 vincamine-treated and 3 placebo-treated patients, whose baseline scores on the BGP scale 'need for help' were 0. They were excluded from this change classification.

bining the two most favorable change categories ('much' and 'very much' improved), the respective figures are 48% for vincamine and 10% for placebo ($p < 0.01$). The relevance of a global improvement qualified as 'much' or 'very much' improved is obvious because it indicates marked alleviation of symptoms.

The uniform pattern of improvements from baseline to the evaluation after 12 weeks of treatment could also be confirmed when the diagnostic subgroups of DAT and MID patients were analysed separately ($p < 0.05$). Table 2 shows the mean values of the four target variables at baseline and after 12 weeks of treatment for both subgroups. There is a distinct decrease in the scores for both subgroups under vincamine and only a small change or no change under placebo.

Responder Analysis

Table 3 outlines the results of the responder analysis for the target variables SCAG, BGP subscale 'need for help' and SKT. It shows the number and the percentage of

patients who improved or deteriorated with vincamine and placebo after 12 weeks of treatment. With a response criterion set at 15%, 54% of the vincamine-treated patients improved in cognitive performance (SKT), 50% in 'need for help' (BGP) and 23% in clinical symptoms (SCAG). Under placebo there was no patient whose clinical symptoms improved beyond the 15% limit. These results indicate that vincamine is more effective than placebo and can be considered as additional evidence of therapeutic efficacy.

Tolerability

Relevant drug-related changes in blood pressure or in laboratory parameters were not observed during the treatment period, except for triglyceride values, which showed a more marked decline with vincamine than with placebo. This effect of the substance, however, is already known from previous studies [18]. Adverse events were reported for a total of 19 patients, of whom 7 received placebo and 12 active drug. The most-reported adverse effects were diarrhea, vomiting, nausea, hypotension, nervousness, insomnia and vertigo. None of the stated symptoms were rated as very severe or persisted over a longer period of time.

Discussion

In spite of the fact that several recommendations regarding the methodology of clinical trials with nootropics have recently been published, the problems involved in demonstrating clinical relevance of nootropic effects in phase III trials are still subject of continuous critical debates. Although an efficacy proof of nootropic drug therapy can be maintained on the basis of differences in mean values or any other suitable sample statistic between treatment groups, so far there is no generally accepted strategy of how to implement a phase III trial to achieve a clinically relevant outcome. In the present trial, the evidence of clinical relevance of therapeutic effect measured in the study was based on the following conditions:

- previous definition of the methods for confirmatory data analysis;
- convergence of the results detected from different observation levels and derived from different sources of information;
- specification of the extent of improvements considered indicative of a clinically relevant change;
- evaluation of the probable benefit to the patient

The therapeutic efficacy of vincamine after 12 weeks of treatment with 60 mg daily was clearly demonstrated in the confirmatory analysis for each of the four target variables CGI, SCAG, subscale 'need for help' of the BGP and SKT. The drug was statistically significantly superior to placebo in all four target variables. The beneficial effect of vincamine in improving the core symptoms of dementia was also demonstrated separately for the diagnostic subgroups DAT and MID. The clinical relevance of the outcome was further underlined by the results of the descriptive variables, on one side by the evaluation of the extent of improvements and clear convergence of the results assessed by the physician, the psychologist and the nurse at different observation levels and on the other side in particular by the responder analysis.

A common way to evaluate the extent of clinically relevant improvements and to arrive at an appropriate definition of therapy response is to express an individual change in terms of change categories, percent and by setting a cut-off point. The most obvious problem with this approach is the arbitrariness of the cut-off point. Based on the consideration that nearly all experts in the field agree on the fact that a change criterion for nootropic drug therapy should be less stringent than with other ethical drugs, the response criterion in this trial was set at the generally approved limit of 15%, as suggested by Herrmann and Schärer [19].

Admittedly, there is no definite way of answering the question of clinical relevance of a therapeutic outcome achieved by nootropic drug therapy. Valid criteria, however, for the unequivocal proof of efficacy do exist. On the basis of firm evidence concerning the efficacy of a drug, plausible inferences can be made with respect to the clinical relevance of therapeutic effects. As shown with the present trial, differences between treatment groups in several predefined outcome measures were the basis of the attempt to illustrate the meaning of the treatment to the individual patient. The outcome of this trial indicates that about one half of the patients suffering from mild to moderate dementia should benefit from the treatment with vincamine, irrespective of the underlying etiology. According to the selection of the target variables, beneficial effects can be expected in the core symptoms of dementia, in cognitive performance and most important, in need for help with daily routine activities.

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99-10-35

MULTI-CENTER CLINICAL STUDY OF THE EFFECTS OF A VASOREGULATORY-EUMETABOLIC DRUG (VINCAMINE HYDROCHLORIDE) ON THE PSYCHOLOGICAL SYMPTOMS OF CHRONIC CEREBROVASCULAR INSUFFICIENCY

By

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The efficacy of any kind of therapeutic measure in the complex and multiform symptomatology of the elderly in conditions of chronic cerebrovascular insufficiency is rather controversial. In such situations, so-called "vasoregulatory-eumetabolic vasoregulatory" drugs, including vincamine, are being used extensively at this time. The alkaloid agent with indole structure extracted from Vinca minor exerts a double effect at the level of the brain: a metabolic effect,

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The names of the physicians who participated in the trial and the detailed tables are reported in the reprints.

increasing the consumption and utilization of O2 and glucose [ref. 1, 8, 26, 29], and a hemodynamic effect, and a hemodynamic effect, with increase in blood flow by reducing the cerebral vascular resistance [ref. 2, 4, 7, 12, 13, 14,

15, 17, 18, 20, 21, 28, 30, 31, 33); on the contrary, there are few reports [ref. 10, 11, 18, 19, 23, 31] regarding its efficacy on the psychic symptomatology of these patients. In most cases, however, the trials were conducted in hospitalized patients, to the effect that the length of the studies was limited to relatively short therapeutic periods.

The main objective of the present trial was to document the activity of a vincamine preparation on the psychic symptomatology of a large population of patients affected by chronic cerebrovascular insufficiency, who were treated with the said preparation for a long period of time. On this basis, the study population evidently consisted of outpatients, which also allowed the adequate monitoring of the side effects induced by the drug in ordinary use conditions. The patients were selected by a large number of general practitioners who offered their active participation.

The test drug was vincamine hydrochloride (Anasclerol), whose vasoactive effect was determined in the past by means of

both laboratory [ref.2, 25] and therapeutic [ref. 22] tests and which, when administered orally, as compared to vincamine base, presents the advantage of an increased bioavailability [ref. 32]. Finally, the optimal cardiovascular tolerance of the drug [ref. 16] provides a wide safety margin for a long-term outpatient treatment.

MATERIALS AND METHODS

The trial was performed with the participation of 205 physicians distributed throughout the entire country, who consented to participate in the study on the basis of a single protocol which essentially consisted of the following points:

1) identification of patients with generic chronic general insufficiency;

2) treatment of the said patients with the drug studied in a fixed daily dose of 3 capsules/day (60 mg/day) for a period of 6 months;

3) control of a series of 10 psychic symptoms (sleep/wakefulness rhythm, concentration, recent memory, remote memory, ideational deficiency - delirium, fixed ideas, sociability, anxiety, excitation, depression, agitation, confusion, immobility) before and after 1, 3, and 6 months of treatment;

4) at each control, classification of the severity of the said symptoms according to an arbitrary scoring scale (0 = no symptom; 1 = mild; 2 = average severity; severe; very severe);

5) discontinuation of any other treatment with vasoactive drugs or drugs which could interfere with the action of the agent tested for the entire duration of the trial;

6) reporting any eventual side effect attributed to treatment with vincamine hydrochloride, specifying the type, manner and period of appearance and disappearance, and degree of severity.

All the participating physicians were supplied with suitable forms for the recording of the data obtained from the single patients, in which they also entered the single anagraphic data, in addition to the other observations mentioned above.

A total of 2440 patients were entered in trial, 559 of whom were subsequently excluded from final evaluation because of various deviations from the protocol (failure to show up to one or more controls, the patients dropped out from the study or died, absence of anagraphic data, symptomatologic evaluation using criteria other than those required by the protocol). In addition, 27 patients discontinued the treatment, after various periods of time, because of a variety

TABLE 1. - Patients Treated with Vincamine Hydrochloride for 6 Months

	No. of cases	Age		
		Minimum	Maximum	Av. (s.d.)
Total	1854	51	96	71.8 (0.19)
Men	791	51	93	71.7 (0.29)
Women	1063	51	96	72.1 (0.26

of side effects. Accordingly, only the records obtained from a total of 1854 patients, 791 males and 1063 females) were taken into account for the final evaluation (Table 1).

The trial was performed over a period of about 1 year (May 1978 - June 1979).

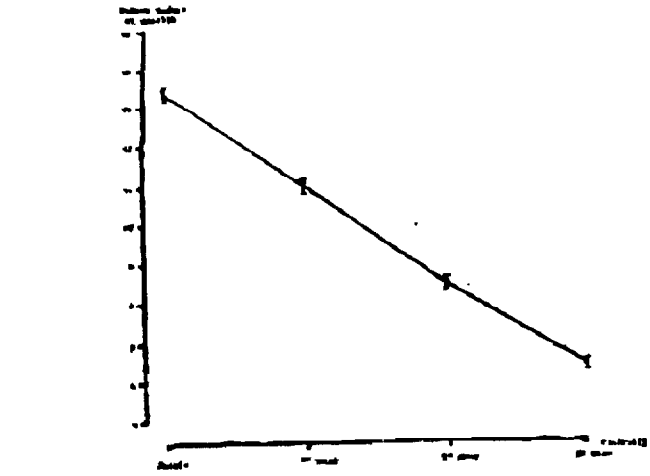
RESULTS

The scores obtained for each patient, at every checkup time, were first of all used to calculate an "index of severity". The said index expresses the sum of the scored recorded for the various symptoms observed in the single patient.

According to figure 1, which shows the course of the average values of this index at the various observation times for the entire study group, there is no question that the severity of symptomatology, taken as a whole, presented a constant and gradual reduction during the 6 months of treatment with vincamine hydrochloride.

Table 2 confirm the positive course of the said index by demonstrating the relationship that exists between the various values of the index and the number of time at the v various checkup times: actually, the number of patients with low severity index values increased gradually during the course of the trial to the point that at the last control, for example, 162 patients had an index of severity = 0. All comparisons, based on the use of chi-square, revealed that the corresponding differences were highly significant (see table 2) not only between the basal values and those recorded later on, but also between 1 and3 months, 1 and 6 months and 3 and 6 months. The results of the detailed analysis of the development demonstrated by the single symptoms are reported in tables 3-7, which show the correlation between the scores assigned and the number of patients at various observation times, the changes in the scores (average and S. D.) and the outcome of the various comparisons based on the use of

Index of severity



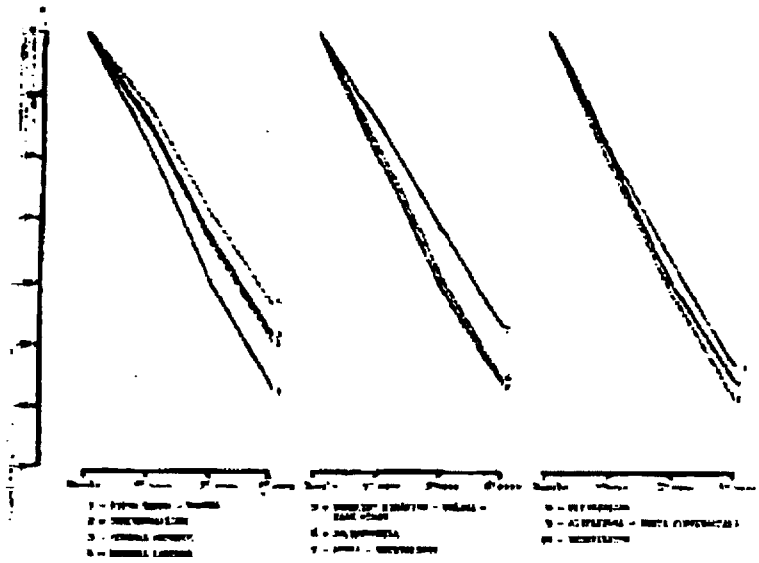
Basal 1 mo 3 mo 6 mo

Fig. 1 - Course of the index of severity (av. and S. D.) for the entire study group (1854 patients) at various checkup times during treatment with vincamine hydrochloride.

chi-square. According to the data reported, rapid and progressive increase in the number of patients with low scores (1.0) took place during the 6 months of treatment with vincamine, for all symptoms, a phenomenon which also applied to the global symptomatology (index of severity), the expression of the improvement induced by treatment in the

great majority of the study population. Statistical analysis confirmed the course of the constant favorable improvement of the various symptoms, as demonstrated by the highly significant differences recorded between the basal data and the data obtained at 1-3, 1-6 and 3-6 months, for each symptom. The development of the various average scores recorded for each symptom during the various controls, which is shown in Fig. 2, in the form of percent changes of the said values, reveals that at the end of the trial (6 months) all the symptoms studied demonstrated appreciable reductions with respect to the basal values, ranging from 43.5 to 58.8 %, depending on the symptom.

To determine the symptoms showing the greatest improvement following the administration of vincamine hydrochloride, for every single symptom tables 8 (1 month), 9, (3 months) and 10 (6 months) shows the number of improved and unchanged/worsened patients with respect to the basal data, according to the corresponding scores, as well as the results of the comparison (chi-squares) "between symptoms" based on the frequency of improved and unchanged/worsened patients. Table 11 reports the same data for the for the assembly of the the three controls performed. Overall, these results demonstrate that agitation, confusion, depression, anxiety and



Illegible.. Illegible.. Illegible..

Fig. 2 – Course of the index of severity (av. and S. D.) for the entire study group (1854 patients) at various checkup times during treatment with vincamine hydrochloride.

excitation presented a particularly favorable and constant improvement during the course of the trial.

The tolerance of the drug used in the present trial was generally excellent. Mild side effects, which did not prevent the continuation of the treatment, were observed in 135 of the 1854 patients included in the trial, a rather low frequency of

only 7.3%. These side effects, which were reported casually by the patients themselves, in most cases appearing as the treatment progressed, to the effect that the existence of a definite cause/effect relationship with the administration of the drug is doubtful, are recorded in table 12. Regarding the 27 patients who were not included in the final evaluation because they failed to complete the entire study period (see materials and methods), it must be noted that the side effects reported by these patients also were mild, most of them affecting the gastrointestinal tract, and appeared some time during the course of the treatment (even after a few months); accordingly, it would be reasonable to attribute them to coexisting diseases, rather than the administration of the drug tested. In any event, considering all the patients treated with vincamine hydrochloride for whom individual records were available (2440 subjects), the treatment was discontinued because of side effects which were generally attributed by the patients, but not the physicians, to the administration of the drug, in only 1.1% of the cases (the 27 patients mentioned above), which confirm the excellent clinical tolerance of the preparation used in the present trial.

significantly significant differentials were also recorded at 1-3, 1-6 and 3-6 months.

These results emphasize the therapeutic value of the long-term treatment with vincamine hydrochloride, considering that further symptomatologic improvement was observed even after several months of treatment, which should be attributed to gradual regulatory action exerted by the drug at the level of the cerebral dysmetabolism (ref. 1, 8, 26, 29). The course of the single psychic symptoms investigated [fig. 2], follows the pattern demonstrated by the global symptomatology: based on the scores assigned to each symptom during the 6 months of treatment, there was a gradual and constant average improvement with respect to the basal controls and between a given control and the next one, which is confirmed by the statistical workup. Particularly interesting is the effect of the drug on agitation, confusion, depression, anxiety and excitation, in confirmation of earlier reports [ref. 10, 11] which indicated that the administration of vincamine hydrochloride in patients with mental deterioration due to insufficient cerebral circulation produces greater improvement in confusion, anxiety, agitation and apathy. Treatment has a lesser effect on remote memory: actually, 60.5% of the patients showed improvement in this symptom at the end of the treatment. (table 11).

As mentioned earlier, the nature of the study population (outpatients), the large number of cases controlled and the long therapeutic period also accounted for an adequate monitoring of the possible side effects induced by the drug in ordinary conditions of clinical use. Of the 2440 subjects who filled the form, only 27 (1.1%) discontinued the treatment because of side effects, which were mild in all instances, affecting primarily the gastrointestinal tract in most cases, at some point after the start of the treatment, while of the 1884 patients who were included in the final analysis, 135 (7.3%) reported transient mild side effects which did not require the discontinuation of the treatment. Accordingly, the tolerance of vincamine hydrochloride was excellent even when given for long periods of time.

In conclusion, the present study, whose main objective was to assess the effects of long-treatment with vincamine hydrochloride on the psychic symptomatology of a large group of outpatients affected generically by chronic cerebrovascular insufficiency, demonstrated clearly that the drug has a positive effect on the said symptomatology, particularly on agitation, confusion, anxiety and depressive manifestations; the favorable effect of the drug, which was manifested rapidly and progressively throughout the treatment, is due to the

regulatory action exerted by the preparation at the level of the cerebral metabolism. Accordingly, the long-term treatment with vincamine hydrochloride reported herein yielded reliable results, with optimal tolerance.

SUMMARY

To test the effect of vincamine hydrochloride on the psychic symptoms of patients with cerebrovascular insufficiency, a 6-months trial was carried out by 201 physicians in 2440 outpatients, 1884 of whom were included in the final evaluation.

A set of individual symptoms was assessed according to a scoring scale applied in basal conditions and after 1, 3 and 6 months of treatment.

Based on the clinical condition of the patients and the statistical analysis of the results obtained, the test drug induced rapid and progressive improvement of both the global psychic condition of the patients and the individual symptoms, a particularly favorable effect being recorded against agitation, anxiety and depression. The drug was well tolerated, as demonstrated by the fact that only 135 cases (7.1%) of slight and transient side effects were reported by the patients themselves or by the physicians, involving primarily the gastrointestinal tract. None of the said side effects required the discontinuation of the treatment.

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STUDIO CLINICO MULTIAMBULATORIALE DEGLI EFFETTI DI UN FARMACO VASOREGOLATORE-EUMETABOLICO (VINCAMINA CLORIDRATO) SULLA SINTOMATOLOGIA PSICHICA DELL'INSUFFICIENZA CEREBRO-VASCOLARE CRONICA

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L'efficacia di ogni tipo di intervento terapeutico sulla complessa e multiforme sintomatologia presente nell'anziano e nel vecchio in condizioni di insufficienza cerebro-vascolare cronica risulta a tutt'oggi assai controversa. Grande impiego trovano nella comune pratica in tale situazione patologica i farmaci « vasoregolatori-eumetabolici », tra i quali la vincamina occupa un posto di rilievo. La sostanza, alcaloide a struttura indolica ottenuta dalla Vinca minor, esplica a livello cerebrale un duplice effetto: metabolico, con aumento del consumo e dell'utilizzazione di O_2 e glucosio (1, 8, 26, 29) ed emodinamico, con incremento di flusso per riduzione delle resistenze vascolari cerebrali (3, 7, 8, 9, 13, 14, 27). Di tale principio attivo risultano ampiamente documentati gli effetti positivi sulla sintomatologia clinico-somatica di pazienti affetti da insufficienza cerebro-vascolare cronica (2, 4, 7, 12, 13, 14, 15, 17, 18, 20, 21, 28, 30, 31, 33), mentre assai scarsi sono i contributi (5, 6, 10 11, 18, 19, 23, 31) nei riguardi della sua efficacia sulla sintomatologia psichica presente in detti pazienti. In ogni caso il più delle volte i « trials »

Lavoro ricevuto il 6 maggio 1980.

Negli estratti sono riportati i nomi dei medici che hanno collaborato allo studio e le Tabelle per esteso.

sono stati condotti in soggetti ospedalizzati, con gli inconvenienti di casistiche alquanto ristrette e di periodi di trattamento assai brevi.

Scopo principale del presente studio è stato pertanto quello di documentare l'attività di un preparato vincaminico sulla sintomatologia psichica di una vasta casistica di soggetti affetti genericamente da insufficienza cerebro-vascolare cronica e sottoposti a trattamento con detto preparato per un lungo periodo di tempo. La casistica prescelta, stante tali presupposti, è stata ovviamente di tipo ambulatoriale, il che ha anche consentito un adeguato monitoraggio degli eventuali effetti collaterali del farmaco nelle comuni condizioni di impiego. La casistica stessa è stata reperita presso un numeroso gruppo di medici generici, che hanno offerto la loro attiva collaborazione.

Il farmaco utilizzato è stato la vincamina cloridrato (Anasclerol), il cui effetto vasoattivo è stato documentato sia dal punto di vista strumentale (2, 25) che terapeutico (22) e che, assunto per via orale, presenta il vantaggio, rispetto alla vincamina base, di una maggiore biodisponibilità (32). L'ottima tollerabilità cardiovascolare di tale preparato (16) offriva inoltre un ampio margine di sicurezza per il protratto trattamento ambulatoriale previsto.

MATERIALE E METODI

Allo studio hanno collaborato 205 medici, dislocati in tutto il territorio nazionale, che hanno aderito a partecipare alla ricerca in base ad un protocollo unico che prevedeva sostanzialmente i seguenti punti:

1) reperimento di soggetti con diagnosi generica di insufficienza cerebro-vascolare cronica;

2) trattamento di tali soggetti con il farmaco in studio alla dose fissa di 3 capsule/die (60 mg/die) per un periodo di 6 mesi;

3) controllo di una serie di 10 sintomi psichici (ritmo sonno/veglia, concentrazione, memoria recente, memoria lontana, povertà ideativa — deliri — idee fisse, socievolezza, ansia-eccitazione, depressione, agitazione-stati confusionali, immobilismo) prima dell'inizio del trattamento e dopo 1-3-6 mesi di trattamento;

4) ad ogni controllo classificazione della gravità di tali sintomi in base ad una scala arbitraria di punteggi (0 = assenza sintomo; 1 = lieve; 2 = media gravità; 3 = grave; 4 = molto grave);

5) sospensione per tutto il periodo dello studio di ogni altro trattamento con farmaci vasoattivi o comunque con farmaci che potevano interferire con gli effetti del preparato in studio;

6) segnalazione di ogni eventuale effetto collaterale attribuibile al trattamento con vincamina cloridrato, specificandone il tipo, le modalità e periodo di comparsa e scomparsa, la gravità.

Tutti i medici partecipanti alla ricerca sono stati dotati di apposite schede, per la raccolta dei dati relativi ad ogni singolo paziente, nelle quali dovevano essere riportati, oltre alle rilevazioni succitate, i singoli dati anagrafici.

Sono stati complessivamente ammessi alla ricerca N. 2440 soggetti, 559 dei quali sono stati

esclusi nelle valutazioni finali a causa di inaderenze di vario tipo rispetto al protocollo stabilito (assenza di 1 o più controlli, trattamento interrotto per abbandono da parte del paziente o per decesso, assenza di dati anagrafici, valutazione della sintomatologia mediante criteri differenti rispetto a quelli stabiliti). Inoltre, altri 27 soggetti hanno sospeso il trattamento, dopo periodi variabili, per effetti collaterali di diverso tipo. Pertanto sono state considerate valide, agli effetti dei risultati, le schede relative a N. 1854 soggetti, 791 di sesso maschile e 1063 di sesso femminile (Tabella 1).

TABELLA 1. — *Casistica sottoposta a trattamento con vincamina cloridrato per 6 mesi.*

	N. casi	Età		
		minima	massima	media (e.s.)
Totale	1854	51	96	71,9 (0,19)
Maschi	791	51	93	71,7 (0,29)
Femmine	1063	51	96	72,1 (0,26)

Lo studio è stato condotto in un periodo di tempo di circa 1 anno (maggio 1978 - giugno 1979).

RISULTATI

In base ai punteggi assegnati è stato anzitutto calcolato per ogni soggetto e ad ogni tempo di rilevazione un « indice di gravità ». Tale indice rappresenta la somma dei punteggi dei diversi sintomi presenti nel singolo paziente.

La Fig. 1 mostra l'andamento dei valori medi di detto indice ai diversi tempi di osservazione per la totalità della casistica: è possibile constatare chiaramente come la gravità della sintomatologia, considerata nel suo insieme, abbia in media subito, nel corso dei 6 mesi di trattamento con vincamina cloridrato, una costante e progressiva riduzione.

La tabella 2 conferma la positiva evoluzione dell'indice di gravità mettendo in evidenza il rapporto tra i diversi valori di tale indice ed il numero di pazienti ai vari tempi di osservazione: col procedere dello studio è divenuto sempre più elevato il numero di soggetti con valori bassi di indice di gravità tanto che, ad esempio, all'ultimo controllo ben 162 pazienti hanno presentato indice di gravità = 0. Tutti i confronti, effettuati tramite χ^2, hanno d'altronde messo in mostra per tali dati differenze altamente significative (V. tabella 2) non solo tra basale e tempi successivi, ma anche tra 1°-3°, 1°-6° e 3°-6° mese. L'analisi dettagliata dell'andamento dei singoli sintomi viene presentata nelle tabelle 3-7, nelle quali figurano il rapporto

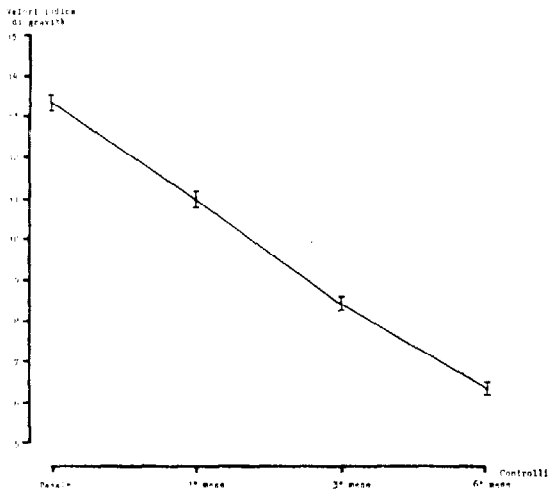

Fig. 1. — Andamento dell'indice di gravità (valori medi ed e.s.) della casistica complessiva (N. 1854 soggetti) ai diversi tempi di osservazione durante trattamento con vincamina cloridrato.

tra punteggio assegnato e numero di pazienti ai diversi tempi di osservazione, le modificazioni dei punteggi (media ad e.s.) e l'esito dei vari confronti praticati con il χ^2. In base ai dati riportati è possibile osservare come per tutti i sintomi si sia constatato, durante i 6 mesi di trattamento con vincamina cloridrato, un rapido e progressivo aumento del numero di pazienti con punteggi bassi (1-0), fenomeno del resto già rilevato per la sintomatologia globale (indice di gravità), ad espressione del miglioramento indotto dal trattamento in tali sintomi nella stragrande maggioranza della casistica. L'analisi statistica ha confermato l'evoluzione costantemente favorevole dei diversi sintomi evidenziando per ciascuno di essi differenze altamente significative tra i dati basali e quelli dei tempi successivi nonché tra i dati del 1°-3°, 1°-6° e 3°-6° mese. L'andamento dei valori medi dei punteggi di ogni sintomo ai diversi controlli viene mostrato, sotto forma di modificazioni percentuali di detti valori, nella Fig. 2, in base alla quale è in particolare constatabile come al termine dello studio (6° mese) tutti i sintomi presi in considerazione abbiano mostrato un notevole decremento rispetto ai valori di base, tra il 43,5 ed il 58,8% a seconda del sintomo.

Allo scopo di indagare quali tra i diversi sintomi il trattamento con vincamina cloridrato abbia maggiormente influenzato vengono riportati per ogni singolo sintomo nelle tabelle 8 (1° mese), 9 (3° mese) e 10 (6° mese) il numero di pazienti migliorati e invariati/peggiorati rispetto al basale come da punteggi assegnati, un riordinamento dei 10 sintomi studiati secondo la percentuale di pazienti migliorati, nonché i risultati dei confronti (χ^2) « tra sintomi » in base alla frequenza di soggetti

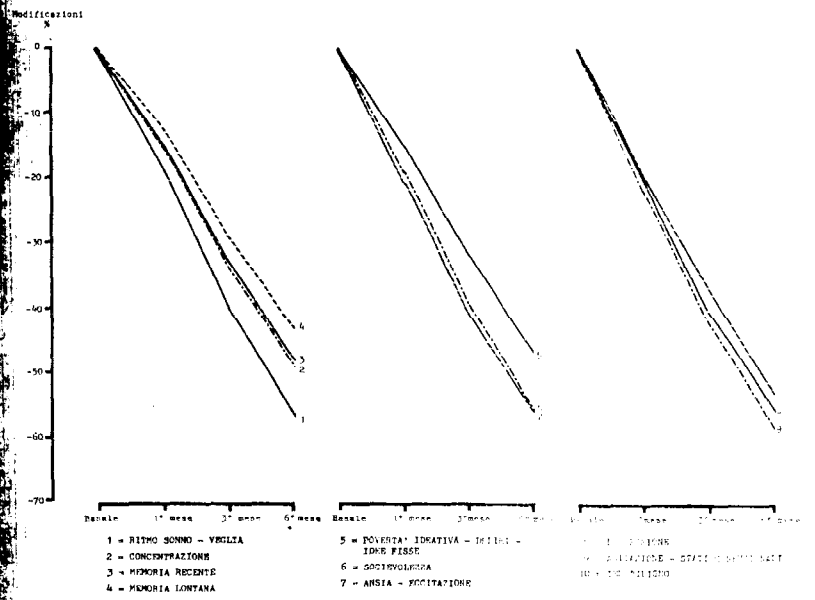

Fig. 2. — Andamento dei singoli sintomi nell'intera casistica (N. 1854 soggetti) ai diversi tempi di osservazione durante trattamento con vincamina cloridrato (modificazioni percentuali delle medie dei punteggi).

migliorati e invariati/peggiorati. Nella tabella 11 figurano i medesimi dati per l'insieme dei 3 controlli effettuati. Da tali dati si evidenzia in sintesi che andamento particolarmente favorevole hanno presentato costantemente nel corso dello studio nell'ordine i sintomi « agitazione - stati confusionali », « depressione », « ansia - eccitazione ».

La tollerabilità del farmaco utilizzato nel corso dello studio è apparsa in genere eccellente. Effetti collaterali lievi, che non hanno impedito la prosecuzione del trattamento, sono stati segnalati in 135 dei 1854 soggetti facenti parte della casistica analizzata, con una frequenza quindi assai bassa, solo del 7,3%. Tali effetti collaterali, riportati saltuariamente dai pazienti stessi e nella grande maggioranza dei casi scomparsi pur con la prosecuzione del trattamento, tanto da far dubitare di un sicuro rapporto causa/effetto con la somministrazione del farmaco vengono comunque elencati nella tabella 12. Per quanto concerne i 27 soggetti già citati (v. materiale e metodi), non compresi nella casistica studiata per non aver portato a termine l'intero periodo dello studio, è da sottolineare che gli effetti collaterali segnalati sono sempre apparsi anche in tali casi di lieve entità, per lo più interessanti l'apparato gastro-intestinale, e con comparsa frequente dopo un certo periodo di trattamento (a volte mesi), sì da poter più ra-

gionevolmente essere posti in relazione con affezioni intercorrenti piuttosto che con l'assunzione del farmaco in studio. In ogni caso, prendendo in considerazione l'intera casistica trattata con vincamina cloridrato e di cui sono pervenute le regolari schede individuali (N. 2440 soggetti), la sospensione del trattamento per segnalati effetti collaterali, in genere attribuiti dai pazienti e non dai medici alla somministrazione del farmaco, è avvenuta quindi solamente nell'1,1% dei casi (i 27 soggetti citati), a conferma della eccellente tollerabilità clinica del preparato utilizzato nel corso del presente studio.

DISCUSSIONE E CONCLUSIONI

Le vaste dimensioni del campione analizzato nel corso del presente studio (N. 1854 soggetti), nonché la notevole durata del trattamento con vincamina cloridrato (6 mesi), praticato nelle reali e più comuni condizioni di impiego della pratica clinica, cioè in soggetti ambulatoriali, ci sembra consentano anzitutto di trarre interessanti e convincenti conferme in riguardo all'attività che detto farmaco è in grado di esplicare nei confronti della sintomatologia psichica del paziente anziano, affetto da insufficienza cerebro-vascolare cronica. Detta sintomatologia, controllata a vari tempi mediante assegnazione di punteggi, considerata nel suo globale (indice di gravità) ha subito infatti un notevole miglioramento durante i 6 mesi di trattamento, miglioramento espresso chiaramente dal decremento dell'indice di gravità (Fig. 1), passato da un valore medio basale di 13,3 ad uno medio finale di 6,4, con una riduzione quindi del 48,1%. Da sottolineare inoltre che gli effetti favorevoli del trattamento sulla sintomatologia psichica globale sono apparsi rapidi e progressivi, come può essere constatato dallo studio delle frequenze di pazienti migliorati ai vari controlli in base all'indice di gravità (tabella 2), dal quale sono emerse tra tali frequenze differenze altamente significative (χ^2) nei confronti del basale già al 1° controllo, dopo 1 mese di terapia con vincamina cloridrato, e differenze altamente significative anche nei confronti 1°-3°, 1°-6° e 3°-6° mese.

Tali risultati mettono in luce l'interesse terapeutico di un trattamento con vincamina cloridrato di lunga durata, datosi che è possibile osservare in molti casi un ulteriore miglioramento della sintomatologia presente anche dopo mesi di terapia, da attribuirsi ragionevolmente all'azione di regolazione del dismetabolismo cerebrale (1, 8, 26, 29) che gradatamente il farmaco è in grado di svolgere. L'andamento dei singoli sintomi psichici presi in considerazione (Fig 2) ha riflesso quello della sintomatologia globale: in base ai punteggi assegnati ciascuno di tali sintomi, nel corso dei 6 mesi di trattamento, ha mostrato in media una evoluzione costantemente favorevole, confermata dai confronti statistici praticati tra basale e controlli e tra controlli stessi. Di particolare interesse appare comunque la rilevazione del maggiore effetto svolto dal farmaco utilizzato nello studio sui sintomi « agitazione - stati confusionali », « depressione », « ansia - eccitazione », rilevazione del resto già riportata da altri (10, 11) che, dopo trattamento con vincamina di soggetti con deterioramento mentale da insufficienza di circolo cerebrale, hanno potuto osservare un maggior effetto del farmaco sui sintomi confusione, ansia, agitazione, apatia. Nella casistica qui selezionata il sintomo che meno è apparso rispondere al trattamento è risultato la « memoria lontana », pur rilevandosi al termine dello studio per detto sintomo un miglioramento nel 60,5% dei pazienti (tabella 11).

Come già accennato, il tipo di casistica prescelta (ambulatoriale), il grande numero di casi controllati ed il lungo periodo di trattamento hanno anche consentito un valido ed adeguato monitoraggio degli effetti collaterali che il farmaco utilizzato può eventualmente provocare nelle comuni condizioni di impiego clinico. Dei 2440 soggetti di cui sono pervenute le schede, solo in 27 (1,1%) si è registrata la sospensione del trattamento per effetti collaterali sempre di lieve entità, interessanti per lo più l'apparato gastro-enterico, insorgenti nella maggior parte dei casi dopo un certo periodo dall'inizio della somministrazione del farmaco, mentre, dei 1854 soggetti facenti parte della casistica analizzata, in 135 casi (7,3%) sono stati riportati effetti collaterali lievi e saltuari, che non hanno richiesto la sospensione del trattamento. La tollerabilità clinica della vincamina cloridrato è apparsa pertanto, sulla base dei dati suesposti, risultare eccellente anche in seguito a impiego del farmaco per lunghi periodi.

Il presente studio in conclusione, condotto allo scopo principale di valutare gli effetti di un trattamento protratto con vincamina cloridrato sulla sintomatologia psichica di una vasta casistica di soggetti ambulatoriali affetti genericamente da insufficienza cerebro-vascolare cronica, ha permesso di evidenziare chiaramente come il farmaco sia in grado di agire positivamente sulla sintomatologia suddetta, migliorando in modo particolare l'agitazione, gli stati confusionali ed ansiosi, i sintomi depressivi. I miglioramenti appaiono in ogni caso rapidi ed anche progressivi nel tempo, verosimilmente a causa dell'azione di regolazione a livello del metabolismo cerebrale svolta dal preparato. Da ciò l'esigenza di una lunga durata del trattamento che risulta in questo caso di piena affidabilità, stante l'ottima tollerabilità della vincamina cloridrato pure evidenziatasi nel corso dello studio.

RIASSUNTO

Allo scopo di verificare gli effetti della vincamina cloridrato sulla sintomatologia psichica di pazienti affetti da insufficienza cerebro-vascolare cronica, è stato condotto uno studio basato sulla somministrazione di detto preparato alla dose di 3 capsule/die (60 mg/die) per un periodo di 6 mesi in una vasta casistica di soggetti ambulatoriali selezionati da 205 medici, che hanno aderito a partecipare alla ricerca secondo un protocollo unico. Sono stati ammessi allo studio in totale 2440 soggetti e successivamente, agli effetti delle valutazioni finali, sono stati considerati validi i risultati relativi a 1854 soggetti. L'andamento dei singoli sintomi presi in considerazione è stato valutato mediante punteggi assegnati in condizioni di base e dopo 1 mese, 3 mesi e 6 mesi di trattamento con vincamina cloridrato.

Il preparato in oggetto, sulla base e delle condizioni cliniche dei pazienti controllate nel corso dello studio e delle valutazioni statistiche praticate, si è dimostrato in grado di indurre un miglioramento rapido e progressivo sia della sintomatologia psichicha globale che dei singoli sintomi, influenzando in modo particolarmente favorevole gli stati di agitazione, ansia, depressione. Ottima la tollerabilità clinica del farmaco agli effetti del quale, durante tutto il periodo dello studio, è stata attribuita dal paziente e/o dal medico solamente in 135 casi (7,3%) l'insorgenza saltuaria di effetti collaterali di lieve entità, tale da non portare mai alla sospensione del trattamento, interessanti per lo più l'apparato gastro-intestinale.

SUMMARY

In order to check the effects of vincamine hydrochloride on the psychic symptoms of patients suffering from cerebrovascular insufficiency, a 6-months study has been carried out by 205 physicians in 2,440 outpatients, of whom 1,854 were considered suitable for evaluation.

The pattern of individual symptoms was evaluated according to a score system with points allotted in basal conditions, after 1, 3 and 6 months.

On the basis both of the patients' clinical conditions and the statistical evaluation of the results obtained, the drug proved apt to induce rapid progressive improvement of the overall psychic condition as well as of individual symptoms, its action being particularly favorable as far as conditions of agitation, anxiety and depression are concerned. The drug was well tolerated as is shown by the fact that only in 135 cases (7.3%) slight and transient side effects were attributed to its action either by the patient or by the physician; none of these side effects, usually concerned with the gastro-intestinal tract, made drug withdrawal necessary.

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TREATMENT OF INITIAL CEREBRAL VASCULAR INSUFFICIENCY WITH VINCAMINE. POLY-CENTRIC RESEARCH ON 828 CASES.

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SUMMARY. - A multi-center study was performed to determine the effect of vincamine in a large population of patients with initial cerebrovascular insufficiency.

A total of 824 patients were treated at 11 centers, most of whom received the drug for 30 days at the rate of 6 tablets/day. The methodology used in the collection and the processing of the data is described.

The classical single symptoms encountered in initial cerebrovascular insufficiency were observed and evaluated after 7, 14, 21 and 30 days of treatment.

An index of "severity" pertaining to the symptomatology as a whole also was established and assessed.

The results obtained demonstrated that treatment resulted in both global and particular improvement of the single symptoms starting in the early days of the treatment, followed by gradual increase as a function of time and a high rate of remission. Moreover, overall tolerance was good, with a very low frequency of side effects.

KEYWORDS. - Cerebrovascular insufficiency.
Cerebrovascular disease. Vinca mina.

INTRODUCTION

Arteriosclerotic changes, the most important characteristics of aging, as a result of the fact that they can affect all the vessels, can result in a series of consequences of both functional and anatomic nature directly at the level of the vessels affected, as well as the organs irrigated by them.

As a result of their long- and short-term consequences, the arteriosclerotic processes that affect the cerebral vessels are particularly important. The most immediate consequence of these phenomena is the gradual reduction of the cerebral blood flow: in effect, its average normal value, which in resting adults of up to 50 years of age is equal to 55 ml/minute for every 100 g of brain weight, declines to 42 ml/minute at about the age of 60 years and reaches the level of 35 ml/minute after the age of 70 years [ref., 1a

This means the the reduction of blood flow due to structural changes induced by arteriosclerosis in the cerebral vessels are responsible the reduction of the supply of blood and, therefore, oxygen reaching the sensitive structures of the encephalon.

Sooner or latter, the slow progression of the cerebral hemodynamic and metabolic changes result in weight loss of the

entire encephalon, atrophy of the ganglionic cells and reduction in the activity of the enzymatic systems, with subsequent decrease in the complex activities of the brain.

All this accounts for the creation of the anatomico-functional prerequisites for the appearance of cerebrovascular insufficiency syndromes, which represent the initial manifestation of cerebral parenchymal disorders.

Although the appearance of these manifestation before the age of 45 years is rare, they are not encountered only in old age, as demonstrated by their occasional occurrence in children.

The corresponding functional disorders are accompanied by coexisting premonitory signs of varied frequency and severity, which are well known by the practicing physicians who encounter them quite frequently in their outpatients.

The most frequently encountered manifestations are oppressive sub-continuous headaches, auricular buzzing, tinnitus accompanied by eventual hearing loss, visual disorders consisting primarily of phosphene, and attacks of vertigo.

The patients can also present fast mental fatigue and sleep disorders, especially in the form of nocturnal insomnia, and memory loss; in the latter case, which accounts for a

decrease in learning ability, the patients can present both depressive and euphoric mood disorders.

As a general rule, the development of these manifestations is very slow and gradual, although occasional unexpected or outright true and proper episodes of stroke can take place.

The final stages can take the form of a massive softening of the brain, with hemorrhages, due to the breakdown of the vascular walls, which can be life threatening.

Briefly, these are the reasons indicating that early measures are required for the treatment of the symptomatologic picture described above, representing the clinical expression of initial manifestations of cerebrovascular insufficiency, which are frequently reversible.

There is no question that the corresponding therapeutic problem is quite complex, considering the variety of approaches available to the physician at this time in terms of both the treatment and, especially, the prevention of these pathological forms.

During the past few years, vincamine, a relatively recently discovered Vinca minor alkaloid derivative, has acquired a particularly significant position in this respect; in effect, the drug has a good therapeutic activity, as

demonstrated by the results recorded in the current medical practice, which were confirmed by a great number of literature reports which confirm the clinical benefits of the product in the treatment of cerebrovascular syndromes [ref. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39, 40].

OBJECTIVE OF THE RESEARCH

According to recent postulates, the mechanism of drugs used in the treatment of cerebrovascular insufficiency is different from the one that prevailed until not long ago, that is, it no longer involves a strong general vasodilation at the level of the cerebrovascular circulation, but rather a regional vaso-regulation limited to the zones affected by cerebrovascular deficiency (without affecting the healthy zones, in order to avoid the so-called "intra-cerebral steal"), in combination with a coexisting good metabolic action.

These actions are very slight and, therefore, difficult to prove, especially in clinical practice, although methods for the measurement of the regional blood flow, arterio-venous oxygen difference, and the determination of labelled glucose consumption and of various metabolites, are available.

The serial application of such techniques to the same patient over a period of time is difficult and it involves shortcomings and hazards, carotid artery cannulation, for instance, which cannot be overcome; moreover, the results are affected frequently by changes in blood gases, which affect the data obtained.

Accordingly, as of now, for the study of cerebrovascular insufficiency, especially in the initial stage, in order to prevent its future development, the best technique is still the clinical method for the evaluation of the symptomatologic manifestations which, in the last analysis, are the expression of both the vascular situation and the metabolic conditions prevailing at the level of the brain.

On this basis, the present study represents a contribution to the evaluation of the clinical picture, which is more objective than that reported in a series of studies used to draw statistical conclusions directly proportional to the size of the sample.

Another useful feature is that the present study provides information based on observations made over a long period of time, as a result of the multi-form aspects of the initial cerebrovascular insufficiency. As a matter of fact, the said symptoms present a bizarre and, at time, contradictory course:

thus, frequently they are transient with spontaneous remission and temporary recovery of the abnormal function, occasionally recurring and, more often, with slow and gradual deterioration.

Their appearance and course, other than being affected by imponderable factors, can involve other coexisting pathological reasons, that is, dysmetabolic disorders such as diabetes, gout, obesity, alcohol and tobacco poisoning, deprivation conditions, arterial hypertension and related heart conditions with disordered cerebral circulation.

GENERAL PLAN OF THE RESEARCH

The trial did not involve comparison with other drug, it was an open label study, based on a multi-center cooperation.

The tests were performed contemporaneously at 11 sites, corresponding to an equal number of hospital centers, mostly internal medicine and geriatric departments.

The said sites are codified numerically according to a geographic distribution criterion (for ease of expression, this codification is used in this report), as follows:

Site 1 - S. Anna Hospital., Como

Site 2 - Schio General Hospital

Site 3 - Vicenza General Hospital

Site 4 - Bassini Hospital, Milano

Site 5 - Piacenza General Hospital

Site 6 - Tortona General Hospital

Site 7 - Senigallia General Hospital

Site 8 - Civitta Castellano General Hospital

Site 9 - Nocera Inferiore General Hospital

Site 10 - Termini Imerse General Hospital

Site 11 - G. Giglio Hospital, Cefalu

To facilitate the task of the various investigators, the study methods used, within the framework of a single experimental design applied to all sites, were kept as simple as possible.

The investigators were asked to record the data obtained in suitable forms provided for this purpose, all the data from the various sites being subsequently assemble for further processing and analysis.

A facsimile of the forms used are shown in figure 1.

INCLUSION CRITERIA

The patients entered in the trial were hospitalized at various departments or were being treated ambulatorily at the centers listed above, with a diagnosis of cerebrovascular

insufficiency with underlying first stage arteriosclerosis, characterized by functional disorders of the CNS, whose study is the very objective of the present trial.

Patients with locomotor disorders or disorders of superficial and deep sensitivity due to previous focal lesions of the encephalon were not excluded from the trial, although definitely not covered by the symptomatological objectives of the study; since these are primary symptoms of cerebral arteriosclerosis, they were taken into account in the global evaluation of the activity of the drug, but not in the calculation of the "severity" index (later on in this report), due to their extraneous nature with respect to the pathological condition investigated.

The presence of other coexisting diseases also was not an exclusion criterion, even in cases when the said diseases were the main reason for the hospitalization of the patients.

Of a total of about one thousand patients admitted to the trial, 828 patients were considered compatible with the objective of the study, 399 males and 429 females, whose ages ranged from 45 to 87 years.

Actually, 180 patients could not be included in the final evaluation and biometric data processing, because they were discharged or transferred for various reasons or because they

failed to show up for follow-up or failed to comply with the directions regarding the dose taken or received treatment with other similar drugs which affected the activity of vincamine, etc.

Examination of the data entered in table 1 shows that the distribution of the sample according to sex is perfectly balanced. The age distribution of the sample is also satisfactory for the purposes of the present trial: most patients belonged to the 45 to 70 year age group, the age at which the pathological manifestations studied usually appear.

TREATMENT PLAN

Vincamine was given in the form of tablets, which is more easy take, especially since many patients studied were treated ambulatorily.

The drug was administered in a daily dose of 60 mg, which is the equivalent of 6 tablets containing 10 mg of active ingredient each, broken down into 2 to 3 daily intakes.

Most patients (70%) were treated for 30 days, while 12.5% received the drug for more than 30 days and some of them for as long as 60 days; the others took the drug for various periods of time, mostly two to three weeks.

The plan allowed the investigators at each site to administer any other treatment required for the coexisting diseases; on the contrary, the administration of vasoactive agents or drugs with action at the level of cardiocirculatory system or CNS, whose action could overlap the effect of vincamine (such as reserpine, indole alkaloids, central and peripheral vasodilators, MAO inhibitors, etc.), was prohibited.

Evidently, as mentioned in the preceding chapter, all patients whose treatment required the use of the drugs mentioned above were excluded from the trial.

ASSESSMENT OF THE THERAPEUTIC ACTIVITY

The clinical tests for the evaluation of the therapeutic activity of the drug involve the following series of parameters, corresponding to the clinical symptoms characteristic of the initial forms of cerebrovascular insufficiency:

- memory disorders;
- phosphene;
- vertigo and equilibrium disorders
- headache;
- insomnia;
- aggressiveness, restlessness, anxiety, depression, etc.

The tests for these parameters were carried out at pre-established times, that is: in basal conditions, after 7, 14, 21 and 30 days of treatment and perhaps more, depending on the case.

When present, the following symptoms also were evaluated:

- locomotor disorders;
- superficial and deep sensitivity disorders;
- other eventual disorders present, which were not originally predicted.

Since the above disorders were not included in the original plan, their investigation was limited only at the beginning and at the end of the treatment.

For the uniform evaluation of the criteria applied by the individual investigators and for the processing of the data recorded during the course of the tests, the severity of the symptoms was assessed according to the following scoring scale:

- 0 = no symptom;
- 1 = mild symptom;
- 2 = average symptom;
- 3 - severe symptom.

In addition, to evaluate the severity of the entire symptomatologic picture of each patient, a "severity index"

was established based on the average scores of each single symptom.

Finally, for a more complete study of the cardiocirculatory condition of the patients, the humeral blood pressure data and, when possible, the results of the EKG tests, obtained before and after treatment, also were determined.

ASSESSMENT OF TOLERANCE

Special attention was given by the investigators to the identification and recording in the corresponding forms of any side effect observed during the treatment, expressing their opinion as to the definite or probable relationship between the appearance of the symptom and the latter.

Moreover, when possible, a series of laboratory tests were performed before and after treatment, such as: hemochrome, blood glucose, blood nitrogen, transaminases, urinalysis and, eventually, other.

RESULTS AND STATISTICAL ANALYSIS

The pre-selected parameters, the criteria for their evaluation and the checkup times were described in the preceding chapter.

The results obtained in the 828 patients studied are

reported below, in the following order: the findings yielded by the study of the index are reported first, followed by the analysis of the single clinical "items".

The severity index established for each patient at the various observation times, was defined as the average of the scores assigned to the patient on the basis of the clinical severity of the symptoms present at the start of the treatment.

Graph A, established for the entire study group and for each experimental center, shows the histograms of the average severity indexes recorded in basal conditions and at the end of the treatment with vincamine; the corresponding values, with the respective standard deviations, are reported also in the first part of table 2. The results of the statistical analysis (analysis of variance according to a split-plot model) performed to evaluate the degree of heterogeneity of the data between the various sites (inter-site source of variation), the degree of reduction, at the end of the treatment, of the initial severity scores (time-related score variation) and the development of the said scores at the various sites ("interaction times X sites source of variation), are reported in the second part of the same table.

The preceding analysis provided a statistical measure of the degree of reduction of the severity index at the end of

the treatment, as compared to the initial condition. The course of the said index during the therapeutic period was also evaluated, using the results of the tests performed during the various follow up times, in addition to the initial observations, that is, after 7, 14, 21 and 30 days of treatment; the five tests scheduled in advance were performed in 671 patients (81.04%).

Graphs B, C, D, E, F, G, H, I, L, M and N show the course of the severity indices recorded at each site: for the corresponding testing time, each point indicates the average value of the index for each site; the interpolating curves were traced according to the results yielded by the polynomial equations of the 1st, 2nd, 3rd and 4th degree, which are adapted best to the course of the experimental points. The equations were calculated based on the data entered on the abscissa (x).

Graph O presents a comprehensive picture of the course of the index at the various sites. For a more clear representation of the whole picture, the linear term of the regression of the transformed log10 data (1 + y) was calculated for each site; the eleven straight lines traced on the basis of the said transformation are well comparable to each other, even better than the results obtained by clustering the interpolating curves studied for each site.

The same graph also shows the regression straight line obtained for the entire study group treated for one month or more (671 cases).

Table 3 presents the average severity indexes recorded at the various stages of the treatment for the entire study group and for the single sites.

A detailed analysis was performed of the single items which contributed to the determination of the severity index mentioned above. For the entire study group, the findings yielded by each test during the five observation times were analyzed; analysis of variance and a classification criterion was used to obtain an overall comparison of the results recorded at various times; after the analysis of all the parameters revealed the existence of highly significant differences between the various observation times, the Scheffe test was applied to perform a binary comparison between the initial data and the data obtained after 7, 14, 21 and 30 days, respectively.

The average scores (+/- standard deviation) recorded for each symptom at various times and the results of statistical analysis are reported in table 4.

The motor disorders and the disorders of superficial and deep sensitivity were recorded at basal time and at the end of the treatment.

One-way statistical analysis was used to evaluate the difference between two observation times.

The results of analysis, with the averages and standard deviations obtained for the initial and final values, are reported in table 5.

DISCUSSION

The results obtained during the entire trial were assessed by the various investigators, as follows:

- optimal or good, when the therapeutic response was decisively positive, with definite improvement or remission of the symptomatology in question;
- moderate, when the extent of the improvement was slighter;
- insufficient or nil, when the recovery of the condition of the patient was nil or, at least, not sufficient for meaningful evaluation.

The data obtained according to the criteria described above are reported in table 6.

The results shown in the table indicate that useful results (optimal, good and moderate) were obtained in 92.4% of the patients treated; this demonstrates that treatment with vincamine had a positive effect on the clinical symptomatology of most of the patients studied.

The above is confirmed by the results yielded by the assessment of the severity index (see table 2), which shows that the said index decreased from an average initial value of 1.812 to an average final value of 0.547, an percent average decrease of 69.81%.

This highly statistically significant reduction indicates that the response obtained is the expression of the real therapeutic efficacy of the treatment, rather than to random or spontaneous symptomatologic fluctuations.

Another important feature is provided by the evaluation of the course of severity index at the individual sites (see graph A).

Statistical analysis, which is reported in table 2, demonstrates a statistically significant difference between the various sites.

This can be interpreted as the outcome of a lack of basic homogeneity of the entire study group, due to differences in the initial severity of the symptoms and the different type of patients (the various centers have sites of general medicine and geriatric or long-term hospitalization units).

The differences in the severity of the inclusion conditions, however, do not affect the results of statistical analysis; on the contrary, they are compatible with the

premises of the research, which involve a large population sample, highly representative of the real population of patients affected by mild cerebrovascular insufficiency (which, characteristic of the clinical course of the disease, presents well different degrees of severity).

Therefore, independently of the severity of the initial symptomatology, the course of the disease at all sites is oriented in same direction, although the dimensions of the said orientation are different for each site (statistically significant interaction), due to the differences in the condition responsible for the inclusion of the patients, as shown in graph O which reports the course of symptomatology at each site.

In addition, the course of regression demonstrated by the severity index at each site was expressed in terms of equations of the 1st, 2nd, 3rd and 4th degree, as shown in graphs B, C, D, E, F. G, H, I, L, M and N. The patterns of the curves are compatible with the course of the biological phenomena: a first phase of symptomatologic remission is followed by consolidation which, in turn, is succeeded by further improvement related to the continuation of the treatment.

The importance of extending the duration of treatment with vincamine is related to the fact that the drug acts not only according to a hemodynamic mechanism, but also at the level of the biochemical and metabolic processes of the brain, which confirm the observations of authors [ref. 19, 31] who reported that vincamine affects the brain concentrations of norepinephrine and serotonin.

For the changes observed in the single symptoms studied, the biometric findings demonstrate significant differences at all the scheduled observations times, as indicated in table 4.

The course of every symptom during the various checkup times is illustrated in graph P.

All this shows that the therapeutic effects of vincamine are evident from the very first day of treatment, followed by constant, gradual and progressive improvement.

Table 7 summarizes the final results regarding the percentages of single symptoms that returned to normal, improved, remained unchanged or worsened.

The highest percentages of single symptoms that returned to normal applied to headache (61.84%), followed by phosphene, insomnia, tinnitus and vertigo. The lowest percentages were recorded in memory disorders, the most complex abnormalities encountered in cerebrovascular insufficiency; the said symptom

returned to normal in 41% of the cases after a relatively short treatment, to the effect that it can be regarded as a positive response.

TOLERANCE

The large number of patients studied accounted for an important contribution to the in-depth evaluation of both the frequency of side effects and the appearance of effects which are seen less often.

Since this was a multi-center trial conducted at 11 different sites, it was necessary to establish uniform criteria for assessing the tolerance of the drug hospitalized and ambulatory patients in environments substantially different from one another.

Accordingly, the single global evaluations, case by case, performed at the various sites were simplified as much as possible *), the various investigators being asked to make schematic but univocal judgements, as follows:

- perfect tolerance: lack of any disorders which could be attributed to the administration of the drug tested;
- moderate tolerance: appearance of disorders or other side effects of moderate severity, for which a causal relationship with the treatment could not be excluded;

- doubtful or poor tolerance: the administration of the drug induced disorders which were severe or such as to require the discontinuation of the treatment.

The number of judgements, and the corresponding percentages, made in terms of the criteria described above are reported in table 8.

The data in the said table confirm the literature reports regarding the good tolerance of vincamine.

In effect, side effects were reported in a rather small percent of the patients, mostly in the form of digestive manifestations and some instances of insomnia.

Treatment had to be discontinued in only five of the study patients: three because of gastric disorders and two for the appearance of allergic skin reactions.

According to the various investigators, a definite cause and effect relationship between the appearance of the said effects and the administration of the treatment was not always possible, especially since many patients presented coexisting diseases which could interfere with the disorders mentioned above.

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*) All the eventual side effects observed during the treatment, when present, were entered in the clinical forms provided for this purpose.

The study of tolerance was completed with a series of blood chemistry tests performed in basal conditions and at the end of the treatment.

The results obtained, which are reported in table 9, demonstrate that the blood chemistry parameters tested did not present significant variations during the entire treatment period.

The blood pressure pattern exhibited by the patients treated deserves special mention.

In effect, during the tests, the blood pressure of the patients tended to return to normal, especially in hypertensives: thus, by the end of the treatment the initial average values of 165 mmHg maximum and 91 mmHg minimum decreased to 155 mmHg and 86 mmHg, respectively.

This finding confirms previous reports made earlier by other investigators.

In particular, more significant in this respect was the fact that there were no instance of sudden changes in blood pressure, which demonstrates that the hemodynamic balance of the cerebral vascular bed, which is already abnormal in such patients, remained unchanged all throughout the treatment.

In 95% of the patients included in the trial, electrocardiographic controls failed to show the presence of

any changes of clinical significance attributable to the administration of the treatment. The EKG tracings obtained, some of which were highly abnormal, were actually due to the prevailing condition of each patient, definitely not related to the administration of vincamine, with the only exception of one patient whose control EKG at the end of the treatment showed signs of lateral ischemia. In this particular patient, the investigator could not exclude a causal relationship with the administration of the drug, although this was the only case of this nature in the study population, isolated and of doubtful interpretation.

CONCLUSIONS

Based on objective clinical analysis supported by solid statistical evidence, the results of the present multi-center trial provide practical confirmation of the data reported in the literature regarding the action of vincamine, with particular conclusions pertaining to the size of the sample studied, effect of prolonged vincamine treatment, course and severity of cerebrovascular insufficiency symptoms in the initial stages.

The results demonstrated a definite and significant improvement of the entire syndrome, while the various

individual symptoms presented a constant and progressive regression trend.

Another important fact is that the great majority of the patients tolerated the treatment well, the few cases of intolerance being rather doubtful and perfectly controlled.

SUMMARY

The effect of vincamine on initial cerebrovascular insufficiency was examined by analysis of the data obtained in 828 patients from 11 centers. Most of then received the drug at the rate of 6 tablets/day for 30 days. The method used in the collection collection and processing of the data is described. Classic symptoms of initial insufficiency were recorded after 7, 14, 21 and 30 days of treatment, along with an index of severity pertaining to the symptomatology as a whole. The results revealed a continuous improvement in both the individual symptoms and overall, starting from the onset of the treatment, eventually leading to high rates of remission. Tolerance was generally good, with very few instances of side effects.

[Min. Med., 68, 2093-2114, (June) 1978. - Treatment of initial cerebrovascular insufficiency with vincamine. Poly-center trial on 828 cases).

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SITE .....

VINCADAR

Case No. Clinical record No Initials M F Yrs.. (≥ 45)

Diagnosis

Cerebrovascular insufficiency on early arteriosclerosis

Eventual coexisting diseases .....

Treatment

Daily dose ...tablets of Vincadar Length of ttmt... days

Parameters(*)	Before	After 7 d	Aft. 14 d	Aft. 21 d	Aft. 30 d	Aft. ..
Memory, attention, concentr. disorders	strong					
	av.					
	mild					
	no					
Tinnitus	strong					
	av.					
	mild					
	no					
Phosphene	strong					
	av.					
	mild					
	no					
Vertigo, equilibr. disorders	strong					
	av.					
	mild					
	no					
Headache	strong					
	av.					
	mild					
	no					
Insomnia	strong					
	av.					
	mild					
	no					
Aggress. restless. anxiety depress.	strong					
	av.					
	mild					
	no					

Other parameters(*)		Before	End of ttmt.	Obs.
Motor dis.	strong			
	av.			
	mild			
	no			
Sensitivity disorders	strong			
	av.			
	mild			
	no			

Other

*) Check the proper box for the severity of the symptom

Fig. 1 a

Fig. 1 a-b - Facsimile of the clinical form

	Before	After treatm
Systolic/diastolic blood pressure		
Laboratory tests		
Erythrocytes		
Leukocytes		
Hb		
Blood glucose		
Blood nitrogen		
Transaminases SGOT		
Transaminases SGPT		
Urine sediment		
Other		
EKG		
Therapeutic activity		
Optimal or good	Moderate	Insufficient or nil
Observations		
Tolerance		
Optimal	Moderate	Poor
Observations		
Eventual side effects:		
. skin		
. gastric		
. cardiocirculatory		
. other		

Fig. 1 b

TABLE 1. - Age and Sex Distribution of the Study Population - Global and by Site

	No. of pats.	Sex		Age (yrs)	
		M	F	45-70	Over 70
Total	828	399	429	379	249
Site 1	100	57	43	63	37
Site 2	38	19	19	16	22
Site 3	31	9	22	20	11
Site 4	100	58	42	82	18
Site 5	102	30	72	59	43
Site 6	98	48	50	77	21
Site 7	80	46	34	68	12
Site 8	100	52	48	84	16
Site 9	89	40	49	68	21
Site 10	63	20	43	27	36
Site 11	27	20	7	15	12

GRAPH A Average values of the index of severity in basal conditions (B) and at the end of the treatment (F) with vincamine, for the entire patient population and by site (1, 2 .... 11)

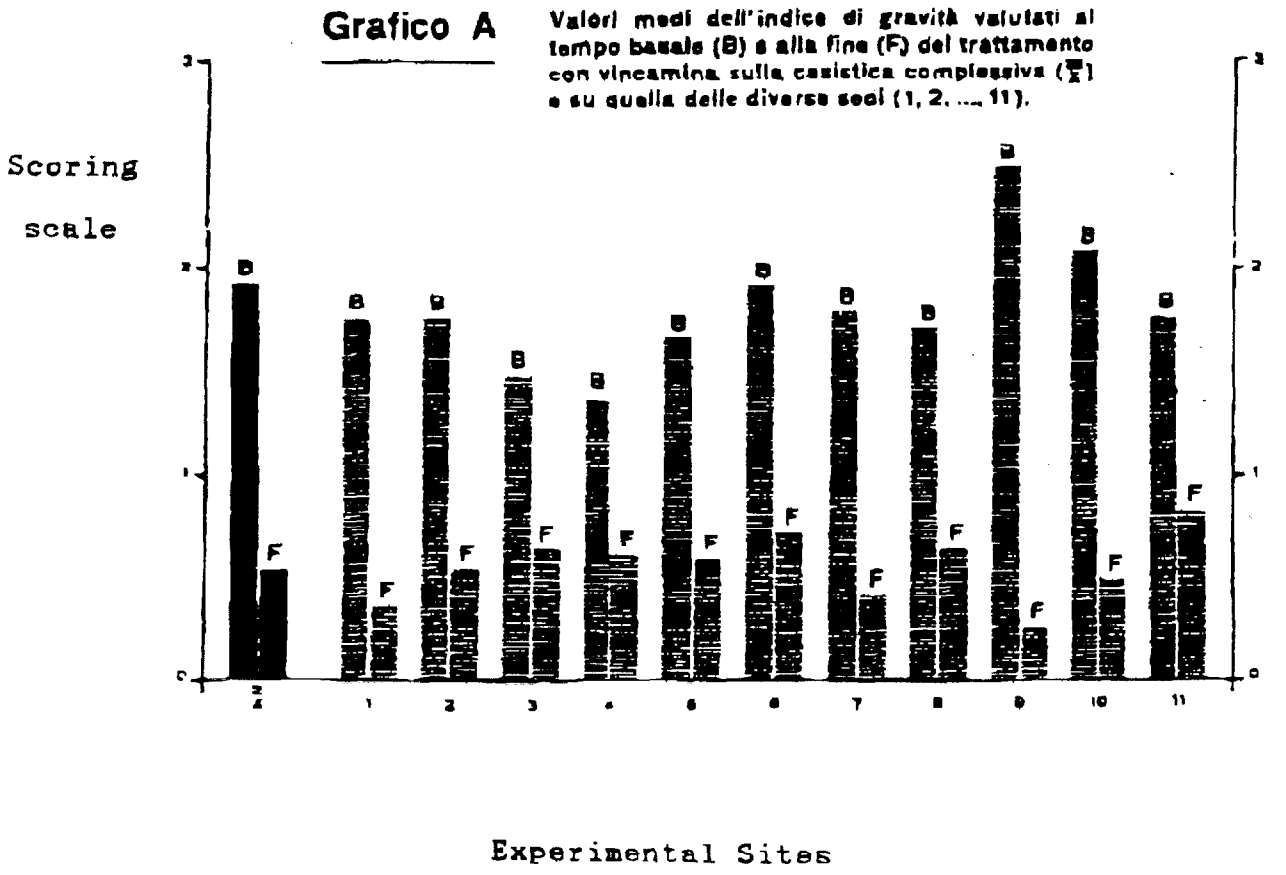


TABLE 2 - Results and Analysis of the Index of Severity

	Average (+/- S. D.) Basal	Final
Global (828 cases)	1,812 ± 0,016	0,547 ± 0,015
Site 1 (100 cases)	1,760 ± 0,024	0,375 ± 0,026
Site 2 (38 cases)	1,797 ± 0,066	0,559 ± 0,060
Site 3 (31 cases)	1,484 ± 0,072	0,666 ± 0,086
Site 4 (100 cases)	1,397 ± 0,044	0,636 ± 0,040
Site 5 (102 cases)	1,674 ± 0,027	0,603 ± 0,041
Site 6 (88 cases)	1,909 ± 0,033	0,732 ± 0,048
Site 7 (80 cases)	1,798 ± 0,067	0,446 ± 0,060
Site 8 (100 cases)	1,704 ± 0,039	0,654 ± 0,028
Site 9 (89 cases)	2,485 ± 0,035	0,255 ± 0,028
Site 10 (63 cases)	2,066 ± 0,054	0,495 ± 0,071
Site 11 (27 cases)	1,754 ± 0,075	0,827 ± 0,089

Analysis of variance according to the "split-plot" model

Sources of variation	G.L.	Deviation	Variance	F	F
Between sites	10	21,69	2,16	9,39	< 0,01
Error 1	817	184,88	0,23		
Between times					
Interaction times X sites	1	662,33	662,33	7359,22	< 0,01
Error 2					
Total	10	67,31	6,73	74,78	< 0,01
	817	81,57	0,09		

TABLE 3. - Evaluation of the Index of Severity in Patients Treated with Vincamine

	Average (+/- S. D.) Basal	7 days	14 days	21 days	30 days
Total cases	1,801 ± 0,089	1,450 ± 0,135	1,070 ± 0,102	0,794 ± 0,065	0,562 ± 0,051
Site 1	1,760 ± 0,024	1,576 ± 0,026	1,153 ± 0,030	0,827 ± 0,031	0,424 ± 0,028
Site 2	1,823 ± 0,068	0,968 ± 0,095	0,738 ± 0,078	0,658 ± 0,071	0,581 ± 0,063
Site 3	1,484 ± 0,072	0,888 ± 0,083	0,735 ± 0,085	0,683 ± 0,086	0,677 ± 0,086
Site 4	1,391 ± 0,058	1,213 ± 0,057	0,928 ± 0,057	0,734 ± 0,050	0,658 ± 0,052
Site 5	1,616 ± 0,035	1,277 ± 0,047	0,708 ± 0,043	0,496 ± 0,044	0,377 ± 0,040
Site 6	1,906 ± 0,034	1,841 ± 0,032	1,516 ± 0,038	1,152 ± 0,045	0,755 ± 0,050
Site 7	1,756 ± 0,193	1,043 ± 0,188	0,711 ± 0,201	0,505 ± 0,150	0,334 ± 0,106
Site 8	1,704 ± 0,040	1,562 ± 0,043	1,211 ± 0,041	0,852 ± 0,035	0,656 ± 0,029
Site 9	2,485 ± 0,036	2,395 ± 0,041	1,895 ± 0,038	0,977 ± 0,042	0,363 ± 0,046
Site 10	2,066 ± 0,058	1,796 ± 0,070	1,194 ± 0,074	0,765 ± 0,071	0,526 ± 0,071
Site 11	1,818 ± 0,095	1,390 ± 0,099	1,181 ± 0,088	1,088 ± 0,089	0,828 ± 0,093

TABLE 4. - Results and Analysis of the Single Items (in Patients who Presented the Symptoms Initially

	Basal	Average (+/- S. D.) 7 days	14 days	21 days	30 days
Memory, attention, concentration disorders (613 cases)	2,005 ± 0,028	1,806 ± 0,031 **)	1,398 ± 0,033 **)	1,005 ± 0,029 **)	0,711 ±
Tinnitus (499 cases)	1,813 ± 0,036	1,599 ± 0,040 **)	1,194 ± 0,038 **)	0,829 ± 0,032 **)	0,547 ± 0
Phosphene (417 cases)	1,738 ± 0,033	1,525 ± 0,035 **)	1,148 ± 0,034 **)	0,774 ± 0,031 **)	0,486 ± 0,
Vertigo, equilibrium disorders (592 cases)	1,984 ± 0,030	1,717 ± 0,033 **)	1,241 ± 0,031 **)	0,895 ± 0,028 **)	0,554 ± 0,
Headache (527 cases)	1,905 ± 0,031	1,673 ± 0,031 **)	1,136 ± 0,031 **)	0,829 ± 0,026 **)	0,459 ± 0,0
Insomnia (522 cases)	1,699 ± 0,031	1,500 ± 0,033 **)	1,078 ± 0,032 **)	0,743 ± 0,027 **)	0,486 ± 0,0
Aggression, restlessness, anxiety, depression, etc. (539 cases)	1,805 ± 0,030	1,571 ± 0,033 **)	1,202 ± 0,031 **)	0,855 ± 0,029 **)	0,556 ± 0,02

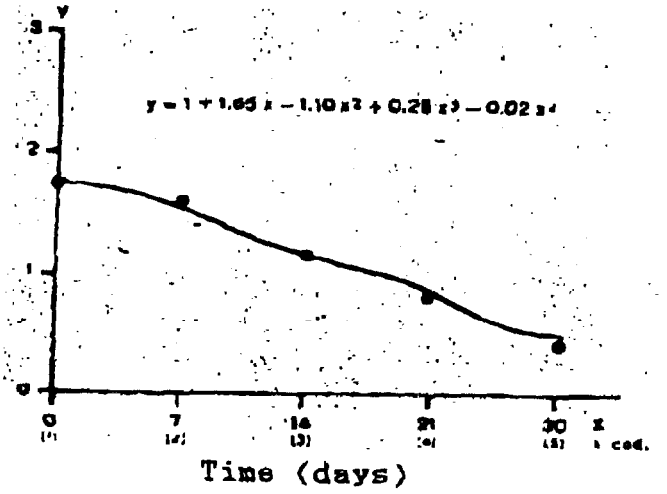
**) Highly significant differences with respect to basal time (Scheffe test)

TABLE 5. - Results and Analysis of Motor Disorders and Sensitivity Disorders Indexes (workup) in Patients who Presented the Symptom Initially

	Average (+/- S. D.) Basal	Final	One-way variance	P
Motor disorders (273 cases)	1,557 ± 0,044	0,597 ± 0,045	F = 233,38 (1,544 g.l.)	< 0,01
Superficial and deep sensitivity disorders (229 cases)	1,629 ± 0,049	0,559 ± 0,043	F = 271,77 (1,456 g.l.)	< 0,01

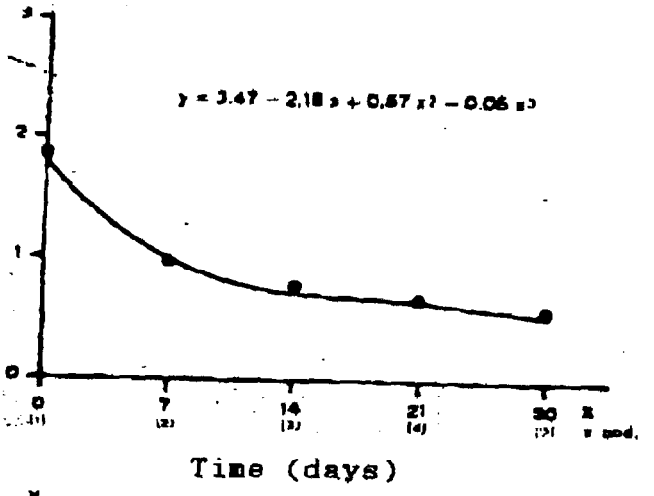
GRAPH E
Site 4

Course of the index of severity



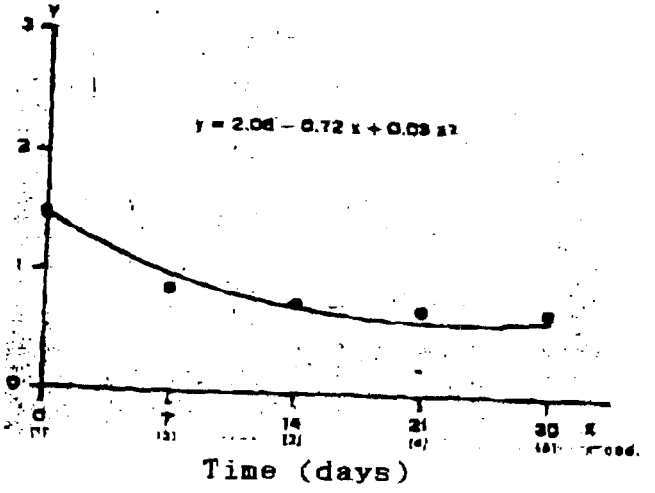
GRAPH F
Site 5

Course of the index of severity



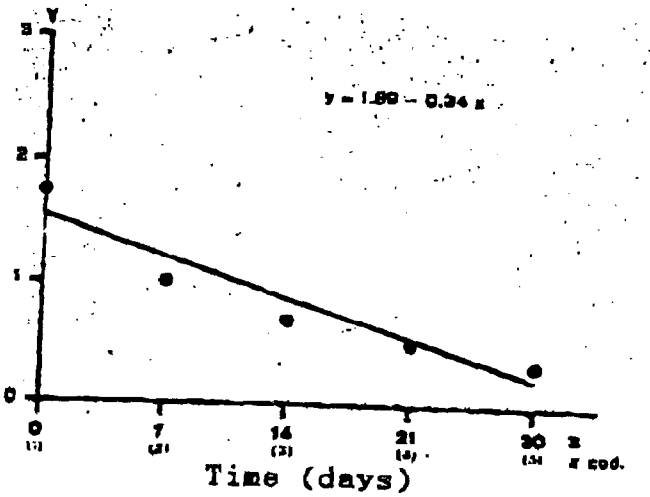
GRAPH G
Site 6

Course of the index of severity



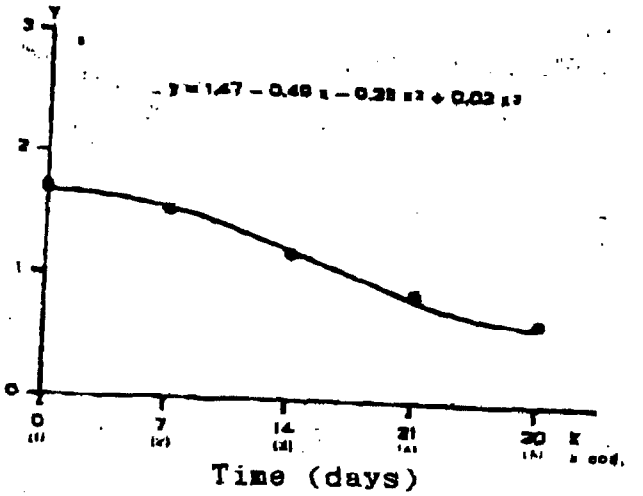
GRAPH H
Site 7

Course of the
index of severity



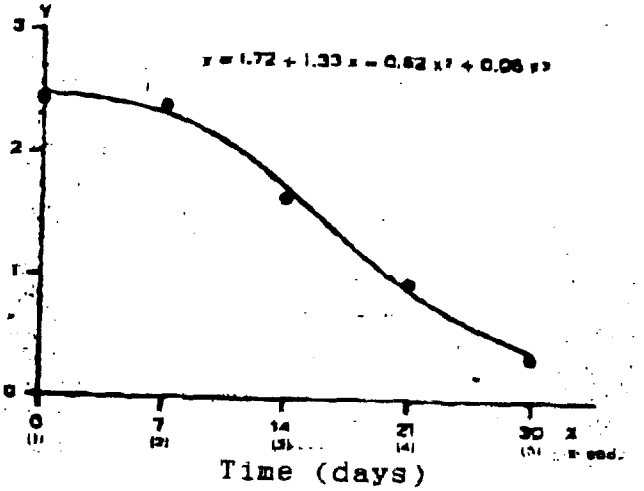
GRAPH I
Site 8

Course of the
index of severity



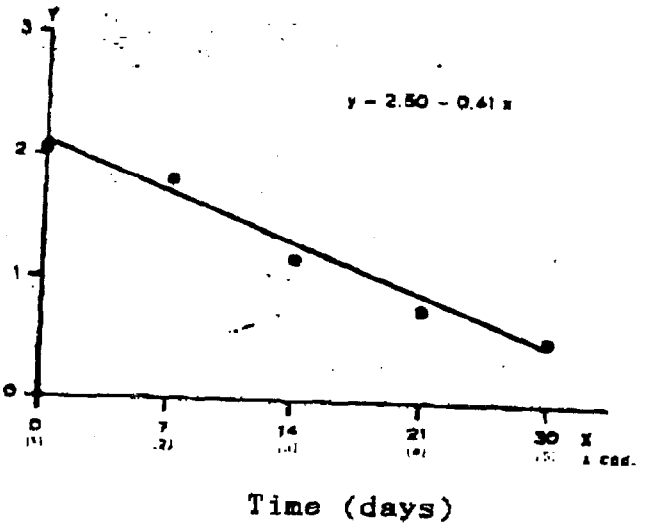
GRAPH L
Site 9

Course of the
index of severity



GRAPH M
Site 10

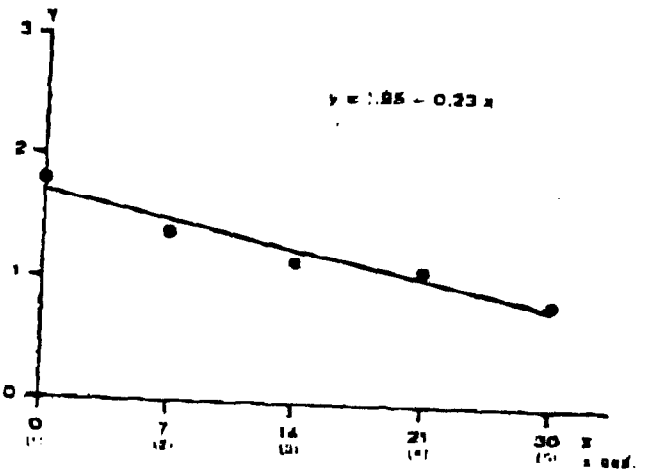
Course of the index of severity



Time (days)

GRAPH N
Site 11

Course of the index of severity



Time (days)

GRAPH 0

Development of the index of severity at the eleven sites (1,..... 11). The straight lines traced to obtain a global comparative picture were obtained by conversion of all log10(1 + y); straight line Z is the interpolating line for the entire study group (671 cases). A semi-logarithmic scale was used for the ordinates.

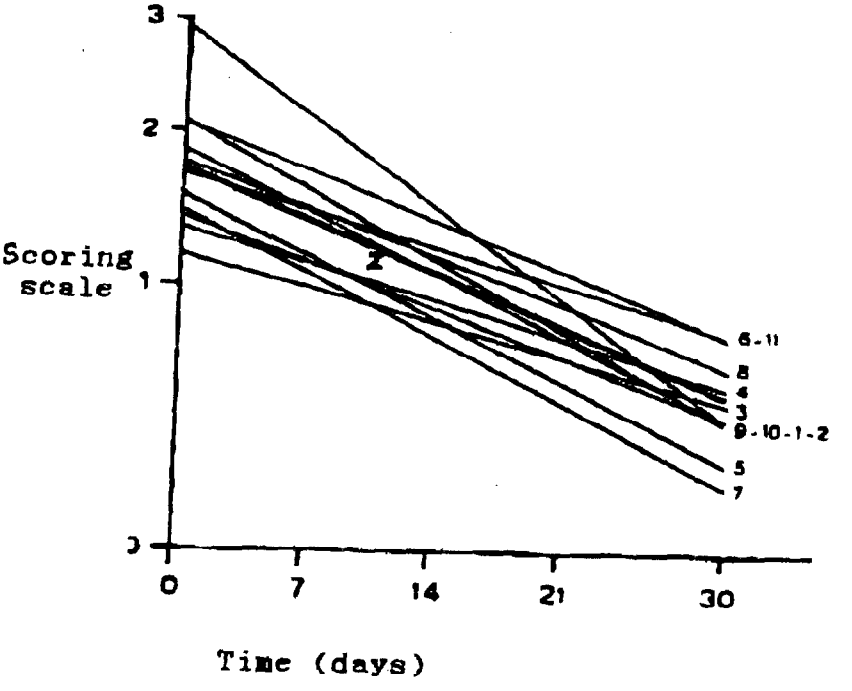


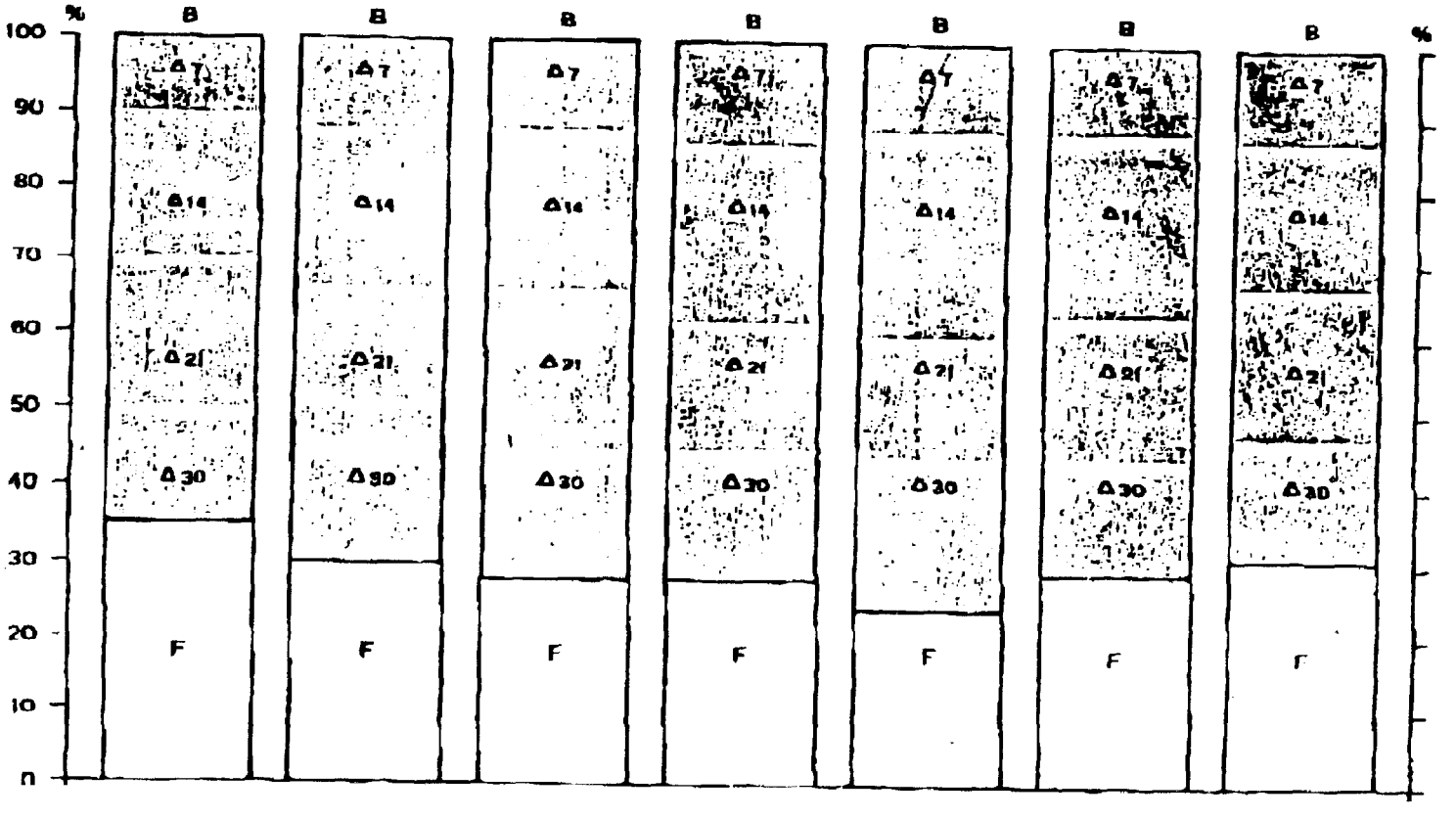
TABLE 6. - Clinical Assessment of the Activity of the Drug, Global and by Site, at the End of the Treatment

	Optimal or good	Moderate	Insufficient or nil
Total cases			
Site 1	58,82 %	33,58 %	7,60 %
Site 2	53,00 %	41,00 %	6,00 %
Site 3	65,79 %	31,58 %	2,63 %
Site 4	45,16 %	35,48 %	19,36 %
Site 5	46,00 %	36,00 %	18,00 %
Site 6	64,71 %	33,33 %	1,96 %
Site 7	72,45 %	24,49 %	3,06 %
Site 8	50,00 %	38,75 %	11,25 %
Site 9	45,00 %	48,00 %	7,00 %
Site 10	83,15 %	14,60 %	2,25 %
Site 11	68,25 %	23,81 %	7,94 %
	37,04 %	48,15 %	[illegible]

GRAPH P Course of symptomatologic severity for the entire population For each symptom, the average severity scores recorded durin, the checkup times (7, 14, 21 and 30 days of treatment with vincamine) were expressed in terms of the corresponding average basal values.

B - average basal severity score = 100
F - average score at the end of the treatment, expressed in % with respect to B

DELTA7 - % difference after 7 days with respect to B
DELTA14 - % difference after 14 days with respect to B
DELTA21 - % difference after 21 days with respect to B
DELTA30 - % difference after 30 days with respect to B



Memory, attention, concenttration disorders | Tinnitus | Phosphene | Vertigo equilibrium disorders | Headache | Insomnia | Aggression, restlessnes depression, etc.

TABLE 7. - Number of cases with initial symptoms and absolute and percent frequency of returns to normal, unchanged and exacerbated at the end of the treatment

Symptoms	Initial	Normalized	Improved	Unchanged	Exacerbated
Memory disord.	751 (100 %)	309 (41,15 %)	369 (49,13 %)	73 (9,72 %)	0
Tinnitus	594 (100 %)	322 (54,21 %)	161 (27,10 %)	111 (18,69 %)	0
Phosphene	483 (100 %)	289 (59,83 %)	99 (20,50 %)	94 (19,46 %)	1 (0,21 %)
Vertigo	726 (100 %)	387 (53,31 %)	253 (34,85 %)	86 (11,84 %)	0
Headache	621 (100 %)	384 (61,84 %)	171 (27,54 %)	65 (10,46 %)	1 (0,16 %)
Insomnia	629 (100 %)	367 (58,35 %)	151 (24,01 %)	110 (17,48 %)	1 (0,16 %)
Aggression	648 (100 %)	325 (50,16 %)	220 (33,95 %)	100 (15,43 %)	3 (0,46 %)

TABLE 8

Tolerance	No. of cases	Percent
Perfect	769	92.88%
Moderate	47	5.67%
Uncertain or poor	12	1.45%

TABLE 9

	Average (+/- S. D.) Basal	Final
Erythrocytes [10(9) mm3] (774 cases)	4411,139 +/- 16,307	4381,868 +/- 15,077
Leukocytes (mm3) (774 cases)	7066,304 +/- 66,254	6682,739 +/- 47,831
Hemoglobin (%) (755 cases)	83.494 +/- 0.321	83.439 +/- 0.303
Blood glucose (mg%)	99.417 +/- 1.228	91.836 +/- 0.702
Blood nitrogen (mg%)	34.632 +/- 0.522	32.452 +/- 0.370
SGOT (mU/ml) (719 cases)	12.115 +/- 0.226	11.669 +/- 0.204
SGPT (mU/ml)	10.063 +/- 0.205	9.701 +/- 0.170

TERAPIA IN CAMMINO

Trattamento dell'insufficienza cerebro-vascolare iniziale con vincamina

Ricerca policentrica su 828 casi

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Riassunto. — Una ricerca policentrica è stata condotta al fine di documentare su una casistica di ampie dimensioni l'azione della vincamina sulle sindromi da insufficienza cerebro-vascolare iniziale.
Le osservazioni interessano 828 pazienti studiati in 11 centri, trattati in massima parte per 30 giorni alla posologia giornaliera di 6 compresse.
Nel testo è stata descritta la metodologia seguita per la raccolta dei dati e quella relativa alle elaborazioni effettuate.
I sintomi presi in considerazione sono stati quelli classici delle sindromi da insufficienza cerebro-vascolare iniziale: il loro controllo è avvenuto a scadenze prefissate e cioè al 7° al 14°, al 21° e al 30° giorno di trattamento.
Le analisi hanno valutato il comportamento dei sintomi ai vari tempi di rilievo e quello di un « indice di gravità » riferito al quadro sintomatologico nel suo insieme.
I risultati conseguiti stanno a dimostrare un miglioramento globale e particolare rispetto ai singoli items della sindrome considerata: tale miglioramento si evidenzia sin dai primi giorni di trattamento per aumentare progressivamente nel tempo fino a raggiungere elevate percentuali di remissione. La tollerabilità è risultata inoltre complessivamente buona, con una frequenza di effetti collaterali estremamente bassa.

Parole chiave. — Insufficienza cerebro-vascolare - Vasculopatie cerebrali - Vincamina.

Premesse

I fenomeni di tipo arteriosclerotico, i più importanti forse tra quelli caratteristici dell'età involutiva, possono dare origine, date le molteplici possibilità di localizzazione in tutti i distretti vasali, a una serie di conseguenze di ordine sia funzionale che anatomico a carico direttamente dei vasi colpiti, nonchè degli organi da questi irrorati.

Particolarmente importanti, per le loro conseguenze a breve e lungo termine, sono i processi arteriosclerotici che colpiscono il distretto vascolare cerebrale. La conseguenza più immediata di questi fenomeni è la diminuzione progressiva del flusso ematico cerebrale: il suo valore normale medio, che nell'adulto a riposo e sino ai 50 anni è di 55 ml/minuto per ogni 100 g di peso della massa cerebrale, attorno ai 60 anni scende a 42 ml/minuto per arrivare, dopo i 70 anni, a 35 ml/minuto [18].

Ciò significa che la diminuzione del flusso ematico, conseguente alle modificazioni strutturali di tipo arteriosclerotico dei vasi cerebrali, determina un minore apporto di sangue e quindi di O_2 alle delicate strutture dell'encefalo.

Il lento progredire delle alterazioni emodinamiche e metaboliche cerebrali causa, a più o meno lunga scadenza, perdita di peso di tutta la massa encefalica, atrofia delle cellule gangliari, riduzione dei sistemi enzimatici, con la risultante di un abbassamento delle complesse attività cerebrali.

Si creano in tal modo le premesse anatomo-funzionali per l'instaurarsi di quelle sindromi di insufficienza cerebro-vascolare che sono l'espressione clinica iniziale di una sofferenza del parenchima cerebrale.

Se è raro che queste forme si rendano appariscenti prima dei 45 anni di età, ciò non toglie che i primi sintomi dell'arteriosclerosi cerebrale siano stati eccezionalmente segnalati anche in età giovanile, non essendo essi esclusivamente appannaggio dell'età avanzata.

Entrano a far parte di questi quadri sintomatologici disturbi funzionali premonitori variamente coesistenti sia per durata che per frequenza, ben conosciuti dal medico pratico che spesso li ritrova nei suoi pazienti ambulatoriali.

Predominano tra questi le cefalee di tipo gravativo subcontinuo, i ronzii auricolari, i classici acufeni accompagnati a volte da diminuzione dell'udito, i disturbi visivi costituiti soprattutto dai fosfeni, le crisi vertiginose.

Può coesistere in questi pazienti una facile esauribilità mentale con disturbi del sonno, specie sotto forma di insonnia notturna, con deficit della memoria, dovuti questi ultimi soprattutto a diminuzione delle facoltà di apprendimento: possono anche essere presenti alterazioni dell'umore sia in senso depressivo che euforico.

Il decorso di queste forme è in genere molto lento e progressivo, anche se possono verificarsi talvolta delle progressioni improvvise o addirittura veri e propri insulti apoplettici.

Gli stadi finali possono essere rappresentati da un rammollimento cerebrale massivo, con emorragie, susseguenti a rotture delle pareti vasali alterate, con prognosi quoad valetudinem, e anche quoad vitam, riservata.

Queste sono in sintesi le ragioni che consigliano un intervento terapeutico tempestivo nella cura dei quadri sintomatologici sopra descritti, espressione clinica di stati iniziali, e in quanto tali di natura spesso reversibile, di insufficienza cerebro-vascolare.

Non ci si può nascondere come il problema terapeutico che si pone al riguardo sia quanto mai complesso: non pochi sono comunque i presidi terapeutici che oggi sono a disposizione del medico per la cura e soprattutto per la prevenzione di queste forme patologiche.

Un posto di particolare importanza è rappresentato tra questi ultimi dalla vincamina, l'alcaloide della Vinca minor di scoperta piuttosto recente, che, già nei pochi anni in cui è stata utilizzata, ha dimostrato di possedere buone proprietà terapeutiche come documentato oltre che dai risultati ottenuti nella pratica medica corrente, anche da una vasta letteratura che ne ha confermato i vantaggi clinici nella terapia delle sindromi cerebro-vascolari [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39, 40].

Scopo della ricerca

Le più recenti vedute prospettano, per i farmaci usati nella terapia dell'insufficienza cerebro-vascolare, un meccanismo d'azione diverso da quello ritenuto il più efficace in un passato anche recente: non più una vasodilatazione intesa in senso generico, anche se circoscritta nei limiti del circolo cerebra-

le, ma una vasoregolazione distrettuale limitata alle zone interessate dal deficit circolatorio (e non interessante quelle sane per evitare il cosidetto «furto intracerebrale») associata ad una concomitante azione di tipo eumetabolico.

Le possibilità di documentare, specie in sede clinica, tali azioni sono estremamente modeste, anche se sono state messe a punto metodiche di rilevazione dei flussi regionali, delle differenze artero-venose in O_2, e di misura del consumo del glucosio marcato e dei vari metaboliti.

L'esecuzione di tali tecniche sullo stesso paziente in modo seriato nel tempo risulta di difficile attuazione e comporta inconvenienti e pericoli, incannulazione carotidea ad es., che non possono essere trascurati: inoltre i risultati risentono spesso delle modificazioni emogasometriche che possono intervenire inficiando seriamente i dati.

Ne consegue che, allo stato attuale delle cose, per lo studio dell'insufficienza cerebrovascolare, in particolar modo allo stato iniziale, ai fini di una prevenzione di quelli che possono essere i suoi sviluppi futuri, la migliore induzione sia ancora quella clinica, che è in grado di seguire le modificazioni della sintomatologia, espressione in ultima analisi sia della situazione vascolare che delle condizioni metaboliche sempre a livello cerebrale.

In considerazione di quanto sopra, risulta interessante il contributo del presente lavoro incentrato su una valutazione delle modificazioni del quadro clinico, valutazione tanto più obiettiva in quanto rapportata a un campione di studio assai vasto che ha permesso inferenze statistiche di importanza direttamente proporzionale alle dimensioni del campione stesso.

Utile risulta inoltre il fatto di poter disporre di osservazioni prolungate nel tempo, proprio in considerazione del multiforme aspetto che caratterizza le sindromi iniziali di insufficienza cerebro-vascolare. Si sa infatti come i sintomi che ne fanno parte si presentino con un decorso bizzarro e siano a volte contraddittori nelle loro manifestazioni: infatti essi sono spesso transitori con remissioni spontanee e con ripristino temporaneo delle funzioni lese, a volte recidivanti, più spesso a lenta e progressiva evoluzione in senso peggiorativo.

La loro insorgenza e il loro decorso, oltre a ubbidire sovente a fattori imponderabili, possono essere influenzati da altre cause patologiche concomitanti: alterazioni dismetaboliche quali il diabete, la gotta, l'obesità, intossicazioni alcooliche e tabagiche, stati carenziali, ipertensione arteriosa e alterazioni cardiache correlate con le turbe della circolazione cerebrale.

Piano generale della ricerca

Si è trattato di una ricerca non implicante confronti diretti con altri farmaci, « al chiaro », articolata su una collaborazione policentrica.

Le prove sono state condotte contemporaneamente in 11 sedi, corrispondenti ad altrettanti centri ospedalieri per lo più di medicina generale o geriatria.

Le sedi sono state codificate numericamente in base a un criterio di distribuzione geografica (tale codifica è sempre stata adottata, per comodità espositiva, nel contesto della relazione) come segue:

Sede 1 - Osped. S. Anna di Como
Sede 2 - Osped. Civile di Schio
Sede 3 - Osped. Civile di Vicenza
Sede 4 - Osped. Bassini di Milano
Sede 5 - Osped. Civile di Piacenza
Sede 6 - Osped. Civile di Tortona
Sede 7 - Osped. Civile di Senigallia
Sede 8 - Osped. Civile di Civita Castellana
Sede 9 - Osped. Civile di Nocera Inferiore
Sede 10 - Osped. Civile di Termini Imerese
Sede 11 - Osped. G. Giglio di Cefalù

Le metodiche di indagine seguite, inquadrate in un unico disegno sperimentale valido per tutte le sedi, sono state improntate alla massima semplicità per favorire l'opera dei vari sperimentatori.

Questi hanno provveduto ad annotare i dati rilevati nel corso delle prove su schede appositamente predisposte: tutti i dati raccolti nelle varie sedi sono stati alla fine riuniti per essere opportunamente elaborati ed analizzati.

Nella figura 1 è riportato un fac-simile delle schede utilizzate.

Criteri di ammissione al saggio

Sono stati ammessi alle prove pazienti ricoverati nei reparti ospedalieri o in cura ambulatoriale presso i centri prima specificati,

SEDE ..... **VINCADAR**

Caso N°	Cartella clinica N° ..... Registro ambul. N°	Iniziali	☐ ♂ ☐ ♀	anni (≥ 45)

Diagnosi

Insufficienza cerebrovascolare su base arteriosclerotica ai primi stadi

Eventuali malattie concomitanti: .....

Trattamento

Posologia pro die ..... compresse di Vincadar Durata trattamento ..... giorni

Parametri di attività (*)		Prima	Dopo 7 gg	Dopo 14 gg	Dopo 21 gg	Dopo 30 gg	Dopo ... gg
Disturbi della memoria, dell'attenzione, del potere di concentrazione	forti	☐	☐	☐	☐	☐	☐
	medi	☐	☐	☐	☐	☐	☐
	lievi	☐	☐	☐	☐	☐	☐
	assenti	☐	☐	☐	☐	☐	☐
Acufeni	forti	☐	☐	☐	☐	☐	☐
	medi	☐	☐	☐	☐	☐	☐
	lievi	☐	☐	☐	☐	☐	☐
	assenti	☐	☐	☐	☐	☐	☐
Fosfeni	forti	☐	☐	☐	☐	☐	☐
	medi	☐	☐	☐	☐	☐	☐
	lievi	☐	☐	☐	☐	☐	☐
	assenti	☐	☐	☐	☐	☐	☐
Vertigini, disturbi equilibrio	forti	☐	☐	☐	☐	☐	☐
	medi	☐	☐	☐	☐	☐	☐
	lievi	☐	☐	☐	☐	☐	☐
	assenti	☐	☐	☐	☐	☐	☐
Cefalea	forte	☐	☐	☐	☐	☐	☐
	media	☐	☐	☐	☐	☐	☐
	lieve	☐	☐	☐	☐	☐	☐
	assente	☐	☐	☐	☐	☐	☐
Insonnia	forte	☐	☐	☐	☐	☐	☐
	media	☐	☐	☐	☐	☐	☐
	lieve	☐	☐	☐	☐	☐	☐
	assente	☐	☐	☐	☐	☐	☐
Aggressività, irrequietezza, ansia, depressione, ecc.	forte	☐	☐	☐	☐	☐	☐
	media	☐	☐	☐	☐	☐	☐
	lieve	☐	☐	☐	☐	☐	☐
	assente	☐	☐	☐	☐	☐	☐

Eventuali altri parametri di attività (*)		Prima	A fine trattamento
Disturbi motori	forti	☐	☐
	medi	☐	☐
	lievi	☐	☐
	assenti	☐	☐
Disturbi sensibilità superficiale e profonda	forti	☐	☐
	medi	☐	☐
	lievi	☐	☐
	assenti	☐	☐
Altro			

Osservazioni:

(*) *Barrare le caselle in base all'intensità dei sintomi ai tempi d'osservazione previsti*

Fig. 1 a.

Fig. 1 a-b. — Fac-simile della scheda clinica.

	Prima	A fine trattamento
Pressione arteriosa sistolica/diastolica	.....	.....
Esami di laboratorio		
Eritrociti	.....	.....
Leucociti	.....	.....
Hb	.....	.....
Glicemia	.....	.....
Azotemia	.....	.....
Transaminasi SGO	.....	.....
Transaminasi SGP	.....	.....
Sedimento urinario		
Altri	.....	.....
.....	.....	.....
ECG		

Attività terapeutica

Ottima o buona ☐ Discreta ☐ Insufficiente o nulla ☐

Osservazioni:

Tollerabilità

Ottima ☐ Discreta * ☐ Cattiva * ☐

* Osservazioni:

Eventuali effetti collaterali:

- a livello cutaneo .....
- a livello gastrico .....
- a livello cardiocircolatorio .....
- altri .....

Fig. 1 b.

per i quali era stata posta diagnosi di insufficienza cerebro-vascolare su base arteriosclerotica ai primi stadi, caratterizzata da quei disturbi di ordine funzionale interessanti in SNC, il cui studio costituisce, come si è visto, lo scopo di tutta la ricerca.

Non ha costituito un criterio di esclusione l'eventuale presenza di turbe a carico dell'apparato locomotore o della sensibilità superficiale e profonda, susseguenti a pregresse lesioni focali dell'encefalo anche se chiaramente non rientranti nel quadro sintomatologico preso in considerazione quale obiettivo del lavoro; trattandosi di sintomi di primaria importanza nell'arteriosclerosi cerebrale se ne è ugualmente tenuto conto « a latere » agli effetti della globale valutazione dell'attività del farmaco, pur non considerandoli nel calcolo dell'« indice di gravità » (v. poi) per la loro natura estranea alla peculiare patologia indagata.

Non è stata inoltre motivo di esclusione la presenza di altre malattie concomitanti, anche nei casi in cui queste rappresentavano la causa principale del ricovero.

Su un totale complessivo di casi ammessi al saggio, aggirantisi sul migliaio di unità, sono stati considerati validi agli effetti della ricerca 828 pazienti, 399 maschi e 429 femmine, di età variante dai 45 agli 87 anni.

In effetti circa 180 casi non hanno potuto essere inclusi nel materiale sperimentale utilizzato per le valutazioni terminali e le elaborazioni biometriche, in quanto dimessi o trasferiti per motivi contingenti o non più presentatisi ai controlli successivi o perchè non attenutisi alle istruzioni ricevute per quanto riguardava posologia, trattamenti con farmaci analoghi interferenti sulla valutazione dell'attività della vincamina, ecc.

Dall'esame dei dati riportati nella tabella 1 si può notare come la distribuzione del campione secondo il sesso si presenti perfettamente equilibrata. Attinente alle finalità della ricerca risulta inoltre la distribuzione secondo le classi di età: nella grande maggioranza dei casi l'età dei pazienti era compresa tra i 45 e i 70 anni, età in cui si instaurano più facilmente i quadri patologici studiati.

TABELLA 1. — *Descrizione della casistica, globale e per sede, in relazione al sesso e all'età.*

	N. pazienti	Sesso		Età anni	
		Maschi	Femm.	45-70	Oltre 70
Casistica globale	828	399	429	579	249
Sede 1	100	57	43	63	37
Sede 2	38	19	19	16	22
Sede 3	31	9	22	20	11
Sede 4	100	58	42	82	18
Sede 5	102	30	72	59	43
Sede 6	98	48	50	77	21
Sede 7	80	46	34	68	12
Sede 8	100	52	48	84	16
Sede 9	89	40	49	68	21
Sede 10	63	20	43	27	36
Sede 11	27	20	7	15	12

Modalità del trattamento

La ricerca è stata condotta utilizzando la vincamina nella sua forma in compresse, di più facile somministrazione, soprattutto in considerazione che buona parte dei pazienti in osservazione sarebbe stata seguita ambulatoriamente.

La posologia contemplava 60 mg di vincamina al giorno, equivalente a 6 compresse da 10 mg di sostanza attiva ciascuna, in dosi refratte da 2 a 3 volte pro die.

La durata del trattamento si è aggirata per la massima parte dei pazienti (circa il 70 %) sui 30 giorni, mentre nel 12 % si è andati oltre i 30, a volte fino ai 60 giorni: il rimanente della casistica ha ricevuto un trattamento variante, per lo più, tra le due e le tre settimane.

Il programma previsto lasciava agli sperimentatori di ogni sede la facoltà di attuare tutte quelle terapie indicate per le altre forme morbose eventualmente concomitanti: sconsigliava invece il trattamento con farmaci vasoattivi o a punto di attacco sull'apparato cardiocircolatorio o del SNC, i cui effetti avrebbero potuto sovrapporsi a quelli della vincamina (ad es.: reserpina, alcaloidi indolici, vasodilatatori centrali e periferici, anti-MAO, ecc.).

Ovviamente hanno dovuto essere esclusi dal saggio, come già detto nel capitolo precedente, tutti quei pazienti che per necessità terapeutiche sono stati costretti a far ricorso ai farmaci di cui sopra.

Valutazione dell'attività terapeutica

Le rilevazioni cliniche per la valutazione dell'attività terapeutica riguardavano la seguente serie di parametri, corrispondenti praticamente ai sintomi clinici caratteristici delle forme iniziali di insufficienza cerebro-vascolare:

— disturbi della memoria, dell'attenzione e del potere di concentrazione;

— acufeni;

— fosfeni;

— vertigini e disturbi dell'equilibrio;

— cefalea;

— insonnia;

— aggressività, irrequietezza, ansia, depressione, ecc.

I rilevamenti per questi parametri sono stati effettuati a tempi prestabiliti: in condizioni basali, al 7°, al 14°, al 21°, al 30° giorno di trattamento ed eventualmente oltre, a seconda del caso.

Quando presenti, sono stati valutati anche i seguenti indici:

— disturbi dell'apparato locomotore;

— disturbi della sensibilità superficiale e profonda;

— altri disturbi non previsti originariamente ed eventualmente presenti.

Non rientrando nella ricerca principale, i rilevamenti per questi indici sono stati limitati solo all'inizio e alla fine del trattamento.

La graduazione dell'entità del sintomo, nell'intento di unificare il più possibile i criteri seguiti dai singoli sperimentatori e per permettere l'elaborazione statistica dei dati desunti nel corso delle osservazioni, è stata rapportata alla seguente scala:

0 = sintomo assente;

1 = sintomo lieve;

2 = sintomo medio;

3 = sintomo di forte intensità.

E' stato inoltre attribuito a ciascun paziente, al fine di una valutazione della gravità del quadro sintomatologico considerato nel suo insieme, un « indice di gravità » riferibile alla media dei punteggi relativi a ogni singolo sintomo.

Infine per uno studio più completo delle condizioni cardiocircolatorie dei pazienti, sono stati considerati anche i dati relativi alla pressione arteriosa omerale e, quando possibile, quelli agli esami E.C.G., con rilevamenti fatti prima e dopo il trattamento.

Valutazione della tollerabilità

Particolare cura è stata posta da parte di tutti gli sperimentatori nel rilevare e segnalare sulle apposite schede ogni effetto collaterale verificatosi nel corso del trattamento, da mettersi in sicura o probabile relazione con quest'ultimo.

Sempre nell'ambito delle valutazioni della tollerabilità, si è proceduto, quando possibile, alla rilevazione, prima e dopo il trattamento, di tutta una serie di indagini laboratoristiche quali: emocromo, glicemia, azotemia, transaminasi, esame urine, ed eventualmente altre.

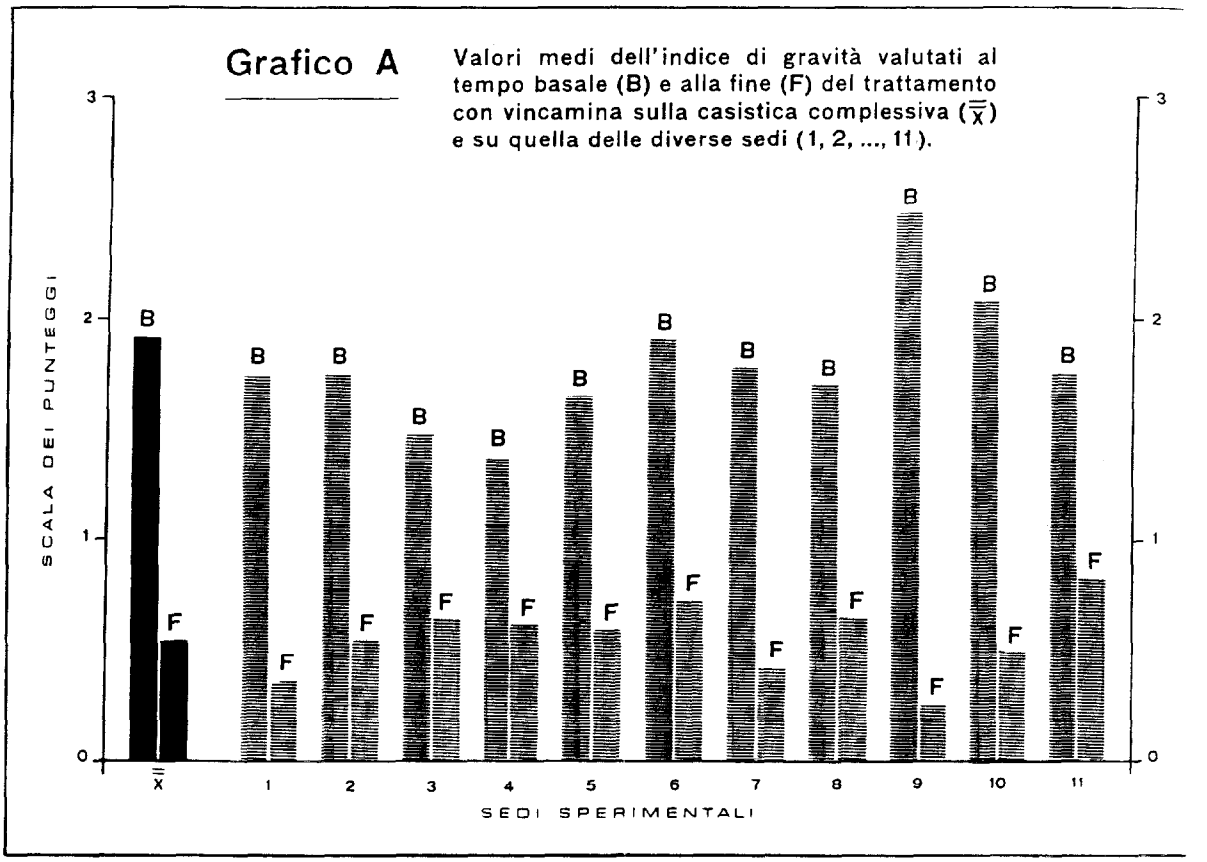
Risultati e analisi statistica

Il tipo di parametri prescelti, il criterio della loro valutazione ed i tempi di rilevamento sono stati descritti nel capitolo precedente.

Di seguito sono esposti i risultati ottenuti negli 828 pazienti oggetto dell'indagine: vengono prima riferite le risultanze dello studio dell'indice di gravità, seguite dall'analisi dei singoli « items » clinici.

Si ricorda che l'indice di gravità, valutato per ciascun paziente, è stato calcolato, ai diversi tempi di osservazione, come media degli « scores » assegnati in base all'intensità clinica dei sintomi presenti all'inizio della terapia.

Nel grafico A, per la casistica complessiva e per quella di ciascuna sede sperimentale, figurano gli istogrammi delle medie degli indici di gravità registrati al tempo di osservazione basale e alla fine del periodo di trattamento con vincamina; tali valori sono ripresi, con i relativi errori standard, anche nella prima parte della tabella 2. Nella seconda parte della stessa tabella sono riportati i risultati dell'analisi statistica (analisi della varianza secondo un modello « split-plot ») che ha consentito di valutare il grado di eterogeneità dei dati tra le diverse sedi (fonte di variazione « tra sedi »), l'entità della riduzione, a fine trattamento, dei punteggi di



gravità iniziali (fonte di variazione « tra tempi ») e l'andamento di tali punteggi nelle diverse sedi (fonte di variazione « interazione tempi × sedi »).

L'analisi precedente ha dato una misura statistica del grado di decremento dell'indice di gravità al termine del trattamento nei confronti della situazione iniziale. Si è quindi valutato anche il tipo di evoluzione di tale indice nell'ambito del periodo di terapia e per questo si sono utilizzati i rilievi programmati a diversi tempi di osservazione e comprendenti, oltre all'osservazione iniziale, quelle dopo 7, 14, 21 e 30 giorni; sono risultati 671 (81,04 %) i pazienti per i quali è stato possibile effettuare i cinque rilievi previsti.

Nei grafici B, C, D, E, F, G, H, I, L, M, N è descritta l'evoluzione degli indici di gravità nelle diverse sedi: ciascun punto, al corrispondente tempo di rilevamento, rappresenta, per ogni sede, il valore medio dell'indice; le curve interpolatrici sono state tracciate dopo aver calcolato le equazioni polinomiali di 1°, 2°, 3° o 4° grado, che meglio si adattavano al tipo di andamento dei punti sperimentali. Nel calcolo delle equazioni si è proceduto alla codifica dei dati di ascissa (×).

Nel grafico O è presentato un quadro complessivo dell'evoluzione dell'indice nelle varie sedi. Allo scopo di offrire una più chiara rappresentazione di assieme, è stato calcolato, per ciascuna sede, il termine lineare della regressione dei dati trasformati in $\log_{10}$ $(1 + y)$; le undici rette costruite dopo tale trasformazione risultano in tal modo visivamente comparabili tra loro forse meglio di quanto si sarebbe ottenuto raggruppando le curve interpolatrici studiate sede per sede.

Nel grafico figura anche la retta di regressione relativa alla casistica complessiva trattata per un mese od oltre (671 casi).

Nella tabella 3 sono riportate, per la casistica complessiva e per quella delle singole sedi, le medie degli indici di gravità ai tempi di osservazione progressivi.

TABELLA 2. — *Risultati e analisi dell'indice di gravità.*

	Medie (± errore standard)	
	Basale	Fine
Globale (n. 828 casi)	1,812 ± 0,016	0,547 ± 0,015
Sede 1 (n. 100 casi)	1,760 ± 0,024	0,375 ± 0,026
Sede 2 (n. 38 casi)	1,797 ± 0,066	0,559 ± 0,060
Sede 3 (n. 31 casi)	1,484 ± 0,072	0,666 ± 0,086
Sede 4 (n. 100 casi)	1,397 ± 0,044	0,636 ± 0,040
Sede 5 (n. 102 casi)	1,674 ± 0,027	0,603 ± 0,041
Sede 6 (n. 98 casi)	1,909 ± 0,033	0,732 ± 0,048
Sede 7 (n. 80 casi)	1,798 ± 0,067	0,446 ± 0,060
Sede 8 (n. 100 casi)	1,704 ± 0,039	0,654 ± 0,028
Sede 9 (n. 89 casi)	2,485 ± 0,035	0,255 ± 0,028
Sede 10 (n. 63 casi)	2,066 ± 0,054	0,495 ± 0,071
Sede 11 (n. 27 casi)	1,754 ± 0,075	0,827 ± 0,089

Analisi della varianza secondo il modello « split-plot »

Fonti di variazione	G.L.	Devianze	Varianze	F	P
Tra sedi	10	21,69	2,16	9,39	< 0,01
Errore 1	817	184,48	0,23		
Tra tempi	1	662,33	662,33	7359,22	< 0,01
Interazione tempi × sedi	10	67,31	6,73	74,78	< 0,01
Errore 2	817	81,57	0,09		
Totale	1655	1017,38			

Si è proceduto quindi ad un esame dettagliato dei singoli « items » che hanno contribuito a formare, nel loro complesso, l'indice di gravità di cui sopra. Per ciascun sintomo sono stati analizzati i rilievi registrati, sulla casistica complessiva, ai cinque tempi di osservazione; è stata quindi impiegata un'analisi della varianza ad un criterio di classificazione per un confronto complessivo dei risultati ai diversi tempi; dopo che tale analisi ha indicato, per tutti i parametri, l'esistenza di differenze altamente significative tra i vari tempi, si è operato un confronto binario, mediante il test di Scheffé, tra i dati iniziali e quelli ottenuti rispettivamente dopo 7, 14, 21 e 30 giorni.

Nella tabella 4 sono riportate le medie (± errore standard) dei punteggi attribuiti, per ciascun sintomo, ai diversi tempi, e i risultati dell'analisi statistica.

I disturbi motori ed i disturbi della sensibilità superficiale e profonda sono stati registrati al tempo basale e alla fine del trattamento.

Mediante un'analisi della varianza a una via è stata statisticamente valutata la differenza ai due tempi di osservazione.

I risultati delle analisi, con le medie ed errori standard dei valori iniziali e finali, sono riportati nella tabella 5.

TABELLA 3. — *Evoluzione degli indici di gravità dei pazienti trattati con vincamina.*

	Valori medi (± errore standard)				
	Basale	Dopo 7 giorni	Dopo 14 giorni	Dopo 21 giorni	Dopo 30 giorni
Casistica totale	1,801 ± 0,089	1,450 ± 0,135	1,070 ± 0,102	0,794 ± 0 065	0,562 ± 0,051
Sede 1	1,760 ± 0,024	1,576 ± 0,026	1,153 ± 0,030	0,827 ± 0,031	0,424 ± 0,028
Sede 2	1,823 ± 0,068	0,968 ± 0,095	0,738 ± 0,078	0,658 ± 0,071	0,581 ± 0,063
Sede 3	1,484 ± 0,072	0,888 ± 0,083	0,735 ± 0,085	0,683 ± 0,086	0,677 ± 0,086
Sede 4	1,391 ± 0,058	1,213 ± 0,057	0,928 ± 0,057	0,734 ± 0,050	0,658 ± 0,052
Sede 5	1,616 ± 0,035	1,277 ± 0,047	0,708 ± 0,043	0,496 ± 0,044	0,377 ± 0,040
Sede 6	1,906 ± 0,034	1,841 ± 0,032	1,516 ± 0,038	1,152 ± 0,045	0,755 ± 0,050
Sede 7	1,756 ± 0,193	1,043 ± 0,188	0,711 ± 0,201	0,505 ± 0,150	0,334 ± 0,106
Sede 8	1,704 ± 0,040	1,562 ± 0,043	1,211 ± 0,041	0,852 ± 0,035	0,656 ± 0,029
Sede 9	2,485 ± 0,036	2,395 ± 0,041	1,698 ± 0,038	0,977 ± 0,042	0,363 ± 0,046
Sede 10	2,066 ± 0,058	1,796 ± 0,070	1,194 ± 0,074	0,765 ± 0,071	0,526 ± 0,071
Sede 11	1,818 ± 0,095	1,390 ± 0,099	1,181 ± 0,088	1,088 ± 0,089	0,828 ± 0,093

TABELLA 4. — *Risultati e analisi dei singoli « items » (elaborazioni effettuate sui pazienti presentanti il sintomo all'inizio).*

	Medie (± errore standard)				
	Basale	Dopo 7 giorni	Dopo 14 giorni	Dopo 21 giorni	Dopo 30 giorni
Disturbi della memoria, dell'attenzione, del potere di concentrazione (n. 613 casi)	2,005 ± 0,028	1,806 ± 0,031 **)	1,398 ± 0,033 **)	1,005 ± 0,029 **)	0,711 ± 0,027 **)
Acufeni (n. 499 casi)	1,813 ± 0,036	1,599 ± 0,040 **)	1,194 ± 0,038 **)	0,829 ± 0,032 **)	0,547 ± 0,031 **)
Fosfeni (n. 417 casi)	1,738 ± 0,033	1,525 ± 0,035 **)	1,148 ± 0,034 **)	0,774 ± 0,031 **)	0,486 ± 0,031 **)
Vertigini, disturbi equilibrio (n. 592 casi)	1,984 ± 0,030	1,717 ± 0,033 **)	1,241 ± 0,031 **)	0,895 ± 0,028 **)	0,554 ± 0,020 **)
Cefalea (n. 527 casi)	1,905 ± 0,031	1,673 ± 0,031 **)	1,136 ± 0,031 **)	0,829 ± 0,026 **)	0,459 ± 0,024 **)
Insonnia (n. 522 casi)	1,699 ± 0,031	1,500 ± 0,033 **)	1,078 ± 0,032 **)	0,743 ± 0,027 **)	0,486 ± 0,025 **)
Aggressività, irrequietezza, ansia, depressione, ecc. (n. 539 casi)	1,805 ± 0,030	1,571 ± 0,033 **)	1,202 ± 0,031 **)	0,855 ± 0,029 **)	0,556 ± 0,027 **)

**) Differenze altamente significative rispetto al tempo basale (test di Scheffé).

TABELLA 5. — *Risultati e analisi degli indici « disturbi motori » e « disturbi della sensibilità » (elaborazioni effettuate sui pazienti presentanti il sintomo all'inizio).*

	Medie (± errore standard)		Analisi della varianza a una via	P
	Basale	Fine		
Disturbi motori (n. 273 casi)	1,557 ± 0,044	0,597 ± 0,045	F = 233,38 (1,544 g.l.)	< 0,01
Disturbi della sensibilità superficiale e profonda (n. 229 casi)	1,629 ± 0,049	0,559 ± 0,043	F = 271,77 (1,456 g.l.)	< 0,01

Grafico B
Sede 1

Evoluzione dell'indice di gravità

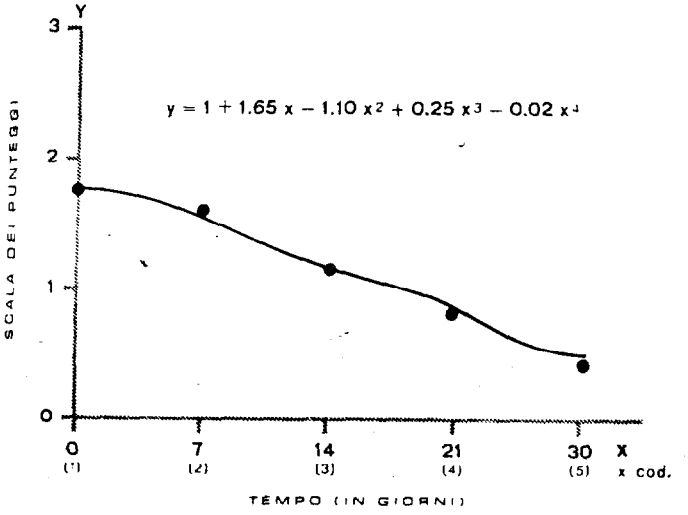


Grafico C
Sede 2

Evoluzione dell'indice di gravità

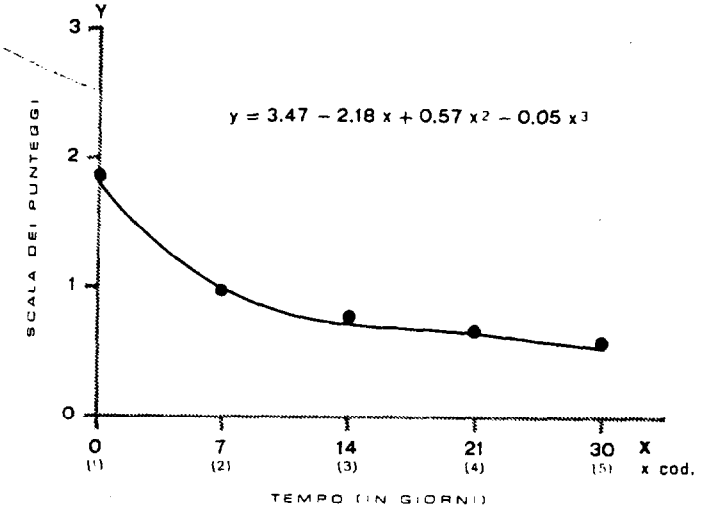


Grafico D
Sede 3

Evoluzione dell'indice di gravità

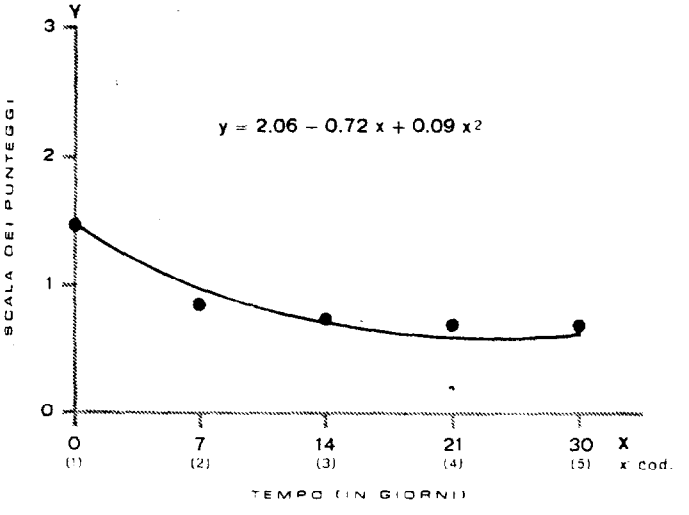


Grafico H
Sede 7

Evoluzione dell'indice di gravità

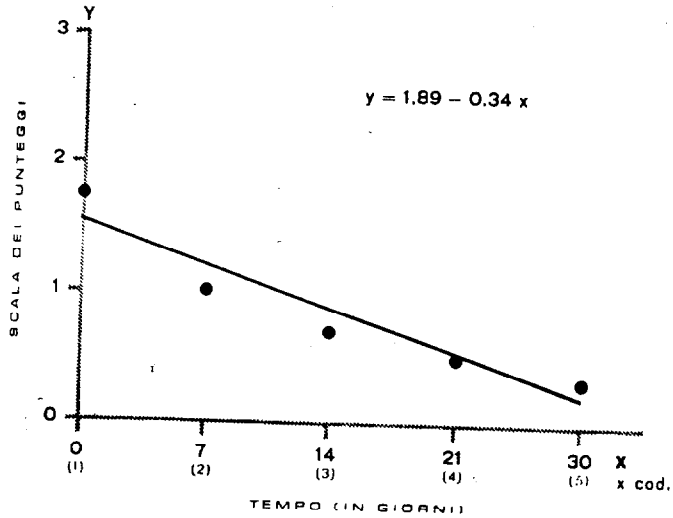


Grafico I
Sede 8

Evoluzione dell'indice di gravità

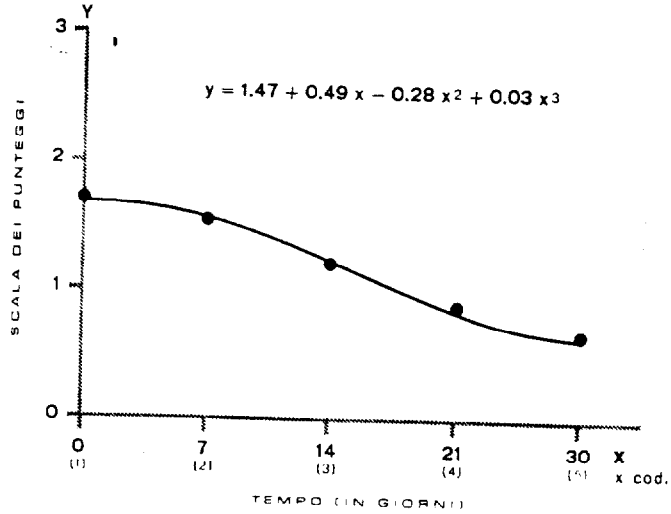


Grafico L
Sede 9

Evoluzione dell'indice di gravità

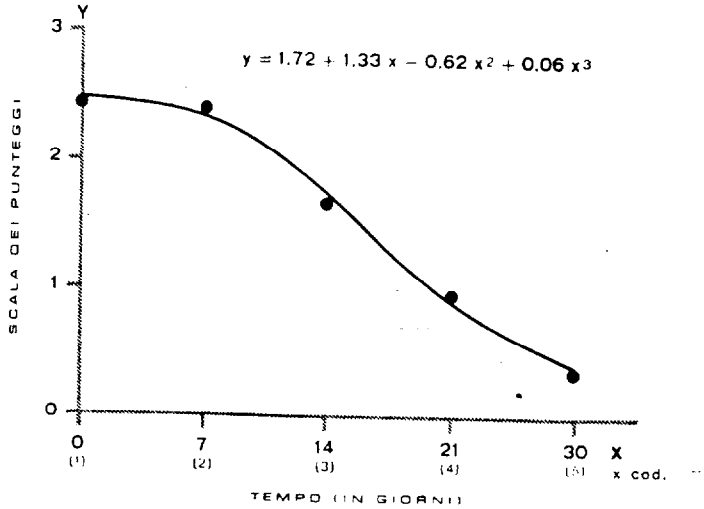


Grafico M
Sede 10

Evoluzione dell'indice di gravità

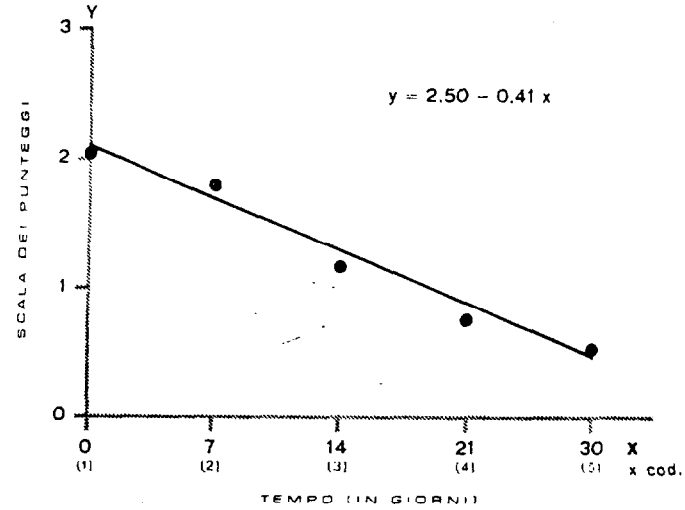
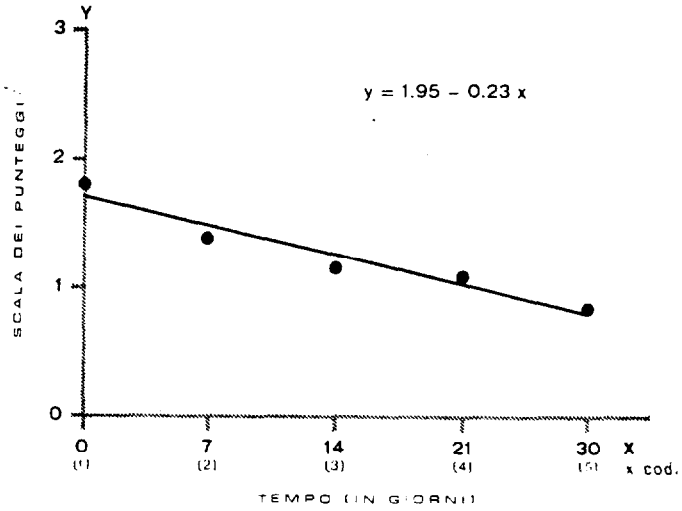


Grafico N
Sede 11

Evoluzione dell'indice di gravità



Discussione

I risultati conseguiti nel corso di tutta la ricerca sono stati nel loro complesso giudicati dai vari sperimentatori:

— ottimi o buoni, quando la risposta al trattamento è stata decisamente positiva, con netto miglioramento o remissione della sintomatologia considerata;

— discreti, quando il miglioramento, pur presente, è stato di più lieve entità;

— insufficienti o nulli, quando la ripresa delle condizioni del paziente è stata nulla o per lo meno non sufficientemente apprezzabile.

I dati ottenuti a tale riguardo sono riferiti nella tabella 6.

Da una sua lettura si può dedurre come i risultati utili (tra ottimi, buoni e discreti) abbiano raggiunto una percentuale del 92,40 % dei pazienti trattati: questo dato sta indubbiamente a dimostrare come la terapia con vincamina abbia influenzato positivamente, nella grande maggioranza dei casi, la sintomatologia clinica oggetto della ricerca.

Tale giudizio clinico trova una ulteriore conferma nei risultati ottenuti dallo studio dell'« indice di gravità » (vedi tab. 2): come si può osservare tale indice è passato da un valore medio iniziale di 1,812 ad uno medio

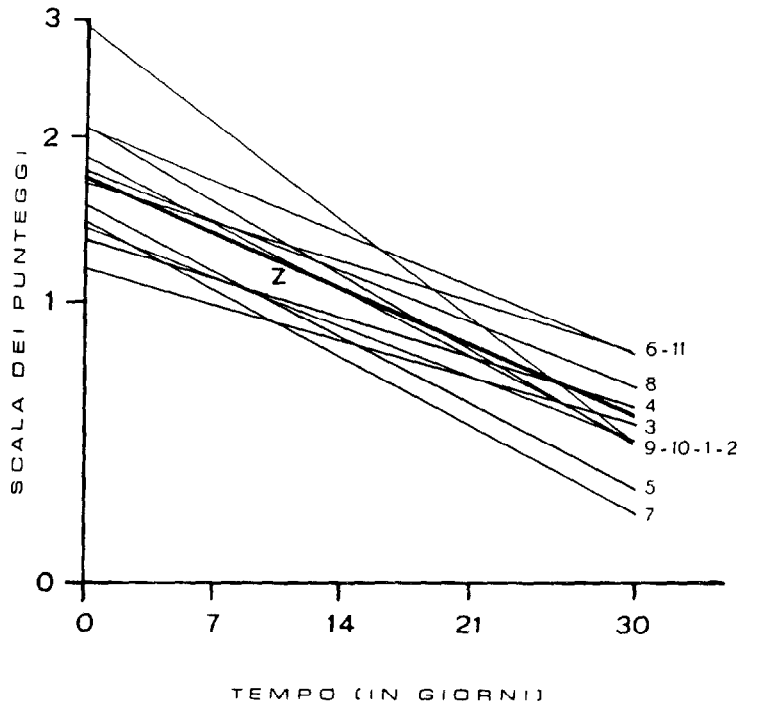


Grafico C

Evoluzione dell'indice di gravità nelle undici sedi (1, ..., 11). Le rette costruite per una visione comparativa di assieme, sono state ricavate dopo trasformazione di tutti i dati in $\log_{10}(1+y)$; la retta Z è l'interpolatrice relativa alla casistica totale (671 casi). La scala delle ordinate è semilogaritmica.

finale di 0,547, con una riduzione percentuale media del 69,81 %.

Tale riduzione, statisticamente altamente significativa, indica come il risultato conseguito sia espressione della reale efficacia terapeutica del trattamento e non sia legato al caso o a fluttuazioni spontanee della sintomatologia.

Motivo di ulteriore interesse costituisce poi la valutazione dell'andamento, sede per sede, di tale indice (vedi grafico A).

L'analisi statistica relativa, riportata nella tabella 2, dimostra una differenza statisticamente significativa tra le varie sedi.

Tale significatività può interpretarsi come dovuta a una certa disomogeneità di base di tutta la casistica, dipendente dalla diversa gravità iniziale dei quadri sintomatologici e dal differente tipo di malati (i vari centri comprendevano sedi di medicina generale e reparti geriatrici o di lungodegenti).

La diversa gravità delle condizioni di ricovero, tuttavia, non influisce sui risultati dell'analisi statistica: al contrario, essa rientrava nei presupposti della ricerca che si proponeva di prendere in considerazione un numeroso campione, il più rappresentativo possibile della reale popolazione di pazienti affetti da piccola insufficienza cerebro-vascolare (che, proprio per l'andamento ciclico della

TABELLA 6. — *Giudizio clinico sull'attività del farmaco, globale e per sede, al termine del trattamento.*

	Ottimi o buoni	Discreti	Insufficienti o nulli
Casistica globale	58,82 %	33,58 %	7,60 %
Sede 1	53,00 %	41,00 %	6,00 %
Sede 2	65,79 %	31,58 %	2,63 %
Sede 3	45,16 %	35,48 %	19,36 %
Sede 4	46,00 %	36,00 %	18,00 %
Sede 5	64,71 %	33,33 %	1,96 %
Sede 6	72,45 %	24,49 %	3,06 %
Sede 7	50,00 %	38,75 %	11,25 %
Sede 8	45,00 %	48,00 %	7,00 %
Sede 9	83,15 %	14,60 %	2,25 %
Sede 10	68,25 %	23,81 %	7,94 %
Sede 11	37,04 %	48,15 %	14,81 %

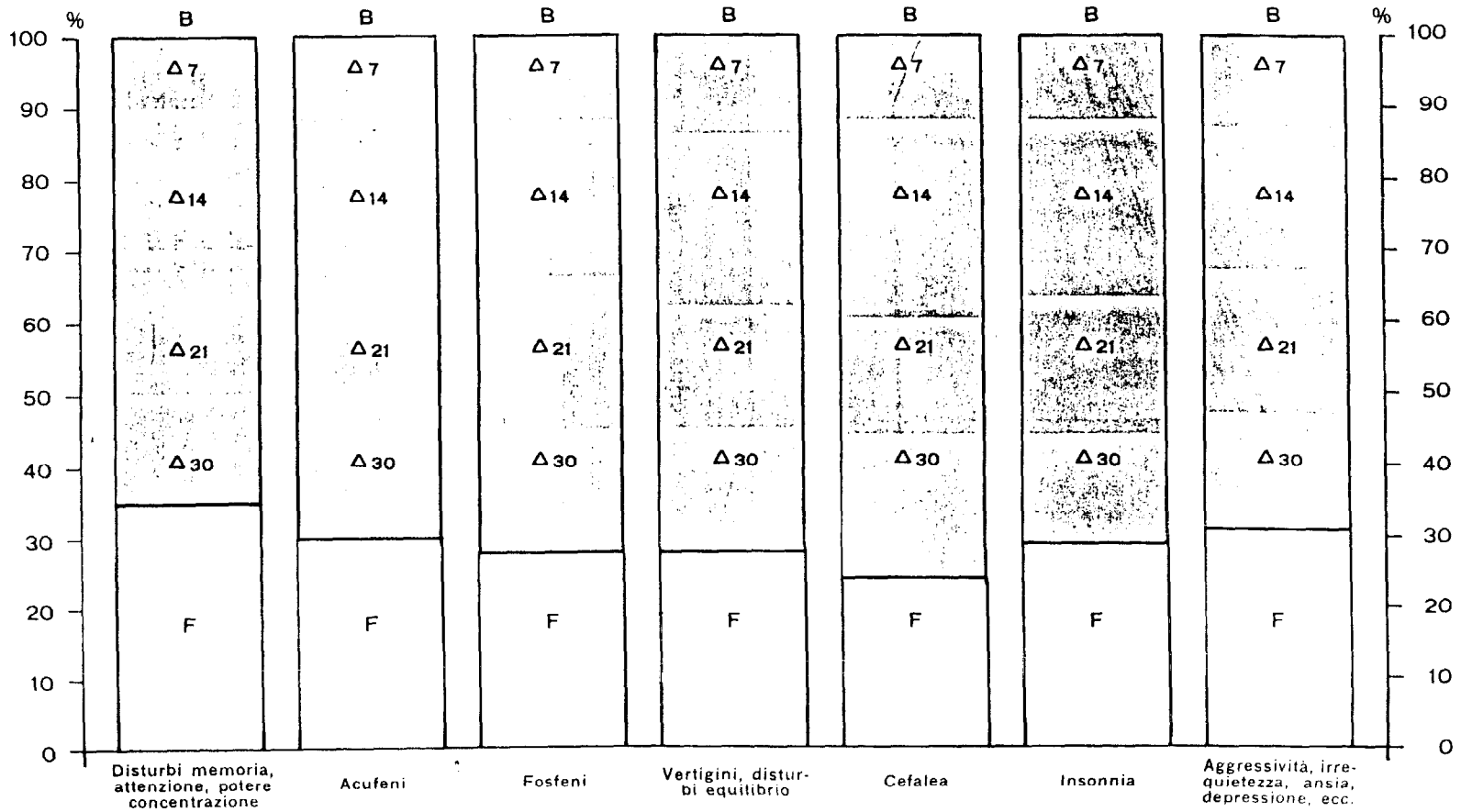
Grafico P

Evoluzione della gravità della sintomatologia nella casistica complessiva. Sono considerati, per ciascun sintomo, i punteggi medi di gravità ai tempi progressivi d'osservazione (7, 14, 21 e 30 gg. di trattamento con vincamina) rapportati percentualmente al valore medio del rilievo basale.

B = punteggio medio di gravità al tempo basale posto uguale a 100

F = punteggio medio a fine trattamento espresso % rispetto a B

Δ_7 = differenza % dopo 7 gg. rispetto a B
Δ_{14} = differenza % dopo 14 gg. rispetto a B
Δ_{21} = differenza % dopo 21 gg. rispetto a B
Δ_{30} = differenza % dopo 30 gg. rispetto a B



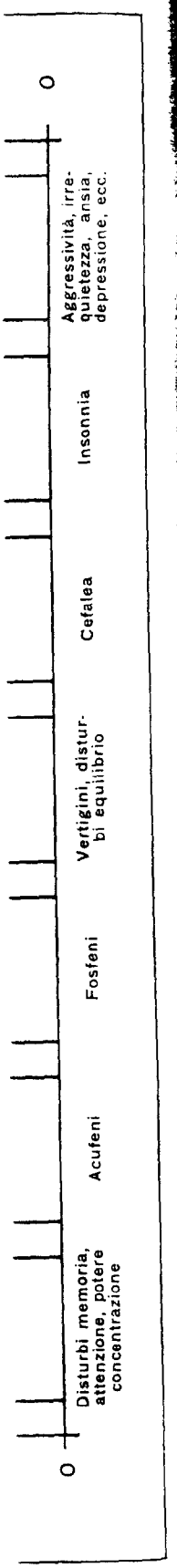


TABELLA 7. — *Numero casi con sintomo presente all'inizio e frequenze assolute e percentuali di casi normalizzati, migliorati, invariati e peggiorati al termine del trattamento.*

Sintomi	Presenti all'inizio	Normalizzati	Migliorati	Invariati	Peggiorati
Disturbi della memoria	751 (100 %)	309 (41,15 %)	369 (49,13 %)	73 (9,72 %)	0
Acufeni	594 (100 %)	322 (54,21 %)	161 (27,10 %)	111 (18,69 %)	0
Fosfeni	483 (100 %)	289 (59,83 %)	99 (20,50 %)	94 (19,46 %)	1 (0,21 %)
Vertigini	726 (100 %)	387 (53,31 %)	253 (34,85 %)	86 (11,84 %)	0
Cefalea	621 (100 %)	384 (61,84 %)	171 (27,54 %)	65 (10,46 %)	1 (0,16 %)
Insonnia	629 (100 %)	367 (58,35 %)	151 (24,01 %)	110 (17,48 %)	1 (0,16 %)
Aggressività	648 (100 %)	325 (50,16 %)	220 (33,95 %)	100 (15,43 %)	3 (0,46 %)

malattia, presenta quadri di gravità anche notevolmente differenti).

Comunque, indipendentemente dalla gravità della sintomatologia iniziale, tutte le sedi mostrano un andamento orientato nello stesso senso, anche se le dimensioni di tale orientamento, proprio per il diverso quadro che ha condizionato il ricovero, sono differenti fra le diverse sedi (interazione statisticamente significativa), come si può osservare dal grafico O che riporta in scala logaritmica l'andamento della sintomatologia per ogni sede.

Inoltre l'andamento della regressione dell'« indice di gravità » sede per sede, è stato espresso con equazioni di 1°, 2°, 3° o 4° grado, come risulta dai grafici B, C, D, E, F, G, H, I, L, M, N. Il comportamento delle curve ben si accorda con l'andamento dei fenomeni biologici: ad una prima fase di remissione della sintomatologia ne segue una di consolidamento cui succedono nuovi miglioramenti legati al proseguimento della terapia.

L'importanza di protrarre il trattamento con la vincamina è da rapportare al fatto che essa agisce non solo con un meccanismo emodinamico, ma anche a livello dei processi biochimico-metabolici dell'encefalo, confermando le osservazioni di quegli Autori [19, 31] che avevano segnalato un intervento della vincamina sulle concentrazioni encefaliche di noradrenalina e di serotonina.

Per quanto riguarda in particolare le modificazioni dei singoli sintomi indagati, l'indagine biometrica ha sempre evidenziato differenze significative a tutti i tempi di rilevamento previsti, come indicato dalla tabella 4.

L'andamento di ogni sintomo ai vari tempi di osservazione risulta dal grafico P.

Questo sta a dimostrare che gli effetti terapeutici della vincamina si sono rivelati subito evidenti sin dai primi giorni di trattamento e si sono dimostrati in seguito costanti, graduali e progressivi.

Sempre in merito all'andamento dei singoli sintomi, la tabella 7 ci mostra un quadro d'assieme finale delle percentuali di situazioni normalizzate, migliorate, invariate e peggiorate.

Le percentuali di normalizzazione più elevate, come si può ben vedere, riguardano le cefalee (61,84 % di casi) seguite da quelle relative ai fosfeni, all'insonnia, agli acufeni e alle vertigini. Quelle minori si riferiscono invece ai disturbi della memoria, disturbi tra i più complessi tra quelli facenti parte del quadro sintomatologico dell'insufficienza cerebro-vascolare e per i quali una normalizzazione nel 41 % dei casi, alla fine di un trattamento di durata pur sempre relativa, può essere senz'altro giudicata positiva.

Tollerabilità

Il grande numero di casi osservati ha offerto un importante contributo conoscitivo per una più approfondita valutazione sia della frequenza di eventuali reazioni collaterali sia della comparsa di possibili effetti di più rara osservazione.

Trattandosi di una ricerca policentrica dislocata in ben 11 sedi diverse, si è ritenuto necessario uniformare il più possibile i criteri di giudizio della tollerabilità al farmaco espressi su casistiche e in ambienti ospedalieri anche notevolmente diversi l'uno dall'altro.

In conseguenza le valutazioni globali singole, caso per caso, e presso le varie sedi, sono state semplificate al massimo *), richiedendo ai vari sperimentatori un giudizio schematico ma univoco, così articolato:

— tollerabilità perfetta, quando non si fossero osservati disturbi di alcun genere, comunque rapportabili alla somministrazione del farmaco allo studio;

— tollerabilità discreta, quando si fossero verificati disturbi, o altri « side effects », di modesta entità, per i quali non era possibile escludere un rapporto causale col trattamento instaurato;

— tollerabilità dubbia o cattiva, quando la somministrazione del farmaco avesse dato luogo a disturbi di entità maggiore o tale da portare anche alla sospensione del trattamento.

Riportiamo nella tabella 8 il numero dei casi, e relative percentuali, dei giudizi emessi seguendo i criteri di cui sopra.

TABELLA 8.

Tollerabilita	N. casi	Percentuali
Perfetta	769	92,88 %
Discreta	47	5,67 %
Dubbia o cattiva	12	1,45 %

I dati sopra riportati confermano i concetti più volte ribaditi dalla letteratura sulla buona tollerabilità della vincamina.

In concreto si può osservare come gli effetti secondari siano stati segnalati in una assai scarsa percentuale di casi: questi si sono manifestati per lo più con disturbi a livello dell'apparato digerente oltre a qualche disturbo del sonno.

Su tutta la casistica considerata i casi che hanno dovuto interrompere il trattamento ammontano in tutto a cinque: tre per disturbi gastrici e due per la comparsa di reazioni cutanee di tipo allergico.

Va rilevato, secondo quanto segnalato da vari sperimentatori, che non sempre è stato possibile porre un sicuro rapporto di causa ed effetto col trattamento, anche per la ragione che in molti pazienti erano coesistenti forme morbose di natura tale da poter interferire con gli effetti sopra segnalati.

Lo studio relativo alla tollerabilità è stato poi completato con una serie di esami ematochimici, eseguiti in condizioni basali e al termine del trattamento.

I risultati relativi, riferiti nella tabella 9, dimostrano come le costanti ematochimiche considerate non abbiano subito variazioni importanti nel corso di tutto il periodo di trattamento.

TABELLA 9. — *Indici di tollerabilità.*

	Medie (± errore standard)	
	Basale	Fine
Eritrociti ($10^3/mm^3$) (n. 774 casi)	4411,139 ± 16,307	4381,868 ± 15,077
Leucociti (mm^3) (n. 774 casi)	7056,304 ± 66,254	6882,739 ± 47,831
Emoglobina (%) (n. 755 casi)	83,494 ± 0,321	83,439 ± 0,303
Glicemia (mg %) (n. 772 casi)	99,417 ± 1,228	91,836 ± 0,702
Azotemia (mg %) (n. 772 casi)	34,652 ± 0,522	32,452 ± 0,370
Transaminasi SGOT (mU/ml) (n. 719 casi)	12,115 ± 0 226	11,669 ± 0,204
Transaminasi SGPT (mU/ml) (n. 719 casi)	10,053 ± 0,205	9,701 ± 0,170

Un cenno a parte merita il comportamento della pressione arteriosa nei pazienti sottoposti al trattamento.

Questa ha dimostrato, nel corso delle prove, una certa tendenza alla normalizzazione, in specie negli ipertesi: infatti da valori medi iniziali di 165 mm/Hg di massima e 91 mm/Hg di minima si passa a valori terminali rispettivamente di 155 e 86 mm/Hg.

Ciò non farebbe che confermare quanto già messo in evidenza sull'argomento da vari Autori.

Il particolare più significativo a questo riguardo consiste però nel fatto che non sono state segnalate brusche oscillazioni della pressione arteriosa, la qual cosa sta a dimostrare come l'equilibrio emodinamico del letto vascolare cerebrale, già compromesso di per se stesso nel tipo di pazienti considerati,

*) Ovviamente sulle schede cliniche (v. figura 1) sono stati registrati, quando presenti, tutti gli eventuali effetti collaterali verificatisi nel corso del trattamento.