Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Lauren Quinn JD
Director
Regulatory Affairs
973.660.6167
quinnL4@wyeth.com

Wyeth

November 17, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

RE: OTC Monograph for Nasal Decongestant Drug Products
Docket 76N-052N

Dear Sir or Madam:

Reference is made to our November 16, 2006 submission to Docket 76N-052N. This letter is to confirm that all attachments to that submission are releasable.

Sincerely,

Lauren Quinn

WYETH CONSUMER HEALTHCARE
Lauren Quinn, JD
Director, Regulatory Affairs

MAY 30 1973

A. H. ROBINS COMPANY

1407 Cummings Drive

Richmond, Virginia 23220

PROTOCOL EVALUATION REPORT

DIMETAPP ELIXIR

(AHR-G1-A) Protocol 01

Investigator: Burton Marcus Cohen, M.D.
230 W. Jersey Street
Elizabeth, New Jersey 07202

May 10, 1973

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044733

PROTOCOL EVALUATION REPORT

Dimetapp Elixir (AHR-G1-A) Protocol 01

Prepared by:

Dorothy K. Ervin, B.S.	Manager, Data Management and Analysi Section
Lester W. Preston, Jr., Ph.D.	Director, Scientific Information Department

The above report has been reviewed and approved by the undersigned.

5/10/73
Date

R. William Dent, M.D.
Associate Physician, Medical Service

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044734

INVESTIGATOR

Investigator:	Cohen, Burton Marcus, M.D.
Address:	230 W. Jersey Street Elizabeth, New Jersey 07202
Academic Affiliati	Associate Clinical Professor of Medicine The New Jersey College of Medicine
Type of Practice:	Internal Medicine
Study Number:	0101
Date Initiated:	05/69
Study Status:	Complete
Status Date:	02/71
Patients Reported:	48

AHP2-REG-004-0044735

TABLE OF CONTENTS

INVESTIGATOR. i

0. SUMMARY 1

1. STUDY PROTOCOL. 11

1.1 Protocol Description 11

1.2 Protocol Deviations. 15

2. INVESTIGATOR INFORMATION. 16

3. DRUG/ASSAY INFORMATION. 29

4. SPECIAL FINDINGS. 30

5. EFFECTIVENESS FINDINGS. . . . . (NA)*

6. SAFETY FINDINGS 60

7. OVERALL DISCUSSION AND CONCLUSIONS. 66

APPENDICES. 67

A1. PROTOCOL 68

A4. SPECIAL FINDINGS 81

A6. SAFETY FINDINGS. 164

* (NA) Not Applicable

AHP2-REG-004-0044736

0. SUMMARY

AHP2-REG-004-0044737

0. SUMMARY

This well controlled clinical trial was conducted to compare the effects of Dimetapp Elixir with those of its components on nasal airway resistances and on nasal mucosal characteristics.

48 subjects were randomly assigned to one of four treatment groups. Single doses of test medication were administered as follows:

1. 24 subjects received 10 cc Dimetapp Elixir (8 mg brompheniramine, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride).
2. 8 subjects received 10 cc Neosynephrine Elixir (10 mg phenylephrine hydrochloride).
3. 8 subjects received 2.5 cc Propadrine Elixir (10 mg phenylpropanolamine).
4. 8 subjects received 20 cc Dimetane Elixir (8 mg brompheniramine maleate)

In order to preserve blindness, test medications were administered by a disinterested third party since the test medications were not identical in appearance and concentration.

Measurements of nasal inspiratory and expiratory resistances and subjective evaluations of nasal mucosal characteristics (viz. Nasal Serous Secretions, Nasal Mucosal Congestion, Nasal Mucosal Hyperemia, and Ease of Nasal Breathing) were made pre-drug and every 30 minutes post-drug for 4.5 hours. At the end of 4 hours (*i.e.* 240 minutes) post-drug, each subject received Afrin Nasal Spray.

Analyses of covariance were performed on the measurements of nasal inspiratory and expiratory resistances. The results of these analyses may be found in Figures 0-1 and 0-2. As shown, the effects of Dimetapp on both nasal inspiratory and expiratory resistances are consistently better than those of any of its components; in fact, many of the differences observed are statistically significant.

Analyses of variance were performed on the ratings of the nasal mucosal characteristics. Prior to these analyses, a covariance-like procedure was utilized, and the resultant variables were transformed to ridits. Results of these analyses may be found in Figures 0-3 through 0-6. These results are consistent with those for the nasal

AHP2-REG-004-0044738

airway resistances - *i.e.* Dimetapp is consistently better than any of its components, and many of the differences observed are statistically significant.

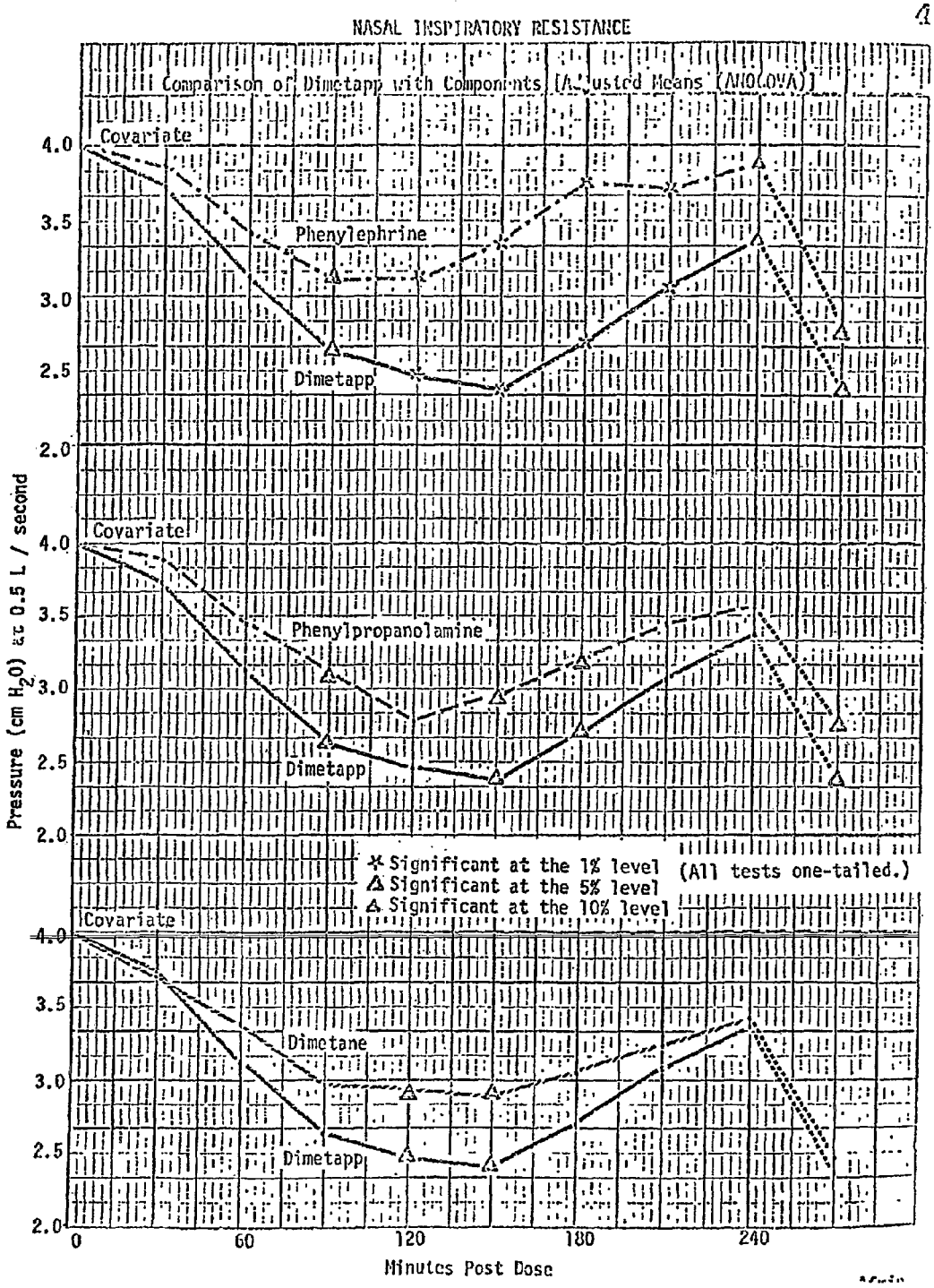
A more detailed discussion of the analyses performed on these data may be found in Section 4 of this report.

As anticipated, few adverse effects were observed, and none of those reported are considered to be significant.

AHP2-REG-004-0044739

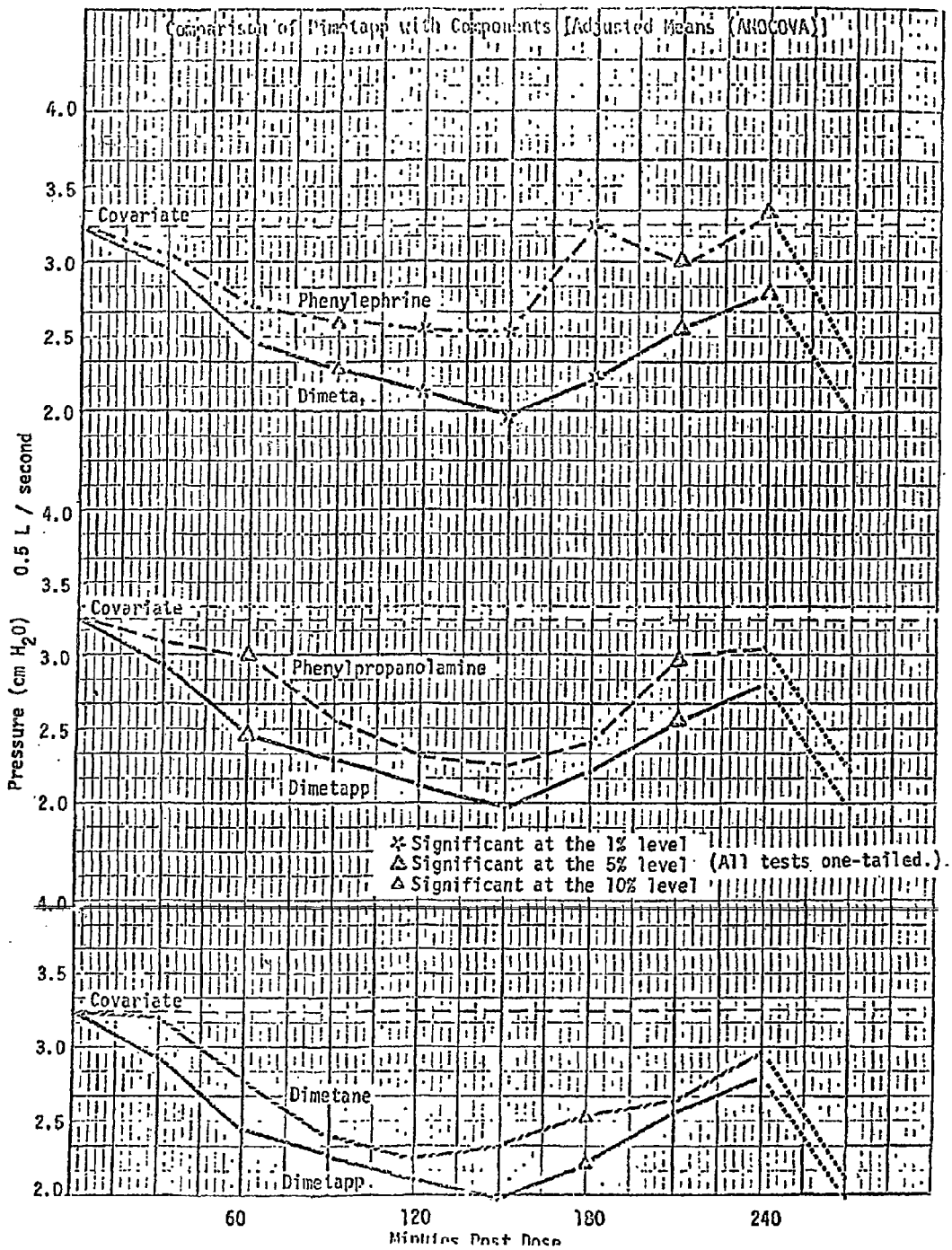
Nasal Inspiratory and Expiratory Resistances

AHP2-REG-004-0044740



AHP2-REG-004-0044741

NASAL EXPIRATORY RESISTANCE



AHP2-REG-004-0044742

G

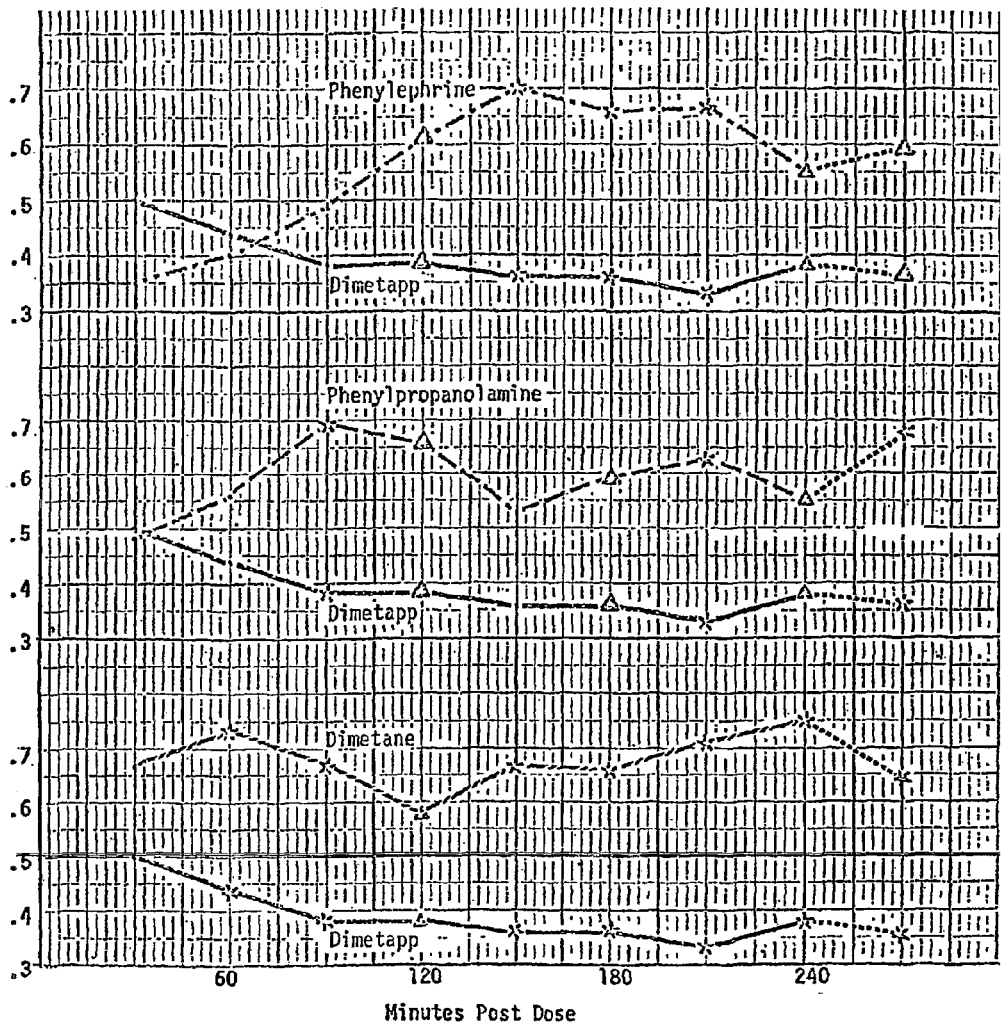
Nasal Mucosal Characteristics

AHP2-REG-004-0044743

Figure 0-3

NASAL SEROUS SECRETIONS

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



✕ Significant at the 1% level
▲ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level.

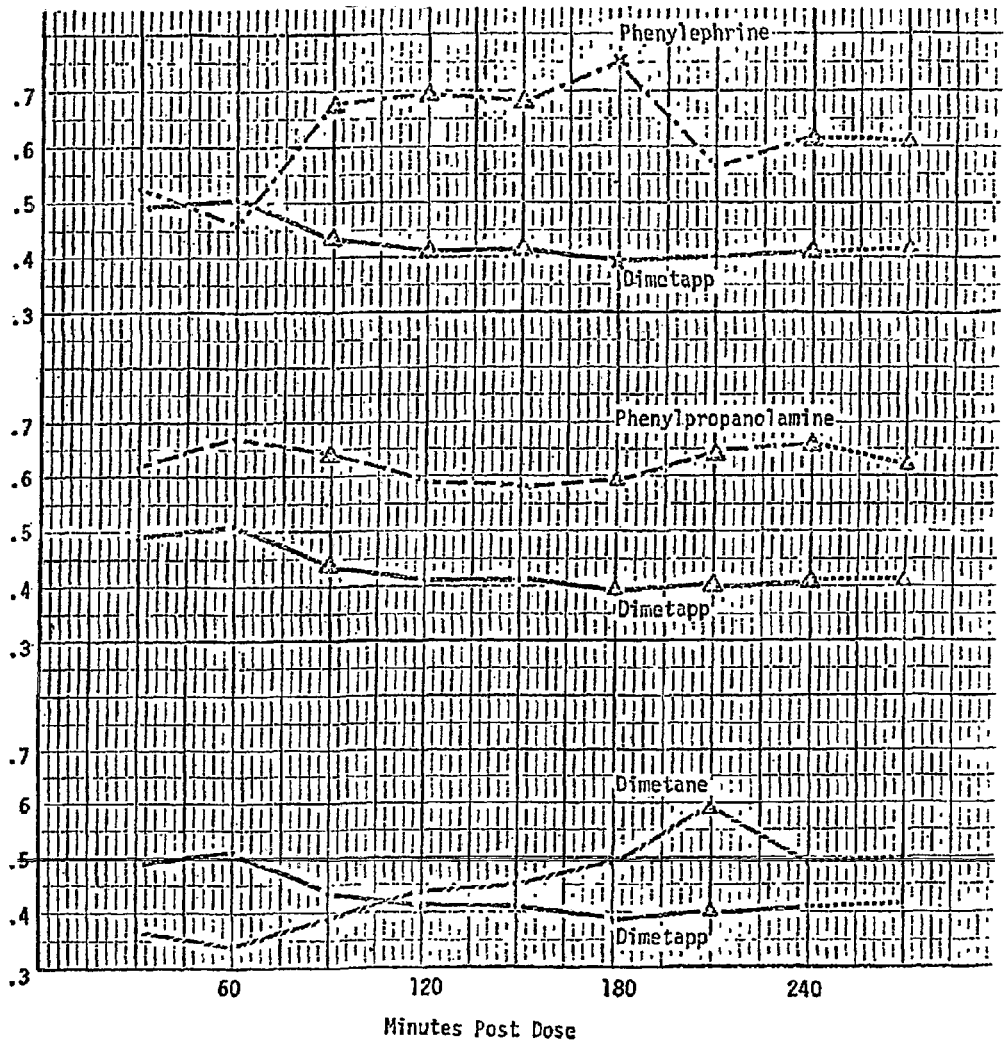
····· Afrin

AHP2-REG-004-0044744

Figure 0-4

NASAL MUCOSAL CONGESTION

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



☆ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level

..... Al

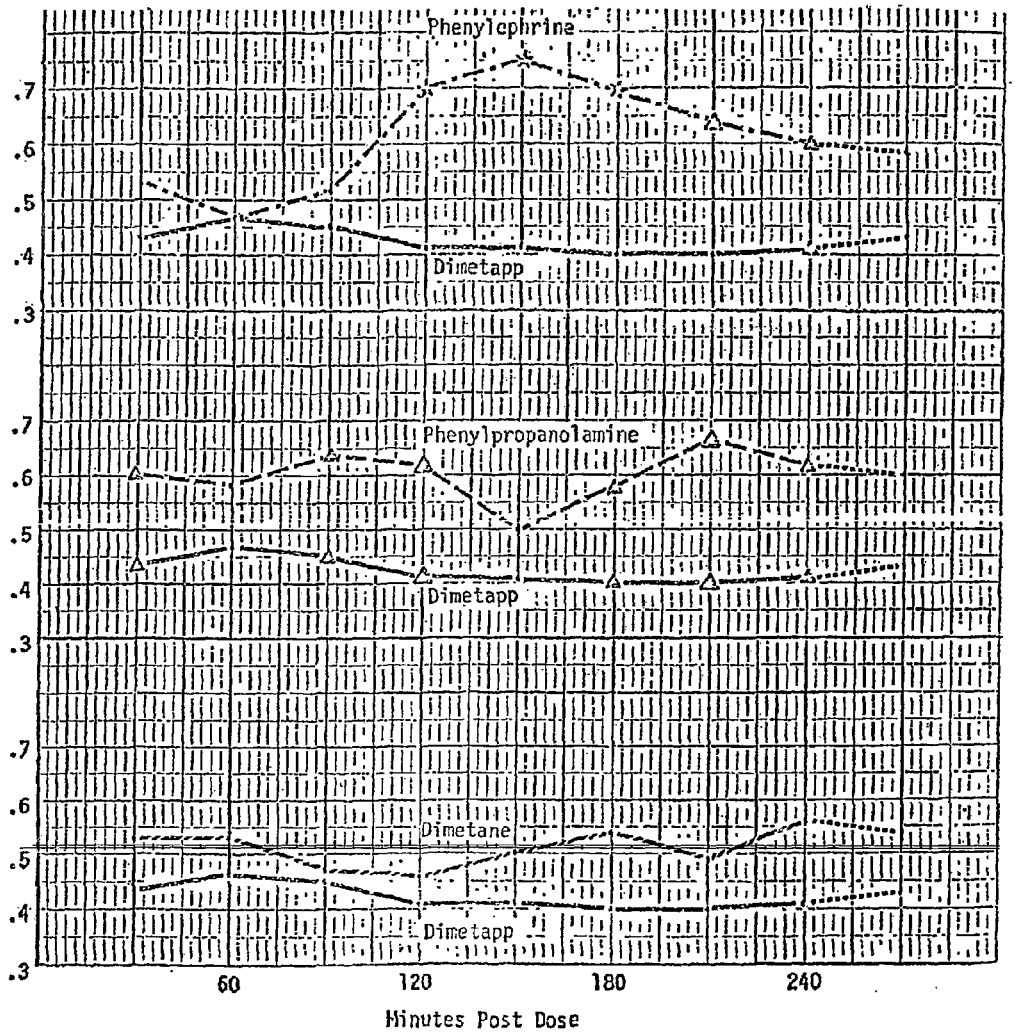
AHP2-REG-004-0044745

Figure 0-5

9

NASAL MUCOSAL WATERING

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



☆ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level

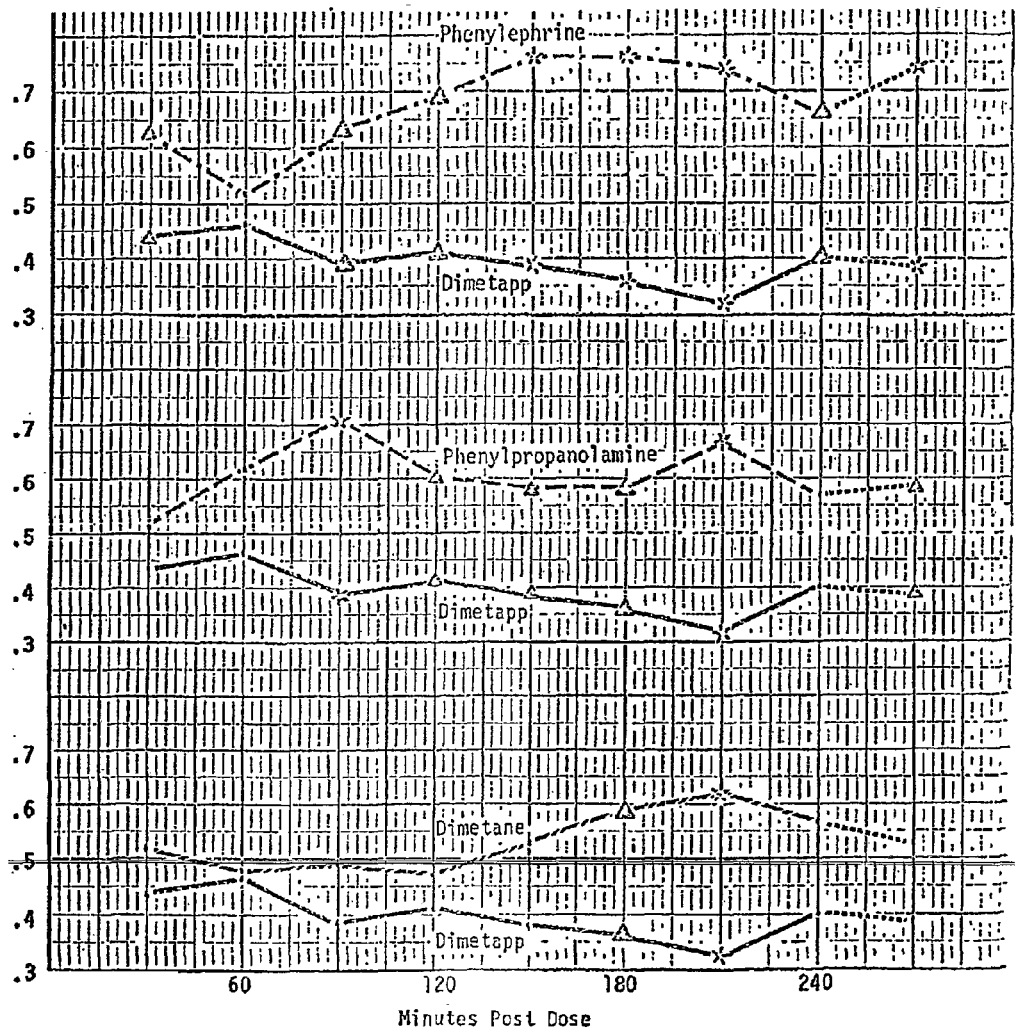
..... Af

AHP2-REG-004-0044746

Figure 0-6

EASE OF NASAL BREATHING

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



✱ Significant at the 1% level
△ Significant at the 5% level
△ Significant at the 10% level
(All tests one-tailed.)

..... Afrin

AHP2-REG-004-0044747

1. Study Protocol

AHP2-REG-004-0044748

1. STUDY PROTOCOL

1.1 PROTOCOL DESCRIPTION

1.1.1 Objective

To compare the effects of single doses of Dimetapp Elixir with each of its components on nasal airway resistance in patients with upper respiratory infections.

1.1.2 Study Design

This is a single investigator well controlled special study in which each of the patients with upper respiratory infections received a single dose of Dimetapp Elixir (24 patients) or one of its three components (8 patients/component) on a single test day; measurements of nasal airway resistance and subjective evaluations of nasal mucosal characteristics were made every 30 minutes after drug administration for 4.5 hours.

1.1.3 Patient Description

A. Selection Criteria

1. Treated Condition(s) and Diagnostic Criteria

   Nasal congestion due to upper respiratory infections whose duration was not less than 24 hours and not more than 72 hours at time of test day.

2. Prior Treatment Criteria

   48 hours off all drugs having the same general pharmacological actions as the study medication.

3. Safety Exclusion Criteria

   a. Chronic pulmonary disease

   b. Allergic rhinitis

   c. Pregnancy

4. Miscellaneous Criteria

   a. Adults

   b. Males and females

   c. Outpatients (office)

   d. Willingness to participate in a one day study.

AHP2-REG-004-0044749

B. The patients were numbered serially as they entered the study and were assigned to one of the study medications on the basis of a randomization schedule (see Appendix A4.3) prepared by the Biometry Unit, A. H. Robins Company.

1.1.4 Treatment Groups

A. Test Groups

1. Dimetapp Elixir containing 4 mg of brompheniramine maleate, 5 mg of phenylephrine hydrochloride, and 5 mg of phenylpropanolamine hydrochloride per 5 cc.

B. Control Groups

1. Dimetane Elixir containing 2 mg of brompheniramine maleate per 5 cc.

2. Neosynephrine Elixir containing 1 mg of phenylephrine hydrochloride per 1 cc.

3. Propadrine Elixir containing 4 mg of phenylpropanolamine hydrochloride per 1 cc.

C. Dosage Schedules

Using the Randomization Schedule in Appendix A4.3 each patient received single doses of test medication on the morning of the test day according to the following schedules:

Treatment Group 1: 10 cc of Dimetapp Elixir (8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride).

Treatment Group 2: 20 cc of Dimetane Elixir (8 mg brompheniramine maleate).

Treatment Group 3: 10 cc of Neosynephrine Elixir (10 mg phenylephrine hydrochloride).

Treatment Group 4: 2.5 cc of Propadrine Elixir (10 mg phenylpropanolamine hydrochloride).

Since the test medications were not identical in appearance they were administered by a disinterested third party; hence, the investigator and the technician making the measurements and assessments were "blind" to the test medication received by each subject.

At four hours (240 minutes) after dosing, each patient received Afrin (oxymetazoline hydrochloride) nasal solution.

AHP2-REG-004-0044750

C. Concomitant Treatments

1. Excluded

Nasal decongestants (oral and topical)

2. Included

Any medications and/or treatments needed for concurrent conditons were permitted but were to be recorded on data sheets.

1.1.5 Assessment of Special Findings

At "0 hour" and at 30, 60, 90, 120, 180, 240 and 270 minutes after test medication was administered, the following assessments were made:

A. Nasal Airway Resistance

Using the Respiron both nasal inspiratory and expiratory resistances were measured. The results were reported as pressure (cm H_2O) at 0.5 5/sec.

See Appendix A5.3 for the following reference on Respiron methodology.

Cohen, Burton M., "Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders." *Respiration* 26:35-46, 1969.

B. Characteristics of Nasal Mucosa

Evaluations were made of the following:

1. Nasal mucosal congestion

2. Nasal mucosal hyperemia

3. Nasal secretion

4. Ease of nasal breathing

Items 1-3 above were rated on a 5-point scale as follows:

0 = absent
1 = mild
2 = moderate
3 = severe
4 = very severe

AHP2-REG-004-0044751

Item 4 above was rated on a 5-point scale as follows:

0 = normal
1 = only mildly impaired
2 = moderately impaired
3 = severely impaired
4 = total obstruction

[It should again be noted that Afrin (oxymetazoline hydrochloride) nasal solution was administered immediately after the above measurements were made at 240 minutes.]

1.1.6 Effectiveness Assessment: See Special Findings (1.1.5)

1.1.7 Safety Assessment

The investigator observed particularly for the following adverse effects: nervousness, headache, nausea, dizziness or light-headed, drowsiness, dry mouth, urticaria, palpitation, and blurred vision.

Blood pressures (right arm, sitting three minutes) and pulse rates (sitting three minutes) were measured pre-drug and post drug according to the following schedule:

"0 hour"	120 minutes
30 minutes	180 minutes
60 minutes	240 minutes
90 minutes	270 minutes

1.1.8 Data Management and Analysis

After initial medical screening by the Data Monitor (M.D.), primarily from a safety viewpoint, the data sheets were carefully monitored by a research physician in order to ascertain if they met the selection and treatment criteria of the protocol (see 4.1.3 and 4.1.4). Standard statistical methods were used to analyze the special findings (see Section 5).

~~1.1.9 Summary of "Bias Minimization" Aspects~~

1. Assignment of patients to treatment groups by a pre-determined randomization schedules.

2. Drug administration of the differing test medications by a disinterested third party (i.e. the investigator and technician were "blind" to the medication each patient received).

3. Careful and independent medical auditing of the data sheets for "acceptability" (e.g. with respect to patient selection criteria, etc.) prior to biometric evaluation of the special findings.

AHP2-REG-004-0044752

2.1 PROTOCOL DEVIATIONS: None

AHP2-REG-004-0044753

4. Investigator Information

AHP2-REG-004-0044754

2. INVESTIGATOR INFORMATION

One clinician supplied the data on the 48 patients participating in this study. The name and address of the investigator and pertinent information about the investigation may be found at the front of this report. The *curriculum vitae* of the investigator follows in this section.

AHP2-REG-004-0044755

Curriculum Vitae: Burton Marcus Cohen, M.D.

AHP2-REG-004-0044756

7-7-61

18

MANG-8

MAY 5 1969

BURTON M. COHEN, M.D., F.A.C.P.
Diplomate, American Board of Internal Medicine
250 WEST JERSEY STREET
ELIZABETH, N. J. 07202

ELIZABETH 4-5050

CARDIOPULMONARY DISEASES
RESPIRATORY PHYSIOLOGY

CURRICULUM VITAE

Name: Burton Marcus Cohen, M.D.

Personal Data: Born: December 13, 1925, Elizabeth, N.J.
Married, four children.

Education: 1945 A.B. Columbia University
1948(March) M.D. University of Rochester School of Medicine and Dentistry.

Positions:

1948-50 Intern, Medical Services, Maimonides Hospital, Brooklyn, N.Y.

1950-51 Assistant Resident Physician, Maimonides Hospital

1951-52 Assistant Resident Physician, Strong Memorial Hospital & Hochstetter Fellow in Medicine, University of Rochester

1952-55 Active Duty-Surgeon(Lieutenant-Commander) U.S. Public Health Service:
- Internist, Phoenix Area
- Deputy Chief of Medicine(Chest Diseases), U.S. Marine Hospital, Detroit, Michigan
- Chief of Medicine, U.S.P.H.S. Out-patient Clinic, New York, N.Y.

1954-57 Goldwater Memorial Hospital, Welfare Island, New York: First (Columbia University) Research Service:
- Research Fellow, 1954-56
- Assistant Visiting Physician, 1956-57

1955-63 Saint Elizabeth Hospital, Elizabeth, New Jersey:
- Assistant Attending Cardiologist 1955-58
- Associate Attending Cardiologist 1958-59
- Senior Attending Cardiologist 1959-61
- Attending in Medicine 1960-61
- Consultant in Internal Medicine and Cardiology 1961-63

1955-- Elizabeth General Hospital, Elizabeth, N.J.
- Assistant Attending Physician 1958-60
- Associate Attending Physician 1960-63
- Attending Physician 1963-
- Electrocardiographer 1966-

1963-- Jersey City Medical Center, Jersey City
- Assistant Attending Physician 1963-D65
- Attending Physician 1965-1967

1967-- Chairman, Department of Medicine-Elizabeth General Hospital

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044757

1955-- Alexian Brothers Hospital, Elizabeth, N.J.
Assistant Attending Physician 1958-59
Consultative Courtesy Staff 1959--

1959-63 Medical Board, Deborah Hospital, Browns Mills, N.J.

1959-64 Associate Director, T.J. White Cardiopulmonary Institute, B.S. Pollak Hospital, JerseyCity, N.J.

1955-57 Consultant in Cardiology, U.S.P.H.S. Outpatient Clinic, New York

Consultant to:
Baxter Laboratories, Morton Grove, Illinois
Irwin, Neisler & Co., Decatur, Illinois
Riker Laboratories, Northridge, California
Squibb Institute for Therapeutic Research, New Brunswick, N.J.
Schering Corporation, Bloomfield, N.J.
Strasenburgh Laboratories, Rochester, N.Y.
A.M. Christians Co., Brussels, Belgium.
A.H. Robins Co., Richmond, Virginia

Academic Positions:

1951-52 Assistant in Medicine, University of Rochester
1954-57 Assistant in Medicine, Columbia University College of Physicians and Surgeons
1959-61 Assistant Professor of Clinical Medicine, Seton Hall College of Medicine
1959-60 Assistant Professor of Clinical Preventive Medicine, Seton Hall College of Medicine
1961-63 Clinical Assistant Professor of Medicine, Seton Hall College of Medicine
1963-65 Associate Professor of Clinical Medicine, Seton Hall College of Medicine
1958-61 Postgraduate Advisory Curriculum Committee, Seton Hall College of Medicine.
1965- Associate Clinical Professor of Medicine, The New Jersey College of Medicine.

Qualifications:

1955 Diplomate, American Board of Internal Medicine
1956 Fellow, American College of Chest Physicians
1957 Fellow, American College of Cardiology
1961 Fellow, AMERICAN COLLEGE OF PHYSICIANS
1961 Fellow, American Society of Clinical Radiology
1955 Fellow, Academy of Medicine of New Jersey
1963 Fellow(Charter), American College of Clinical Pharmacology and Chemotherapy
1965 Fellow, The Royal Society of Medicine (London)
1967 Fellow, American Geriatrics Society

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044758

Memberships:

American College of Physicians
American College of Chest Physicians
American College of Cardiology
American Society of Clinical Radiology
International Cardiovascular Society and North American Chapter
International Society of Internal Medicine
American and New Jersey Societies of Internal Medicine
American Federation for Clinical Research and N.J. Chapter
American Thoracic Society
American Heart Association
N.J. Heart Association
Union County Heart Association (Past President)
Reserve Officers Association of the U.S.
Association of Military Surgeons of the United States
Reserve Officers Association of the U.S.P.H.S.
Clinical Society, U.S.P.H.S.
P & S Club (N.Y.)
Medical Alumni Association, University of Rochester (former Class Chairman)
American Association of Inhalation Therapits (Medical Advisor)
Association of American Physicians and Surgeons
American Association of University Professors
American Association for the Advancement of Science
Fellow, New York Academy of Science
Drug Information Association (Charter Member)
Academyof Science of N.J.
American Geriatrics Society
American Therapeutic Society

Cardiology Editor: MEDECINE et HYGIENE, Geneva Switzerland. 1959--1965

Section on Physiologic Therapy (Committee on Inhalation Therapy), American College of Chest Physicians. 1960--

International Committee on Emphysema, IX International Congress on Diseases of the Chest, Copenhagen, August 20-25, 1966.

ALEXANDER COCHRAN BOWEN-HARLOW BROOKS SCHOLAR, New York Academy of Medicine, 1949-1950.

CIVIC: Rotary Club of Elizabeth, N.J.
Honorary Member, Rotary Club of St. Marylebone, London, England.
Columbia University Club (N.Y.C.)

Military:
U.S.N.R. 1943-44
U.S.P.H.S.(R) and U.S.P.H.S.(Regular Corps) 1952-54
Surgeon, USPHS(R)-Inactive 1955-1966.
Senior Surgeon(Commander) 1966-

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044759

BIBLIOGRAPHY

1. Thrombotic Thrombopenic Purpura. J.A.M.A. 148:546, 1952.

2. MEDICAL PROGRESS: Digitalis poisoning and its treatment. New England J. Med. 246:225 & 254, 1952.

3. Arterial hypertension among Indians of the southwestern United States. Am. J. Med. Sc. 225:505, 1953.

4. Fatal reaction to 1-hydrazinophthalazine (Apresoline). Am. Heart J. 47:931 1953.

5. Diabetes mellitus among Indians of the American southwest. Ann. Int. Med. 40:588, 1954.

6. The ambulatory treatment of arterial hypertension and the early response to oral cryptenamine. N.Y. State J. Med. 55:652, 1955.

7. Cryptenamine plus reserpine in the treatment of hypertension. J. Med. Soc. N.J. 52:342, 1955.

8. Cryptenamine and cryptenamine plus reserpine in the treatment of hypertension. Am. Practitioner & Dig. of Therapy 6:1030, 1955.

9. Studies of the arterial pulse wave. I. The normal human pulse and its modification in the presence of human arteriosclerosis (joint author) J. Chron. Dis. 3:618, 1956.

10. The cough response of normal human subjects stimulated experimentally by Citric Acid aerosol: Alterations produced by anti-tussive agents. Part I. Methodology. (joint author). Am. J. Med. Sc. 232:57, 1956.

11. Ibid: Part II. (joint author). Idem. 234:1957, page 191.

12. Rauwolfia-barbiturate-xanthine mixtures in the treatment of hypertension. Mil. Med. 120:102, 1957.

13. The management of moderately severe hypertension with cryptenamine and Rauwolfia: Observations in patients treated for periods up to two years. Am. J. Cardiology 1:748, 1958.

14. Ethiquinium chloride: an unsymmetric bisquaternary ammonium salt in the therapy of hypertension. New Eng. J. Med. 257:971, 1957.

15. Fatal malignant hypertension in a patient with scleroderma precipitated by prednisone. Proc. Am. Heart Asso., Oct. 1957.

16. Flumethiazide and flumethiazide-Rauwolfia whole root in the office management of patients with moderately severe hypertension. Monographs on Therapy 4:10, 1959.

17. Flumethiazide: a new saluretic agent. Military Med. 124:584, 1959.

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044760

AHP2-REG-004-0044760

18. Chlorothiazide therapy of the ambulatory patient with hypertension. Observations in 140 patients treated for up to two years of continuous therapy. 1959 Scientific Sessions, 25th annual meeting,. Am. Coll. Chest Physicians, Atlantic City, N.J.

19. Some experiences with a family of asymmetric bisquaternary ammonium salts in the treatment of hypertension. Ibid.

20. Methindethyrium, an unsymmetrical bisquaternary ammonium salt: its use in a fixed mixture of hypotensive agents. Am. Practitioner and Dig. of Therapy. 10:983, 1959.

21. Rauwolfia whole root in the long-term treatment of office patients with hypertension. J. Med. Soc. N. J. 56:304, 1959.

22. Intermittent Positive Pressure Breathing. Hospital Counselor. No. 12, Jan. 1959.

23. An approach to the office treatment of the patient with hypertension. J. Indiana State Med. Ass'n. 52:1300, 1959.

24. Clinical use of dihydroflumethiazide in patients with high arterial pressure. Clin. Ther. Res. 1: 49, 1959.

25. Benzydroflumethiazide, a new potent saluretic agent: clinical experience in office patients with high blood pressure. Monographs on Therapy. 5: 4, 1960.

26. Newer saluretic agents in the therapy of hypertension. Medical Times, 88:855 1960.

27. Anti-hypertensive therapy with a fixed mixture of benzydroflumethiazide and Rauwolfia whole root. Curr. Ther. Res. 2: 116, 1960.

28. Two new saulretic agents: methyclothiazide and trichlormethiazide. Sixth International Congress of Internal Medicine, Basel, Switzerland, August, 1960.

29. The Newer Saluretic Agents. Medecine et Hygiene. 19:210, 1961.

30. The treatment of hypercholesterolemic states with sodium dextro-thyroxine. Clinical Medicine. 7: 1781, 1960.

31. Chapter 55: Physiologic Therapy of Bronchopulmonary Disease, in Gordon, B. S. CLINICAL CARDIOPULMONARY PHYSIOLOGY, 2nd. Edition. Grune & Stratton. New York, 1961.

32. Editorial: Atherosclerosis, hypercholesterolemia and the thyroxines. Medecine et Hygiene. 19: 455, 1961.

33. One year of sodium dextro-thyroxine therapy for hypercholesterolemia. Ibid. 19: 464, 1961.

34. Recent advances in the therapy of pulmonary emphysema. J. Med. Soc. N. J. 58:462, 1961.

DEC 4 196

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044761

AHP2-REG-004-0044761

35. One year of sodium dextro-thyroxine therapy for hypercholesterolemia. Angiology. 13: 69, 1962.

36. Physiologic responses to long-term bronchodilator oral therapy: an aminophylline aluminum hydroxide-ethyl aminobenzoate preparation. Curr. Ther. Res. 4:276, 1962.

37. Sodium dextro-thyroxine therapy for hypercholesterolemia: euthyroid patients with cardiovascular disease. Presented at the Congress of the International Cardiovascular Society, Dublin, Ireland, September, 1961. Published: Bulletin de la Societe Internationale de Chirurgie. 21: 177, 1962.

38. Antihypertensive therapy with fixed mixtures of hypotensive agents: methyclothiazide-cryptenamine and methyclothiazide-cryptenamine-reserpine combinations. Curr. Ther. Res. 3:160, 1961.

39. Editorial: Old wine in new bottles, or the renaissance of veratrum in the treatment of hypertension. Medecine et Hygiene. No. 556, 573, 1962.

40. Eight years' experience in the treatment of primary arterial hypertension with cryptenamine. Ibid. No. 556. 578, 1962.

41. Aerosol-induced sputum: an effective, inexpensive method for nebulization of a superheated mixture of 40% propylene glycol in isotonic saline. Dis. Chest. 42:251, 1962.

42. The clinical importance of weight reduction in patients with exogenous obesity. Medical Times. 90: 1087-1091, 1962.

43. Thermo-Fog: Nebulization of a super-heated mixture of 40% propylene glycol in isotonic saline as a vehicle for bronchodilator therapy. Clinical Medicine. 70: 1097, 1963.

44. Sodium dextro-thyroxine therapy of hypercholesterolemia: responses of 29 euthyroid patients with cardiovascular diseases to treatment for periods exceeding two years. (European Cardiovascular Congress, Stockholm, Sweden, July 4, 1962). Applied Therapeutics 4:913, 1962.

45. The helium-mixing curve low point as an index of pulmonary disability: a study of 496 patients. (18th Annual Meeting, Medical Alumni Association, The ~~University of Rochester, October 11-13, 1962). Dis. Chest. 43:496, 1963.~~

46. Ventilatory effects of "Thermo-Fog" as a bronchodilator vehicle. British J. Dis. Chest, 57:86, 1963 (April)

47. Ventilatory responses to aerosols of isoproterenol and isoproterernol-phenylephrine. Curr. Ther. Res. 4:601-609, 1962.

48. Out-clinic ventilation studies in asthmatic children. (with Wittig, H.J.) The New Physician 15: 289-293, 1966 (November)

DEC 4 1967

AHP2-REG-004-0044762

49. Breathlessness, ventilation studies and the "match test". Geriatrics. 18: 265-271, 1963.

50. Lung Function testing in the doctor's office. J. Med. Soc. N. J. 40:484-487, 1963.

51. Ventilation effects of an ephedrine sulfate-methaqualone resin complex. Curr. Ther. Res. 5:176-182, 1963.

52. Clinical Estimation of Breathlessness. Ann. Meeting, Med. Soc. of State of N. J., Atlantic City, May 13, 1963. J. Med. Soc., N. J. 61:23-31, (January) 1964.

53. The fate of hypertensives treated medically. MEDICAL TIMES 91: 645-650 (July), 1963.

54. The treatment of cor pulmonale: methods designed to relieve the altered pulmonary physiology (in French). Med. et Hyg. 21:633-634, 1963 (July 15).

55. Precision in the clinical classification of dyspnea (In French). Ibid, 21: 642-643, 1963 (July 15).

56. Therapeutic Research Note: Pharmacologic reversal of the " Snider Match Test " Curr. Ther. Res., 5:594, 1963.

57. Sodium dextro-thyroxine in hypercholesterolemia. J. Cardiovasc. Surgery, 4: 653-658, 1963.

58. The compleat cardiologist. Editorial. Med, et Hyg. 22:611, 1963.

59. Quantitation of dyspnea as an index of ventilation integrity. Clinical Research. 11: 407, 1963 (December).

60. Acute bronchodilator properties of a steroid microaerosol. Curr. Ther. Res., 6: 73-82, 1964.

61. Physiologic benefits of " Thermo-Fog " as a bronchodilator vehicle: Acute ventilation responses of 93 patients. Am. J. Med. Sc. 247:57, 1964 (Jan.)

62. Sodium dextro-thyroxine therapy for hypercholesterolemia. Geriatrics. 19:585, 1964.

63. The worth of bronchodilator aerosols: I. Pitfalls in the ventilation estimation. (with McIlreath, F. J.) J. New Drugs, 4:237 (Sept-Oct.) 1964.

64. Appraisal of the worth of bronchodilator microaerosols. II. The usefulnes of four common ventilatory indices in a clinical trial. Dis. Chest. 48:471-477, 1965.

65. Management of patients with obstructive breathing handicaps. Clinical Allergy and Immunology. 2: 1-4, 1965 (March)

66. Management of patients with obstructive breathing handicaps. Geriatrics, 20: 999-1005, 1965(December)

67. A Vest-pocket ventilation function device: The Dellono Whistle. Curr. Ther. Res. 7:513-515(September p.

AHP2-REG-004-0044763

68. Sympathomimetic amine aerosol administration in obstructive ventilation disease: a one year trial in patients abstaining from cigarettes and a matched group who continued to smoke. Med. Times, 94: 355-359, 1966.

69. Ventilatory performance of American physicians. A pilot study (with McIlreath, F. J.). Am. J. Med. Sc., 252: 1-8, 1966 , (July)

70. Drug Improvement Ratio (D. I. R.): An objective index of the efficacy of microaerosols of bronchodilator drugs. 61st Annual Meeting, National Tuberculosis Association, 60th Annual Meeting, American Thoracic Society. Chicago, Illinois, May 30-June 2, 1965.

71. Bronchopervlant effects of pimetine. Abstract- Clin. Res., 13: 552, 1965. J. New Drugs, 6: 162-173 (May-June) 1966.

72. The Untilled Garden: Therapeutic opportunity in chronic obstructive ventilatory disease. Applied Therapeutics (Canada), 8: 340-343, 1966(April).

73. Masquerading Malady: The many faces of obstructive ventilatory disease. Consultant, 7: 32-36, 1967(February)

74. A niacinamide-theophylline compound (RC-C-144). I. Human absorption and blood level studies. J. Asthma Res., 4:75-79, (Sept.)1966

75. A niacinamide-theophylline compound (RC-C-144). II. Clinical and spirometric effects. J. Asthma Res., 4: 80-87, 1966(Sept.)

76. Cryptenamine-based mixtures for chronic therapy of benign arterial hypertension. Curr. Ther. Res., 8 : 424-434 (September) 1966.

77. Studies with isoetharine. I. The ventilatory effects of aerosol and oral preparations. J. Asthma Res., 4: 209-218, (March) 1967.

78. Studies with isoetharine. II. Cardiovascular effects in hypertensive patients with expiratory airflow disorders. J. Asthma Res. 4:259-267(March)1967

79. Beta-adrenergic agonist effects of isoetharine. Abstract- Clin. Res. 14: 426, 1966.

80. A progress note on pimetine hydrochloride in obstructive ventilatory disease. Medicina Thoracalis. 24: 306-326 (No. 5 for)1967,

81. Cardiovascular and nervous system effects as indices of the broncholytic potency of microaerosols.

82. Reduction of hypercholesterolemia incardiovascular subjects: Five years of sodium dextro-thyroxine therapy. (Abstract). Circulation 24: Supplement III, p. 74 (October) 1966.

83. Lung function testing in the education of practicing physicians: Factors influencing patient referral to laboratory facilities. (Abstract) J. Med. Educ. 42:878, (September)1967.

84. (with McIlreath, F. J.) Airway resistance measurements in the internist's office. Routine determinations inthe diagnosis and care of breathless patients. pp. 75-76. VI International Congress of Allergology. Int. Congress Series (Excerpta Medical Foundation). No. 144, 1967.

DEC 4 196

AHP2-REG-004-0044764

85. The therapy of hypercholesterolemia and six-years' use of sodium dextro-thyroxine. Progress note. Curr. Ther. Res., 9: 618-622(Dec.) 1967.

86. Chronic bronchopulmonary disease and the disability decision.

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044765

AHP2-REG-004-0044765

EXHIBITS, PAPERS PRESENTED:

Clinical Exhibit: The treatment of Ambulatory Patients with Hypertension. A.M.A. Annual Meeting, San Francisco, July, 1959.

Indiana Academy of General Practice, March, 1959.

Clinical Exhibit: The importance of weight reduction in Internal Medicine. A.M.A. Clinical Meeting, Dallas, Texas, December, 1959.

Bahamas Medical Conference on Hypertension, January, 1961.

Bahamas Conference on Internal Medicine, April, 1962.

VI INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Basle, Switzerland, Aug. 1960.

American College of Angiology, New York, N.Y. (Symposium on Atherosclerosis), June, 1961.

International Cardiovascular Society and International Congress of Cardiovascular Surgery, Dublin, Ireland, September, 1961.

European Cardiovascular Surgical Congress, Stockholm, Sweden, July, 1962.

University of Liege, Faculty of Medicine, June, 1962.

VII INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Munich, Federal Republic of Germany, September, 1962.

Scientific Exhibit (Certificate of Merit). 196th Annual Meeting, The Medical Society of New Jersey, May 12-16, 1962.: Aerosol-Induced Sputum.

18th Annual Meeting, Medical Alumni Association, The University of Rochester, Rochester, N.Y.; October 11-13, 1962.

Scientific Sessions, American College of Cardiology, Los Angeles, California, February 28-March 3, 1963.

~~Medical Society of the State of New Jersey, Atlantic City, N.J.; May 13-20, 1963.~~

Scientific Exhibit: Physiologic Therapy of Obstructive Ventilatory Disorders, Annual Meeting, American Academy of General Practice, Atlantic City, N.J., April 13-16, 1964 and Annual Meeting, American Medical Association, June 21-25, San Francisco, California.

Third Annual Meeting, American College of Clinical Pharmacology & Chemotherapy, Philadelphia, Pa. April 29-30, 1966.

Oxygen Toxicity: Mid-Atlantic Society of Nurse Anesthetists. Mid-Atlantic Hospital Meeting, May 18, 1966, Atlantic City, N.J.

Diagnosis of Obstructive Lung Diseases. N.J. Acad. Gen. Practice, Atlantic City, Jan. 1966.

AHP2-REG-004-0044766

Bronchopervient effects of Pimetine HCl. Annual Scientific Sessions, American College of Chest Physicians, June 23-27, 1966. Chicago, Illinois.

IX International Congress on Diseases of the Chest, H. C. Orsted Institute, Copenhagen, August 20-25, 1966.

Appraisal of the worth of bronchodilator microaerosols: III. Cardiovascular and nervous system effects as indices of broncholytic potency in clinical trials. Annual Meeting, American Medical Association (Meeting of Sections on Diseases of the Chest and Preventive Medicine-June 19, 1967), Atlantic City, N. J., June 18-24, 1967.

Airway Resistance Measurements in the Internist's Office: Routine Determinations in the Diagnosis and Care of Breathless Patients.

VI. International Congress of Allergology, Montreal, Canada, Nov. 5-11, 1967.

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044767

AHP2-REG-004-0044768

3. DRUG/ASSAY INFORMATION

3.1 Drug Information

The test medications were taken from commercial lots. They were as follows:

1. Dimetane Elixir - 2 mg brompheniramine maleate per 5 cc
2. Dimetapp Elixir - 4 mg brompheniramine maleate, 5 mg phenylephrine hydrochloride, and 5 mg phenylpropanolamine hydrochloride per 5 cc
3. Neosynephrine Elixir (Winthrop) - 1 mg phenylephrine hydrochloride per 1 cc
4. Propadrine Elixir (Merck, Sharp, and Dohme) - 4 mg phenylpropanolamine hydrochloride per 5 cc

Since the test medications were not identical in appearance, they were administered by a disinterested third party; hence, the investigator and the technician making the measurements were "blind" to the test medication received by each subject.

AHP2-REG-004-0044769

AHP2-REG-004-0044770

4. SPECIAL FINDINGS

4.1 Patient Accountability

Forty-eight patients with upper respiratory infections were enrolled in the study. Each successfully completed his single test day. A listing of the patients enrolled may be found in Table 4.1-01.

AHP2-REG-004-0044771

Table 4.1-01

PATIENT CHARACTERISTICS

TREATMENT GROUP: Dimetapp Elixir

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
1	38	F	C	125	65.0
3	41	M	C	178	73.0
5	64	F	C	129	61.0
8	46	F	C	136	66.0
9	44	M	C	191	69.0
11	51	F	C	134	65.0
12	69	M	C	201	68.0
14	46	M	C	169	66.0
16	40	F	C	149	65.0
21	40	F	C	138	65.0
23	74	F	C	169	68.0
24	64	M	C	161	68.0
25	39	F	C	123	65.0
26	53	M	C	192	73.0
28	40	F	C	137	65.0
32	48	F	C	147	69.0
34	55	M	C	179	70.5
35	23	F	C	137	65.0
38	69	F	C	149	64.0
39	19	M	C	247	75.5
41	71	M	C	164	69.0
43	58	F	C	154	64.0
44	40	F	C	132	63.0
48	54	M	C	161	68.0

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044772

Table 4.1-01 (Cont'd.)

PATIENT CHARACTERISTICS

TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
7	42	F	C	161	67.0
15	68	F	C	141	63.0
18	56	M	C	194	70.0
19	42	F	C	139	67.0
37	38	M	C	199	69.0
40	37	F	C	137	66.0
42	43	M	C	170	73.0
46	60	F	C	149	65.0

TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
2	62	F	C	168	67.0
4	36	F	C	123	72.0
6	71	F	C	143	64.0
10	64	M	C	156	65.0
29	67	F	C	191	67.0
30	36	F	C	139	67.0
33	64	M	C	179	72.0
47	59	M	C	175	67.0

Continued

AHP2-REG-004-0044773

Table 4.1-01 (Cont'd.)

PATIENT CHARACTERISTICS

TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
13	52	F	C	139	67.0
17	56	F	C	106	61.0
20	51	M	C	184	72.0
22	58	M	C	179	65.0
27	46	F	C	128	65.0
31	39	M	C	171	68.0
36	39	M	C	168	67.0
45	70	F	C	149	63.0

AHP2-REG-004-0044774

4.2 Special Findings

4.2.1 Nasal Inspiratory and Expiratory Resistances (Respiron)

Analyses of covariance were performed on both the nasal inspiratory and expiratory resistances using the pre-drug measurements as the covariates. For both parameters, the adjusted means of the components were compared with the adjusted means of Dimetapp using Dunnett's t (one-tailed). The results of these analyses may be found in Tables 4.2.1-01 and 4.2.1-02 and Figures 4.2.1-01 and 4.2.1-02.

As shown, Dimetapp is consistently better than any of its components and many of the differences are statistically significant.

In addition, the adjusted means for each of the treatment groups were compared with the "control value" (covariate). As shown in Tables 4.2.1-03 and 4.2.1-04 and Figures 4.2.1-03 and 4.2.1-04, Dimetapp and each of its components demonstrate significant decreases in both nasal inspiratory and expiratory resistances - most of these differences are highly significant (i.e., $p < 0.01$).

Listings of the data discussed above and more detailed information on the analyses may be found in Appendix A4.

AHP2-REG-004-0044775

CONFIDENTIAL / TRADE SECRET

Table 4.2.1-01

NASAL INSPIRATORY RESISTANCE: COMPARISON OF DIMETAPP WITH COMPONENTS

Analysis of Covariance and Results of Dunnett's t (WRT Dimetapp)

	Minutes Post Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.055376	0.295830	0.302532	0.210785	0.220289	0.295846	0.300635	0.336042	0.188783
DF	43	43	43	43	42	43	43	43	43
F	1.36	1.21	2.75	4.63	8.62	7.66	3.10	1.50	2.77
P	NS	NS	<0.10	<0.01	<0.001	<0.001	<0.05	NS	<0.10
Adjusted Treatment Means									
Dimetapp (24)	3.735	3.119	2.624	2.485	2.405	2.680	3.070	3.350	2.354
Phenylephrine (8)	3.864	3.405	3.118**	3.123***	3.328***	3.721**	3.710***	3.837	2.768**
Phenylpropanolamine (8)	3.888	3.472	3.121**	2.763	2.942**	3.174**	3.463	3.547	2.752**
Dimetane (8)	3.718	3.367	2.985	2.921**	2.872**	3.053	3.210	3.385	2.472

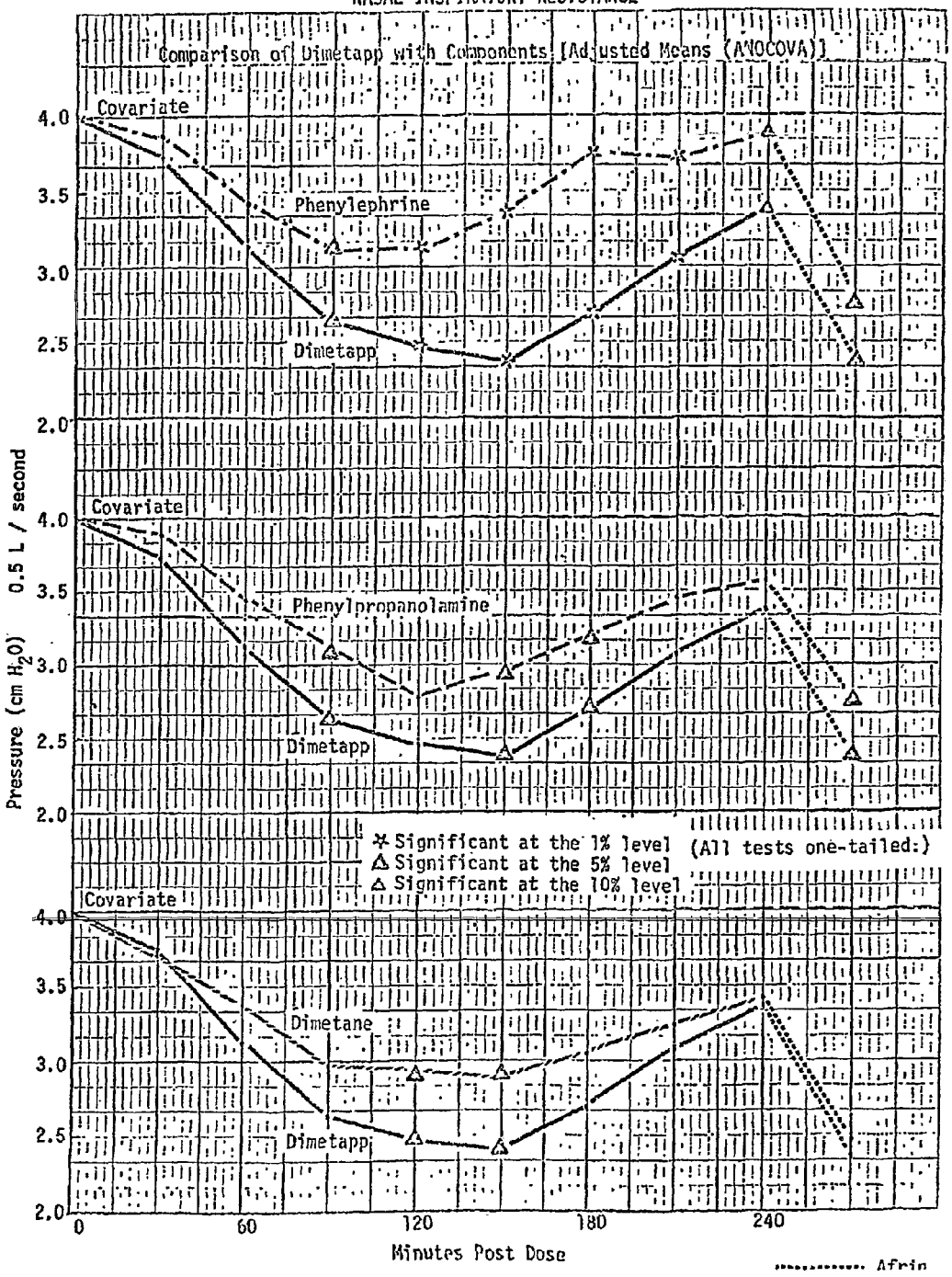
*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

AHP2-REG-004-0044776
AHP2-REG-004-0044776

Figure 4.2.1-01

NASAL INSPIRATORY RESISTANCE



AHP2-REG-004-0044777

Table 4.2.1-02

NASAL EXPIRATORY RESISTANCE: COMPARISON OF DIMETAPP WITH COMPONENTS

Analysis of Covariance and Results of Dunnett's t (WRT Dimetapp)

	Minutes Post Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.125889	0.246921	0.206566	0.140656	0.202280	0.195096	0.224118	0.243040	0.215026
DF	43	43	43	43	42	43	43	43	43
F	1.31	3.02	1.80	2.70	2.96	9.69	2.68	2.01	0.90
P	NS	<0.05	NS	<0.10	<0.05	<0.001	<0.10	NS	NS
Adjusted Treatment Means									
Dimetapp (24)	2.922	2.418	2.236	2.087	1.985	2.204	2.560	2.780	1.992
Phenylephrine (8)	3.040	2.687	2.602 *	2.528 ***	2.522 ***	3.211 ***	2.990 **	3.276 **	2.288
Phenylpropanolamine (8)	3.089	2.988 **	2.562	2.288	2.216	2.388	2.987 **	3.019	2.181
Dimetane (8)	3.188	2.758	2.353	2.233	2.304	2.556 *	2.611	2.973	2.111

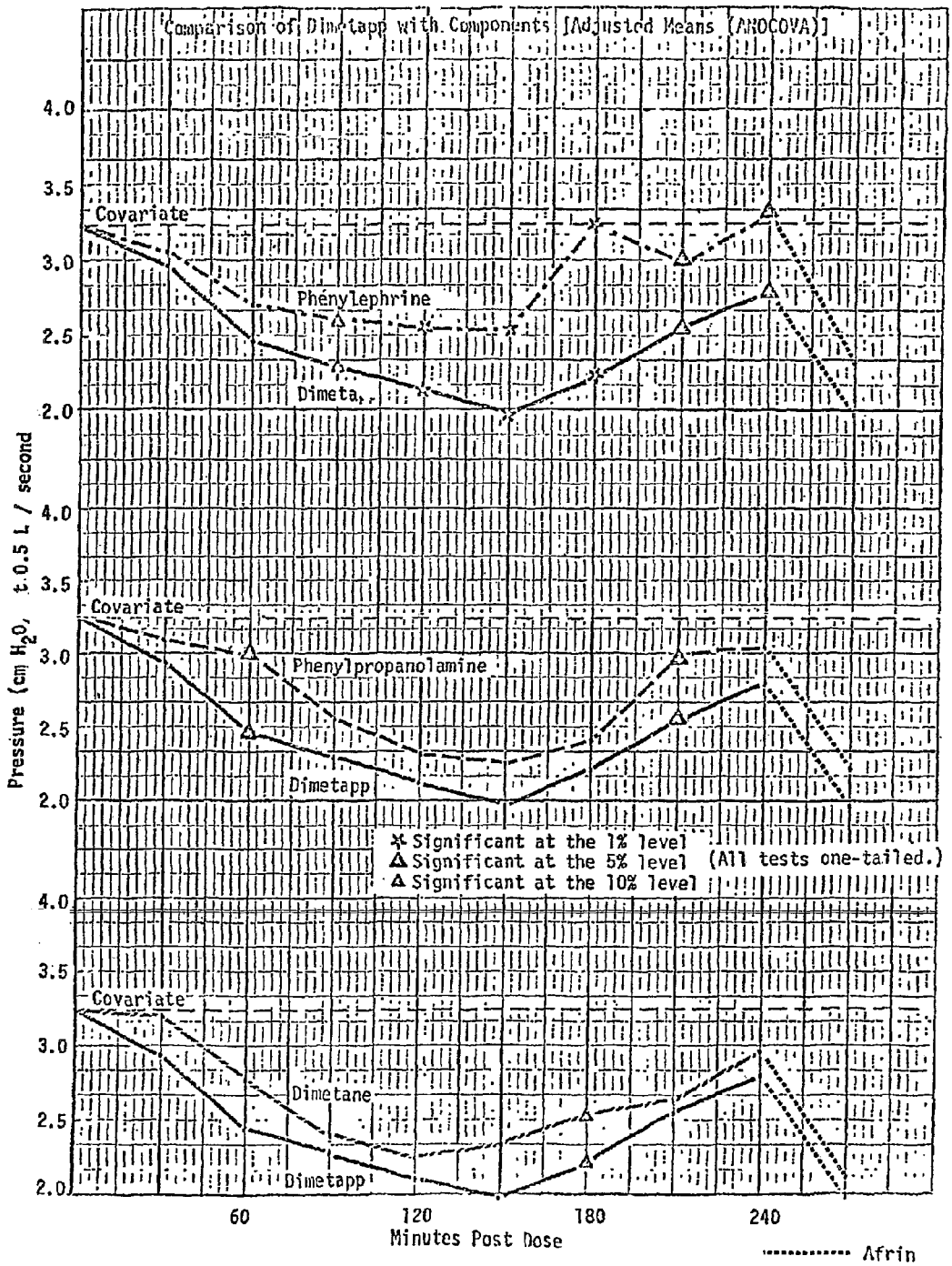
*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044778

AHP2-REG-004-0044778



AHP2-REG-004-0044779

Table 4.2.1-03

NASAL INSPIRATORY RESISTANCE

Comparisons of Adjusted Means with "Control" (Covariate)

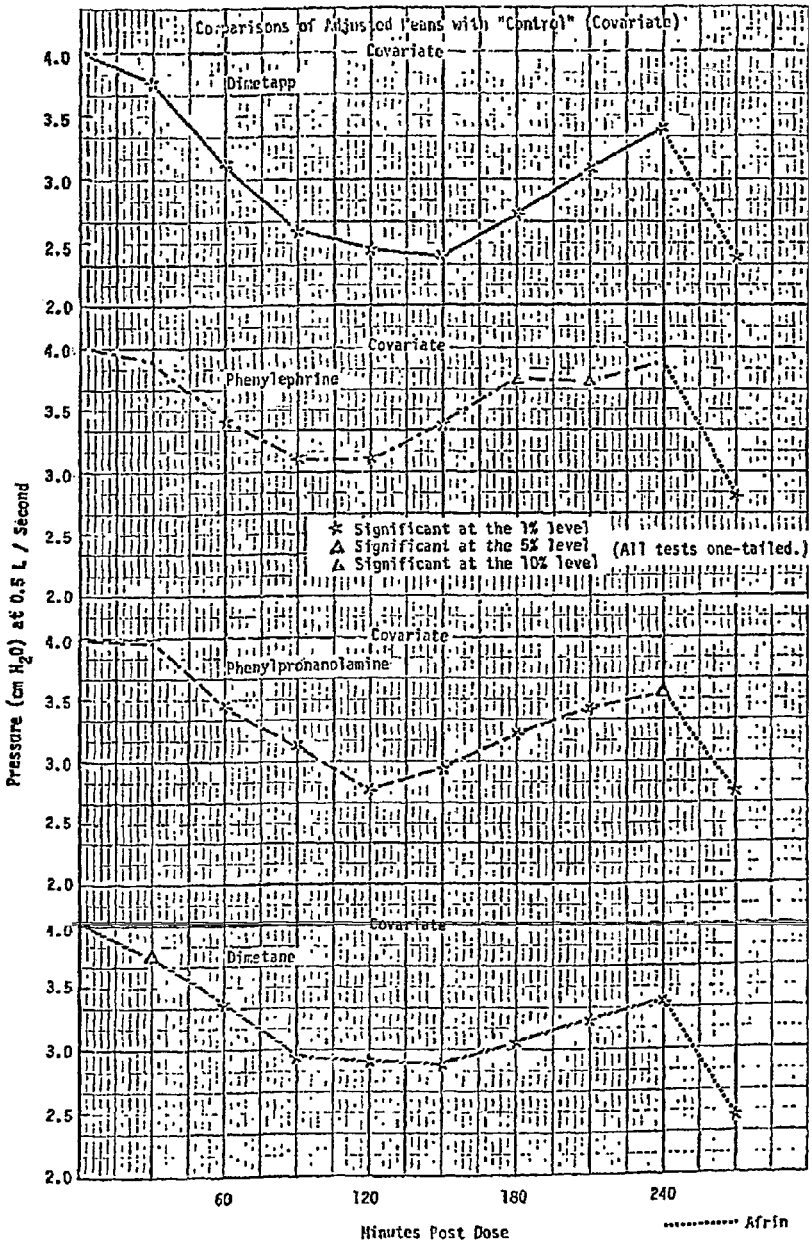
Minutes Post Dose	Adjusted Treatment Means		Covariate	t	P +
30	Dimetapp	3.74	4.0135	-2.784	<0.005
	PE	3.86		-0.979	NS
	PPA	3.89		-0.821	NS
	Dimetane	3.72		-1.934	<0.05
60	Dimetapp	3.12	4.0135	-6.284	<0.005
	PE	3.41		-3.039	<0.005
	PPA	3.47		-2.704	<0.005
	Dimetane	3.37		-3.229	<0.005
90	Dimetapp	2.62	4.0135	-10.539	<0.005
	PE	3.12		-4.446	<0.005
	PPA	3.12		-4.432	<0.005
	Dimetane	2.98		-5.107	<0.005
120	Dimetapp	2.48	4.0135	-12.631	<0.005
	PE	3.12		-4.817	<0.005
	PPA	2.76		-6.765	<0.005
	Dimetane	2.92		-5.910	<0.005
150	Dimetapp	2.41	4.0213	-12.960	<0.005
	PE	3.33		-3.698	<0.005
	PPA	2.94		-5.757	<0.005
	Dimetane	2.87		-6.131	<0.005
180	Dimetapp	2.68	4.0135	-10.173	<0.005
	PE	3.72		-1.461	<0.10
	PPA	3.17		-4.192	<0.005
	Dimetane	3.05		-4.797	<0.005
210	Dimetapp	3.07	4.0135	-7.168	<0.005
	PE	3.71		-1.509	<0.10
	PPA	3.46		-2.738	<0.005
	Dimetane	3.21		-3.996	<0.005
240	Dimetapp	3.35	4.0135	-4.893	<0.005
	PE	3.84		-0.852	NS
	PPA	3.55		-2.252	<0.025
	Dimetane	3.38		-3.034	<0.005
270	Dimetapp	2.35	4.0135	14.032	<0.005
	PE	2.77		-6.894	<0.005
	PPA	2.75		-6.983	<0.005
	Dimetane	2.47		-8.533	<0.005

+ One-tailed tests

AHP2-REG-004-0044780

Figure 4.2.1-03

NASAL INSPIRATORY RESISTANCE



AHP2-REG-004-0044781

Table 4.2.1-04

NASAL EXPIRATORY RESISTANCE

Comparisons of Adjusted Means with "Control" (Covariate)

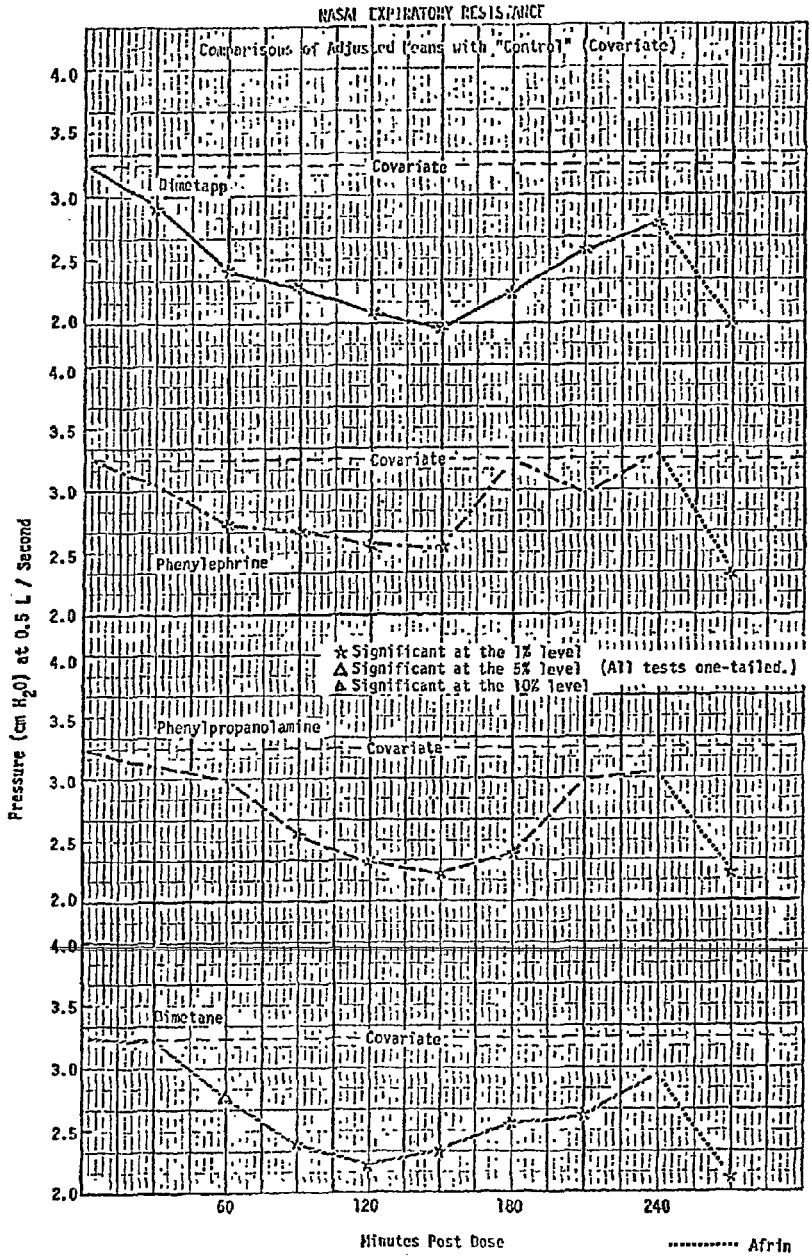
Minutes Post Dose	Adjusted Treatment Means		Covariate	t	P+
30	Dimetapp	2.92	3.2052	-2.646	<0.01
	PE	3.04		-1.011	NS
	PPA	3.09		-0.711	NS
	Dimetane	3.19		-0.105	NS
60	Dimetapp	2.42	3.2052	-6.413	<0.005
	PE	2.69		-2.764	<0.005
	PPA	2.99		-1.158	NS
	Dimetane	2.76		-2.385	<0.025
90	Dimetapp	2.24	3.2052	-8.232	<0.005
	PE	2.60		-3.354	<0.005
	PPA	2.56		-3.576	<0.005
	Dimetane	2.35		-4.738	<0.005
120	Dimetapp	2.09	3.2052	-10.253	<0.005
	PE	2.53		-4.065	<0.005
	PPA	2.29		-5.506	<0.005
	Dimetane	2.23		-5.836	<0.005
150	Dimetapp	1.98	3.1989	-10.190	<0.005
	PE	2.52		-3.796	<0.005
	PPA	2.22		-5.496	<0.005
	Dimetane	2.30		-5.007	<0.005
180	Dimetapp	2.20	3.2052	-8.611	<0.005
	PE	3.21		+0.033	NS
	PPA	2.39		-4.601	<0.005
	Dimetane	2.56		-3.655	<0.005
210	Dimetapp	2.56	3.2052	-5.379	<0.005
	PE	2.99		-1.175	NS
	PPA	2.99		-1.191	NS
	Dimetane	2.61		-3.243	<0.005
240	Dimetapp	2.78	3.2052	-3.477	<0.005
	PE	3.28		+0.379	NS
	PPA	3.02		-0.997	NS
	Dimetane	2.97		-1.243	NS
270	Dimetapp	1.99	3.2052	-10.211	<0.005
	PE	2.29		-5.054	<0.005
	PPA	2.18		-5.644	<0.005
	Dimetane	2.11		-6.029	<0.005

+ One-tailed tests

AHP2-REG-004-0044782

Figure 4.2.1-04

NASAL EXPIRATORY RESISTANCE



AHP2-REG-004-0044783

4.2.2 Nasal Mucosal Characteristics

Parameters evaluated: Nasal Serous Secretion
Nasal Mucosal Congestion
Nasal Mucosal Hyperemia
Ease of Nasal Breathing

In order to compensate for any differences in severity of initial symptomatology among the four treatment groups, a covariance-like procedure was utilized for the four parameters above prior to making ridit transformations. More explicitly, ridit variables were derived on the basis of "Score Changes" between the initial (pre-drug) and each of the serial post-drug evaluations. Analyses of variance were performed on these covariance-like ridit transformed variables. For all four parameters, the mean ridits of the components were compared with those of Dimetapp using Dunnett's t (one-tailed).

The results of these analyses may be found in Tables 4.2.2-01 through 4.2.2-04 and in Figures 4.2.1-01 through 4.2.2-04. As shown, Dimetapp is consistently better than any of its components and many of the differences observed are statistically significant.

In addition, the means for each of the treatment groups were compared with the "No Change" ridits (i.e., the ridit score representing a change = 0). As shown in Tables 4.2.2-05 through 4.2.2-08 and Figures 4.2.2-05 through 4.2.2-08, Dimetapp and each of its components show a definite improvement with respect to all four parameters throughout the study period. In fact, most of the differences are highly significant (i.e. $p < 0.01$).

AHP2-REG-004-0044784

Table 4.2.2-01

NASAL SEROUS SECRETIONS: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and
Results of Dunnett's t (WRT Dimetapp)

Minutes Post Dose

	30	60	90	120	150	180	210	240	270
Mean Square Error	0.05161	0.04640	0.05522	0.05369	0.05464	0.05550	0.03954	0.04112	0.05295
DF	44	44	44	44	43	44	44	44	44
F	2.56	4.45	5.01	3.58	6.21	5.69	11.45	7.03	5.99
P	<0.10	<0.01	<0.005	<0.025	<0.005	<0.005	<0.001	<0.001	<0.005
Adjusted Treatment Means									
Dimetapp (24)	0.500	0.438	0.384	0.383	0.360	0.362	0.334	0.383	0.362
Phenylephrine (8)	0.354	0.398	0.490	0.610 **	0.704 ***	0.664 ***	0.667 ***	0.552 *	0.591 **
Phenylpropanolamine (8)	0.480	0.560	0.685 ***	0.660 **	0.533	0.586 **	0.625 ***	0.548 *	0.620 ***
Dimetane (8)	0.657	0.728 ***	0.672 ***	0.580 *	0.668 ***	0.664 ***	0.708 ***	0.750 ***	0.645 ***

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

CONFIDENTIAL / TRADE SECRET

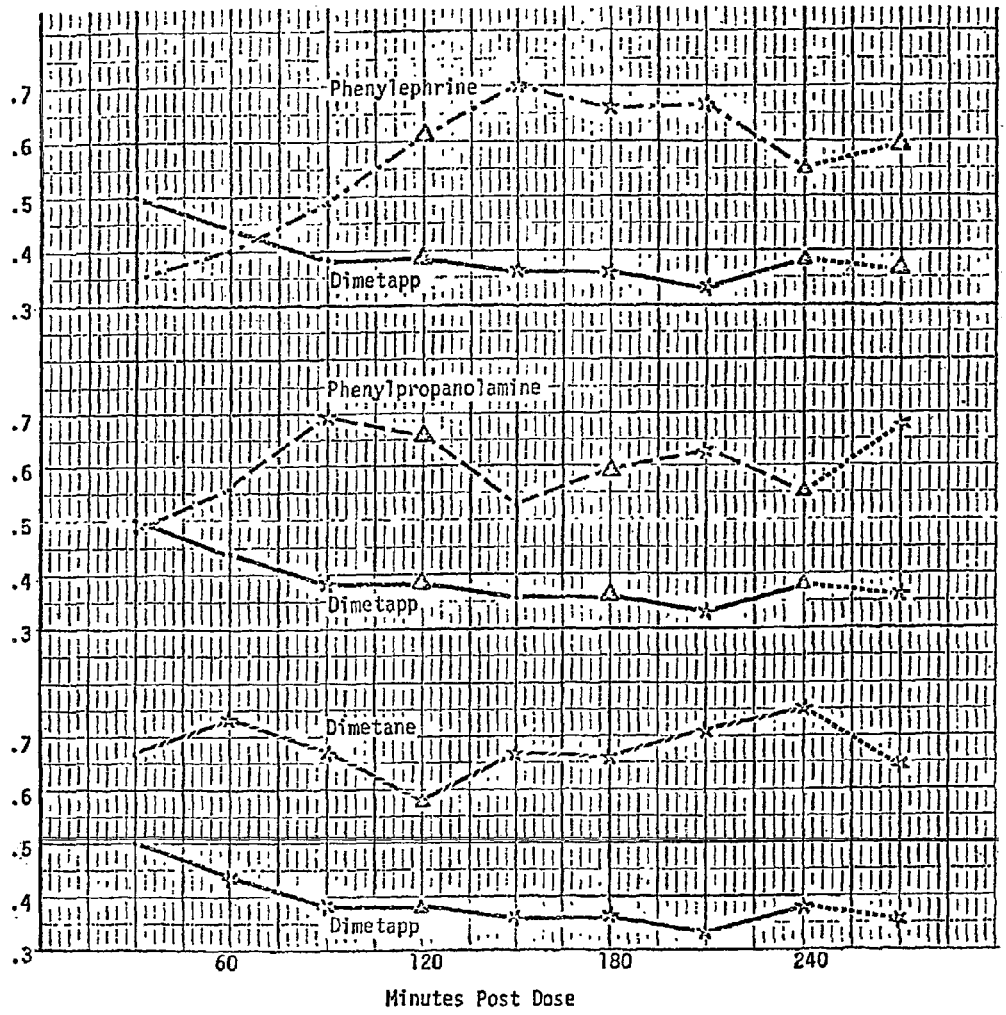
AHP2-REG-004-0044785

AHP2-REG-004-0044785

Figure 4.2.2-01

NASAL SEROUS SECRETIONS

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



✱ Significant at the 1% level
Δ Significant at the 5% level
▲ Significant at the 10% level
(All tests one-tailed.)

····· Afrin

AHP2-REG-004-0044786

CONFIDENTIAL / TRADE SECRET

Table 4.2.2-02

NASAL MUCOSAL CONGESTION: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and
Results of Dunnett's t (WRT Dimetapp)

	Minutes Past Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.04824	0.05784	0.05318	0.06399	0.06762	0.05326	0.05036	0.05376	0.05807
DF	44	44	44	44	43	44	44	44	44
F	1.85	2.61	3.99	2.55	2.33	5.20	2.82	3.06	2.10
P	NS	<0.10	<0.025	<0.10	<0.10	<0.005	<0.10	<0.05	NS
Adjusted Treatment Means									
Dimetapp (24)	0.488	0.509	0.432	0.427	0.424	0.392	0.399	0.412	0.423
Phenylephrine (8)	0.554	0.457	0.682 **	0.685 **	0.582 **	0.747 ***	0.570	0.615 **	0.511*
Phenylpropanolamine (8)	0.615	0.672	0.638 **	0.590	0.584	0.587 *	0.643 *	0.659 **	0.625*
Dimetane (8)	0.370	0.342	0.386	0.444	0.452	0.490	0.588 *	0.491	0.496

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

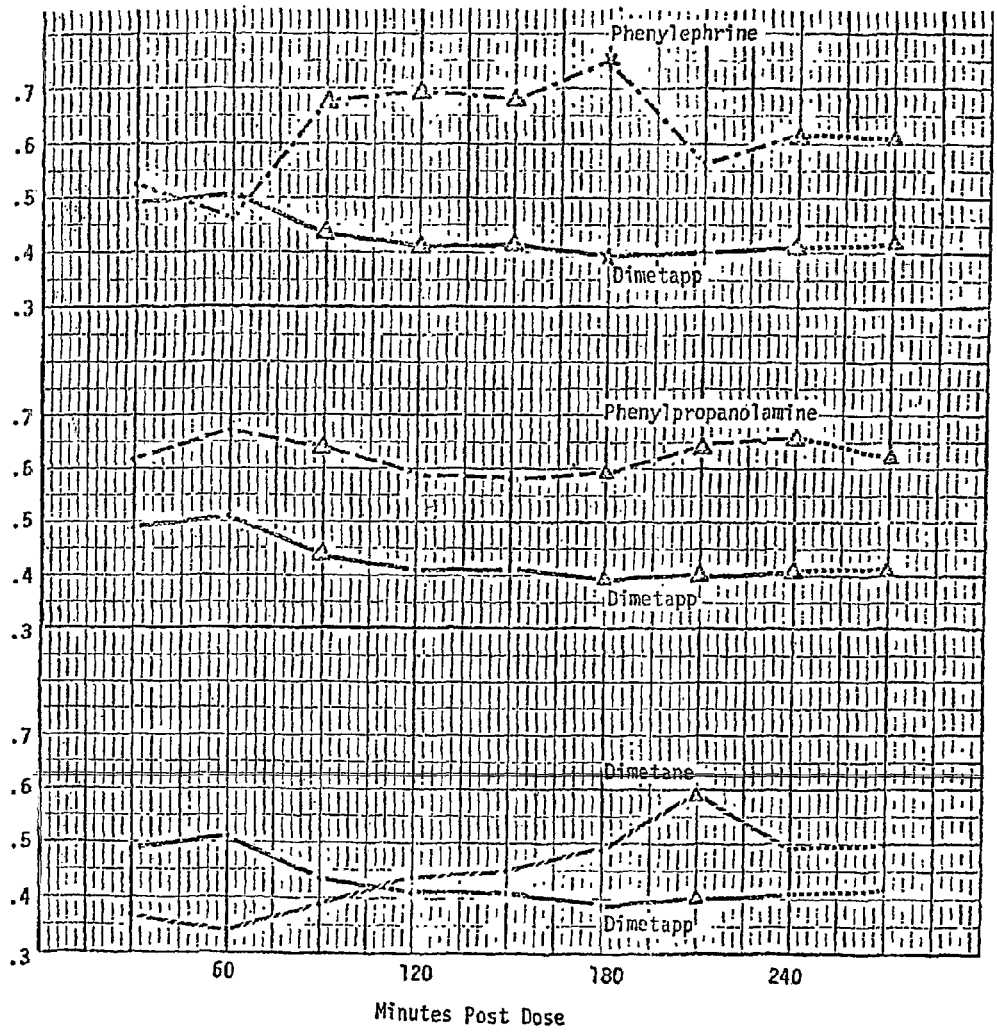
( ) Sample size

AHP2-REG-004-0044787
AHP2-REG-004-0044787

Figure 4.2.2-02

NASAL MUCOSAL CONGESTION

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



☆ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
▲ Significant at the 10% level

Afrin

AHP2-REG-004-0044788

NASAL MUCOSAL HYPEREMIA: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and
Results of Dunnett's t (WRT Dimetapp)

Minutes Post Dose

	30	60	90	120	150	180	210	240	270
Mean Square Error	0.06060	0.04696	0.04949	0.04950	0.05700	0.05660	0.05706	0.05757	0.06112
DF	44	44	44	44	43	44	44	44	44
F	1.57	0.60	1.49	4.57	3.82	3.54	3.84	2.35	1.35
P	NS	NS	NS	<0.10	<0.025	<0.025	<0.025	<0.10	NS
Adjusted Treatment Means									
Dimetapp (24)	0.434	0.473	0.454	0.405	0.414	0.398	0.396	0.410	0.430
Phenylephrine (8)	0.525	0.473	0.522	0.704 ***	0.746 ***	0.690 ***	0.644 **	0.596 *	0.577
Phenylpropanolamine (8)	0.647 *	0.584	0.642 *	0.620 **	0.500	0.581 *	0.670 **	0.617 *	0.596
Dimetane (8)	0.525	0.526	0.474	0.461	0.500	0.537	0.494	0.557	0.536

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

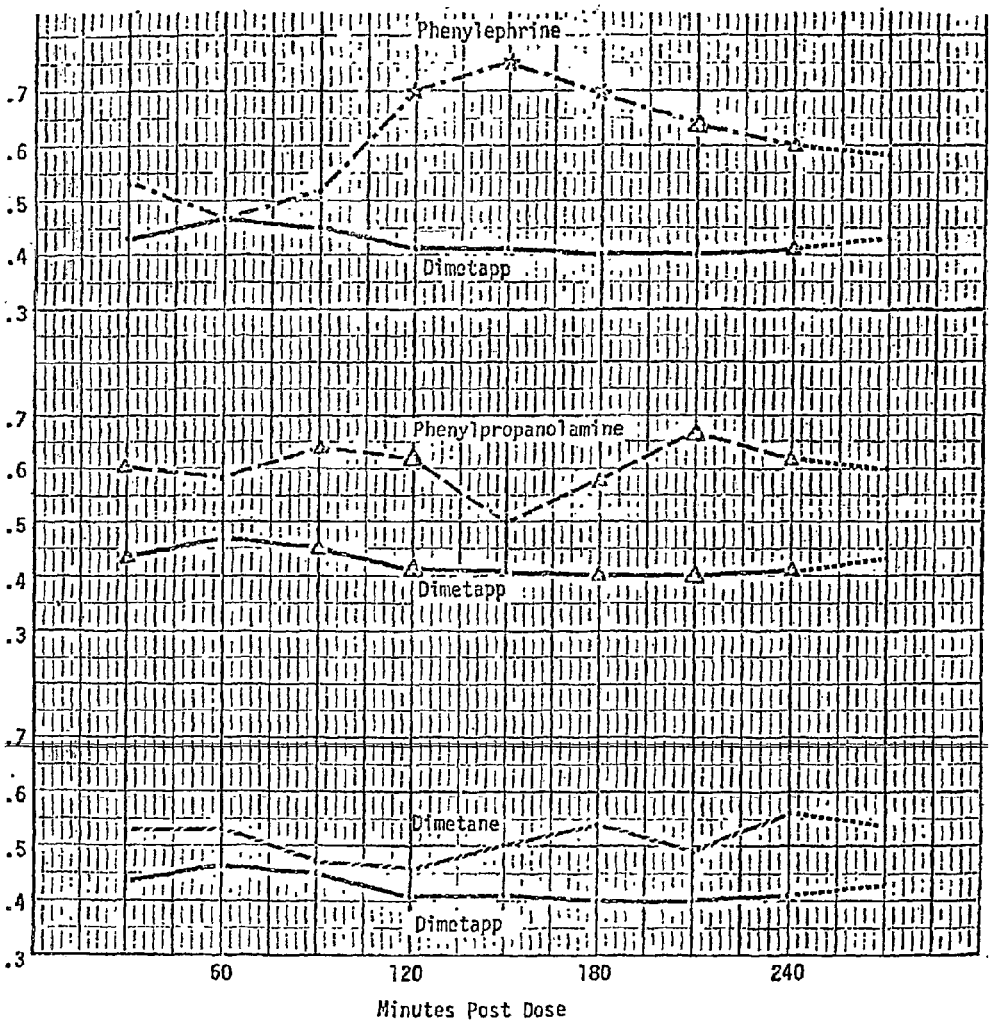
CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044789

Figure 4.2.2-03

NASAL MUCOSAL HYPEREMIA

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



★ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level

..... Afrin

AHP2-REG-004-0044790

Table 4.2.2-04

EAST OF NASAL BREATHING: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and
Results of Dunnett's t (WRT Dimetapp)

	Minutes Post Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.05629	0.06396	0.06069	0.06515	0.05583	0.05385	0.03999	0.05122	0.05756
DF	44	44	44	44	43	44	44	44	44
F	1.31	.82	4.07	2.85	5.60	7.16	12.98	3.22	4.95
P	NS	NS	<0.025	<0.05	<0.005	<0.001	<0.001	<0.05	<0.01
Adjusted Treatment Means									
Dimetapp (24)	0.442	0.464	0.394	0.412	0.375	0.357	0.323	0.403	0.322
Phenylephrine (8)	0.628 *	0.521	0.625**	0.685 **	0.757 ***	0.763 ***	0.737***	0.656 **	0.740 ***
Phenylpropanolamine (8)	0.524	0.620	0.707***	0.608 *	0.577 *	0.581 **	0.674***	0.568	0.584 *
Dimetane (8)	0.524	0.469	0.488	0.470	0.525	0.586 **	0.620***	0.568	0.521

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level . (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

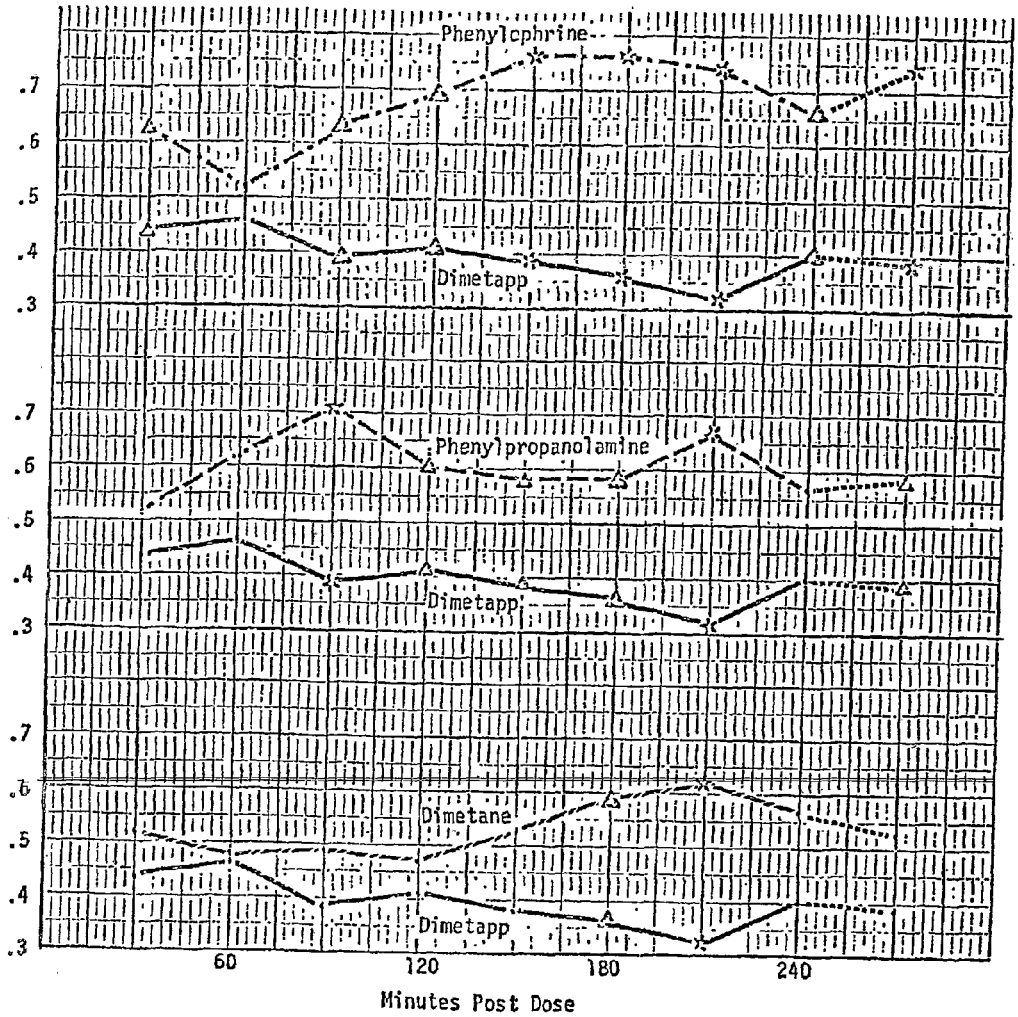
CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044791

Figure 4.2.2-04

EASE OF NASAL BREATHING

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



✱ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
▲ Significant at the 10% level

..... Afrin

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044792

Table 4.2.2-05

NASAL SEROUS SECRETIONS

Comparison of Mean Ridits with "No Change" Ridits

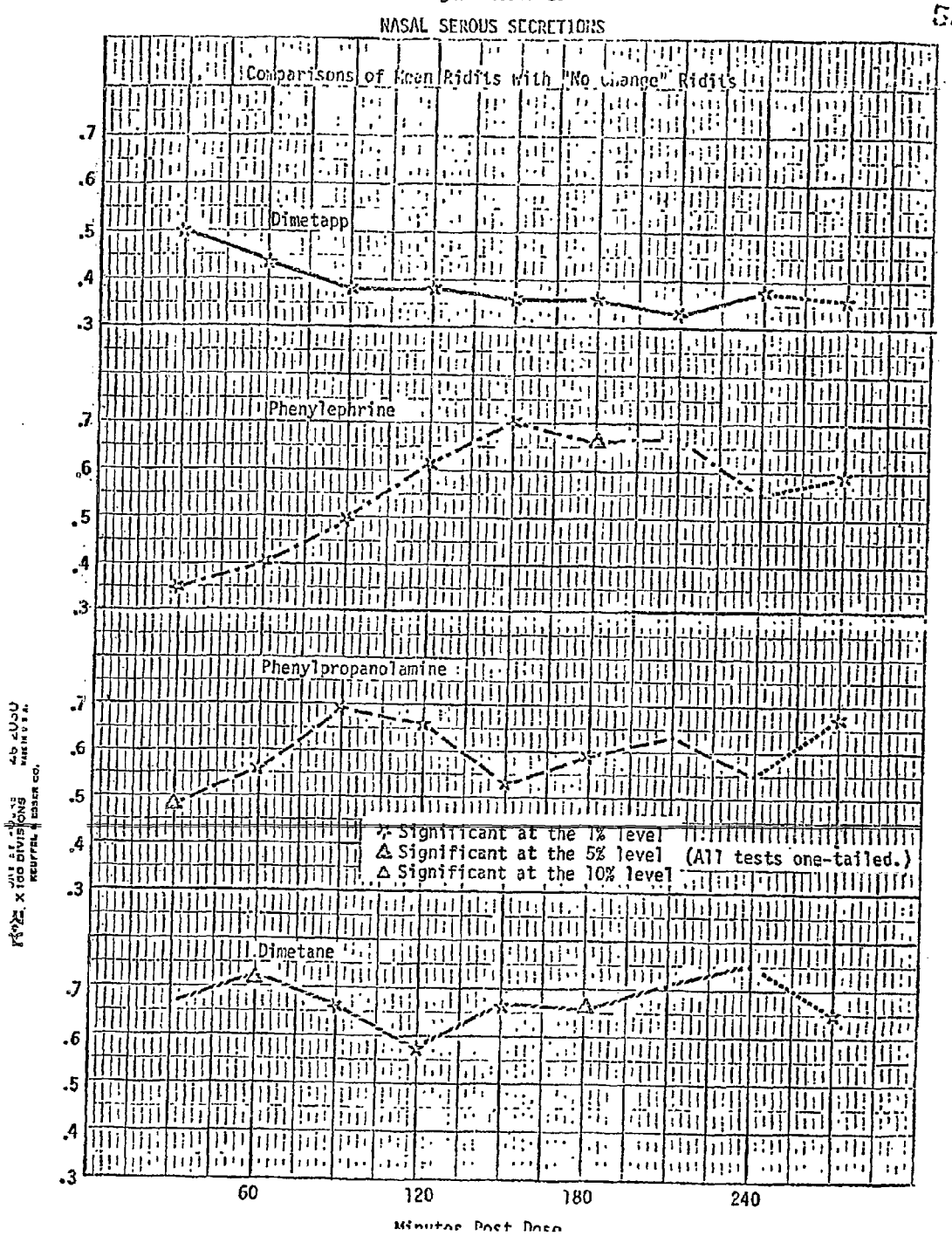
Minutes Post Dose	Treatment	Means (Ridits)	"No Change" Ridits	t	P+
30	Dimetapp	0.500	0.667	-3.601	<0.005
	PE	0.354		-3.897	<0.005
	PPA	0.480		-2.328	<0.025
	Dimetane	0.667		0	NS
60	Dimetapp	0.438	0.896	-10.417	<0.005
	PE	0.398		-6.539	<0.005
	PPA	0.560		-4.412	<0.005
	Dimetane	0.728		-2.206	<0.025
90	Dimetapp	0.384	0.958	-11.966	<0.005
	PE	0.490		-5.633	<0.005
	PPA	0.685		-3.286	<0.005
	Dimetane	0.672		-3.442	<0.005
120	Dimetapp	0.383	0.969	-11.376	<0.005
	PE	0.610		-4.024	<0.005
	PPA	0.660		-3.463	<0.005
	Dimetane	0.580		-4.360	<0.005
150	Dimetapp	0.360	0.915	-11.387	<0.005
	PE	0.704		-2.553	<0.01
	PPA	0.533		-4.623	<0.005
	Dimetane	0.668		-2.989	<0.005
180	Dimetapp	0.362	0.813	-9.379	<0.005
	PE	0.664		-1.789	<0.05
	PPA	0.586		-2.725	<0.005
	Dimetane	0.664		-1.789	<0.05
210	Dimetapp	0.334	0.625	-7.169	<0.005
	PE	0.667		0.597	NS
	PPA	0.625		0	NS
	Dimetane	0.708		1.180	NS
240	Dimetapp	0.383	0.552	-4.083	<0.005
	PE	0.552		0	NS
	PPA	0.548		- .056	NS
	Dimetane	0.750		2.762	NS
270	Dimetapp	0.362	0.979	-13.136	<0.005
	PE	0.591		-4.769	<0.005
	PPA	0.680		-3.675	<0.005
	Dimetane	0.645		-4.106	<0.005

+ One-tailed test

AHP2-REG-004-0044793

Figure 4.2.2-05

NASAL SEROUS SECRETIONS



AHP2-REG-004-0044794

Table 4.2.2-D6

NASAL MUCOSAL CONGESTION

Comparison of Mean Ridits With "No Change" Ridits

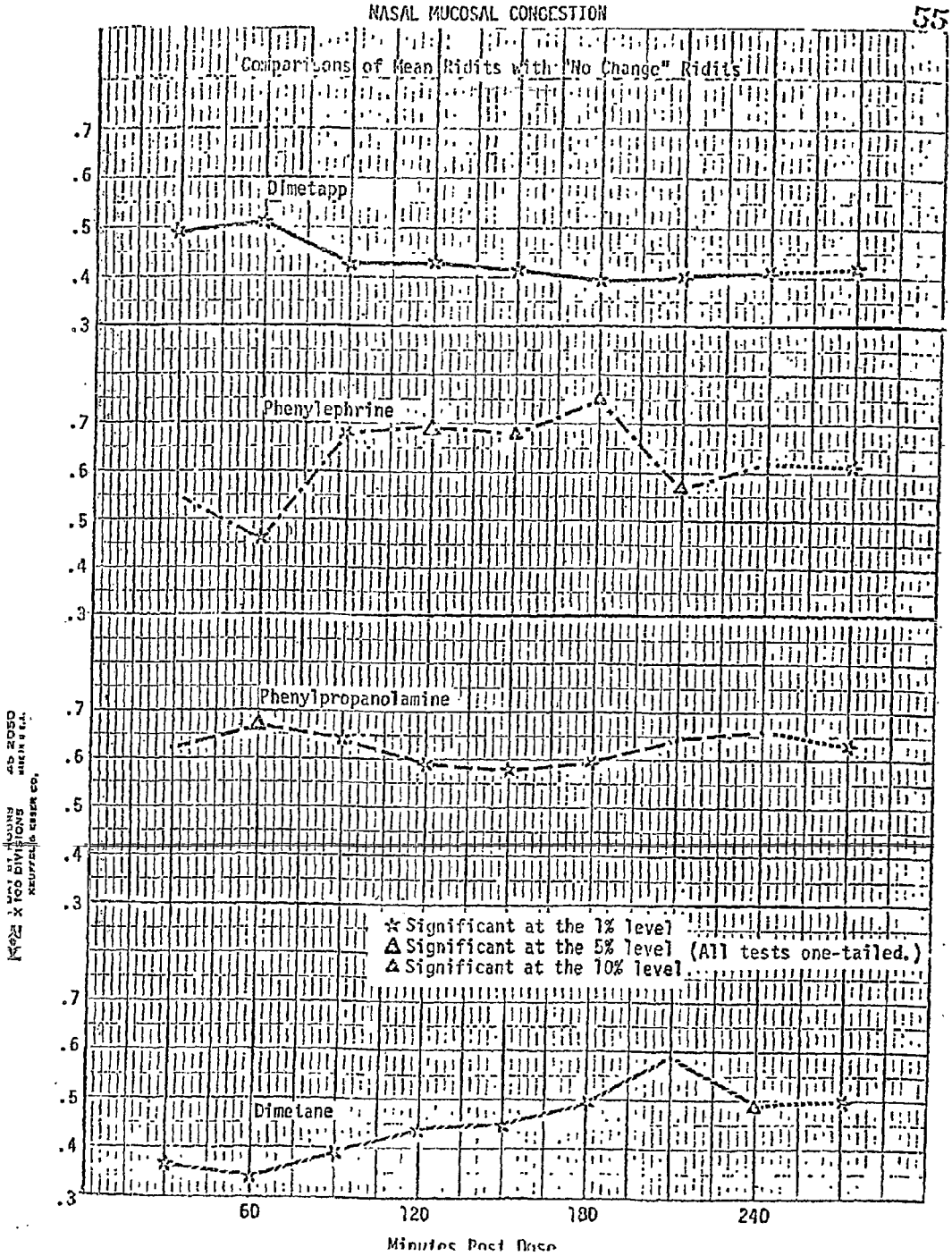
Minutes Post Dose	Treatment Means (Ridits)		"No Change" Ridits	t	P +
30	Dimetapp	0.488	0.615	-2.832	<0.005
	PE	0.554		-0.785	NS
	PPA	0.615		0	NS
	Dimetane	0.370		-3.155	<0.005
60	Dimetapp	0.509	0.844	-6.824	<0.005
	PE	0.457		-4.551	<0.005
	PPA	0.672		-2.023	<0.025
	Dimetane	0.342		-5.904	<0.005
90	Dimetapp	0.432	0.927	-10.516	<0.005
	PE	0.682		-3.005	<0.005
	PPA	0.638		-3.545	<0.005
	Dimetane	0.386		-6.636	<0.005
120	Dimetapp	0.427	0.906	-9.277	<0.005
	PE	0.685		-2.471	<0.01
	PPA	0.590		-3.533	<0.005
	Dimetane	0.444		-5.166	<0.005
150	Dimetapp	0.424	0.830	-7.488	<0.005
	PE	0.682		-1.610	<0.10
	PPA	0.584		-2.676	<0.005
	Dimetane	0.452		-4.111	<0.005
180	Dimetapp	0.392	0.854	-9.807	<0.005
	PE	0.747		-1.311	<0.10
	PPA	0.587		-3.272	<0.005
	Dimetane	0.490		-4.461	<0.005
210	Dimetapp	0.399	0.698	-5.962	<0.005
	PE	0.570		-1.474	<0.10
	PPA	0.643		-0.633	NS
	Dimetane	0.588		-1.266	NS
240	Dimetapp	0.412	0.615	-4.289	<0.005
	PE	0.615		0	NS
	PPA	0.659		0.537	NS
	Dimetane	0.491		-1.513	<0.10
270	Dimetapp	0.423	0.969	-11.100	<0.005
	PE	0.611		-4.202	<0.005
	PPA	0.625		-4.038	<0.005
	Dimetane	0.496		-5.552	<0.005

+ One-tailed tests

AHP2-REG-004-0044795

Figure 4.2.2-06

NASAL MUCOSAL CONGESTION



AHP2-REG-004-0044796

Table 4.2.2-07

NASAL MUCOSAL HYPEREMIA

Comparison of Mean Ridits with "No Change" Ridits

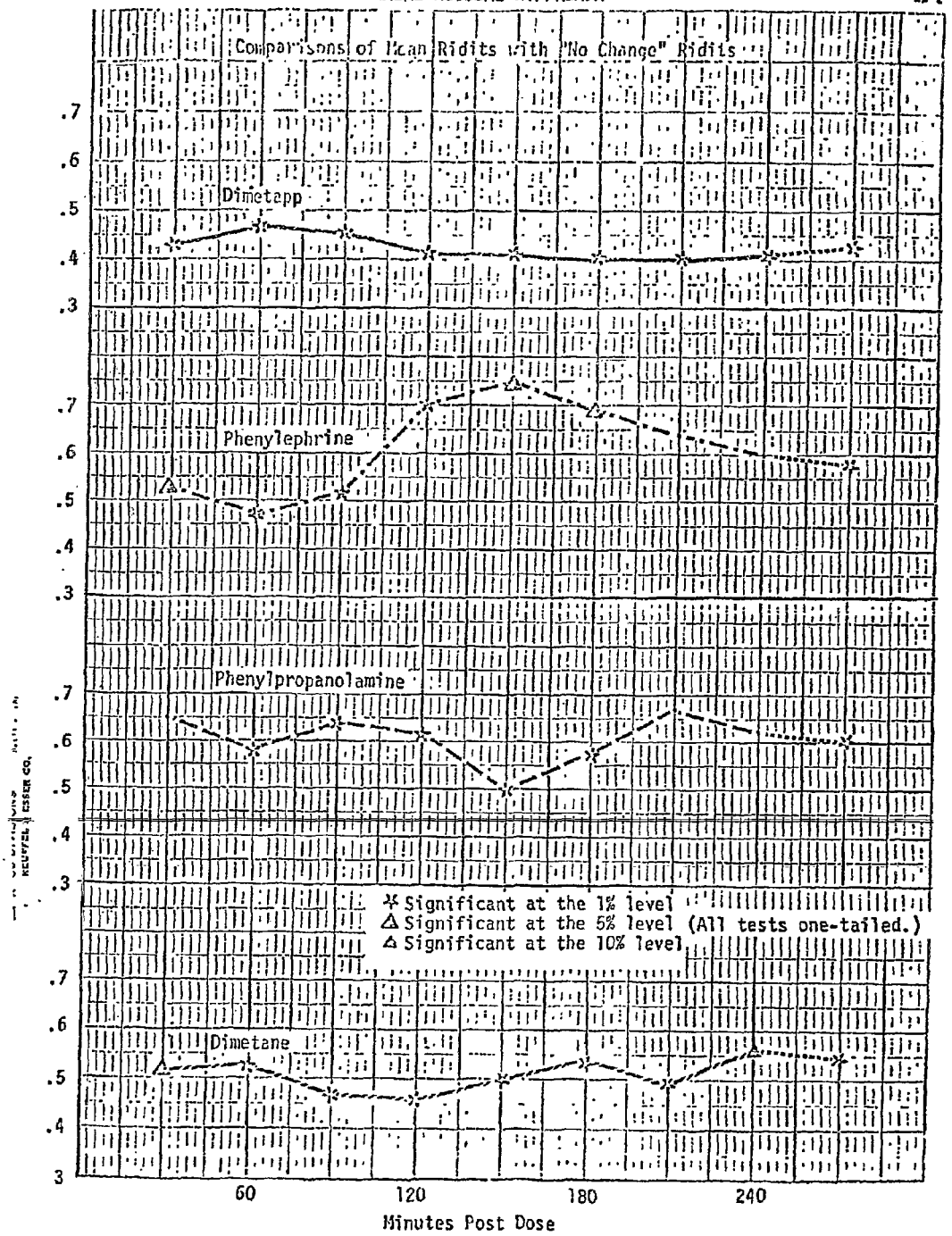
Minutes Post Dose	Treatment	Means (Ridits)	"No Change" Ridits	t	P+
30	Dimetapp	0.434	0.708	-5.453	<0.005
	PE	0.525		-2.103	<0.025
	PPA	0.647		-0.701	NS
	Dimetane	0.525		-2.103	<0.025
60	Dimetapp	0.473	0.927	-10.264	<0.005
	PE	0.473		-5.926	<0.005
	PPA	0.584		-4.477	<0.005
	Dimetane	0.526		-5.234	<0.005
90	Dimetapp	0.454	0.979	-11.451	<0.005
	PE	0.522		-5.810	<0.005
	PPA	0.642		-4.285	<0.005
	Dimetane	0.474		-6.421	<0.005
120	Dimetapp	0.405	0.948	-11.957	<0.005
	PE	0.704		-3.102	<0.005
	PPA	0.620		-4.170	<0.005
	Dimetane	0.461		-6.191	<0.005
150	Dimetapp	0.414	0.894	-9.642	<0.005
	PE	0.746		-1.753	<0.05
	PPA	0.500		-4.668	<0.005
	Dimetane	0.500		-4.668	<0.005
180	Dimetapp	0.398	0.854	-9.389	<0.005
	PE	0.690		-1.950	<0.05
	PPA	0.581		-3.245	<0.005
	Dimetane	0.537		-3.768	<0.005
210	Dimetapp	0.396	0.729	-6.830	<0.005
	PE	0.644		-1.007	NS
	PPA	0.670		-0.699	NS
	Dimetane	0.494		-2.783	<0.005
240	Dimetapp	0.410	0.677	-5.451	<0.005
	PE	0.596		-0.955	NS
	PPA	0.617		-0.707	NS
	Dimetane	0.557		-1.414	<0.10
270	Dimetapp	0.430	0.979	-10.879	<0.005
	PE	0.577		-4.599	<0.005
	PPA	0.596		-4.382	<0.005
	Dimetane	0.536		-5.068	<0.005

+ One-tailed test

AHP2-REG-004-0044797

Figure 4.2.2-07

NASAL MUCOSAL HYPEREMIA



AHP2-REG-004-0044798

Table 4.2.2-08

EASE OF NASAL BREATHING

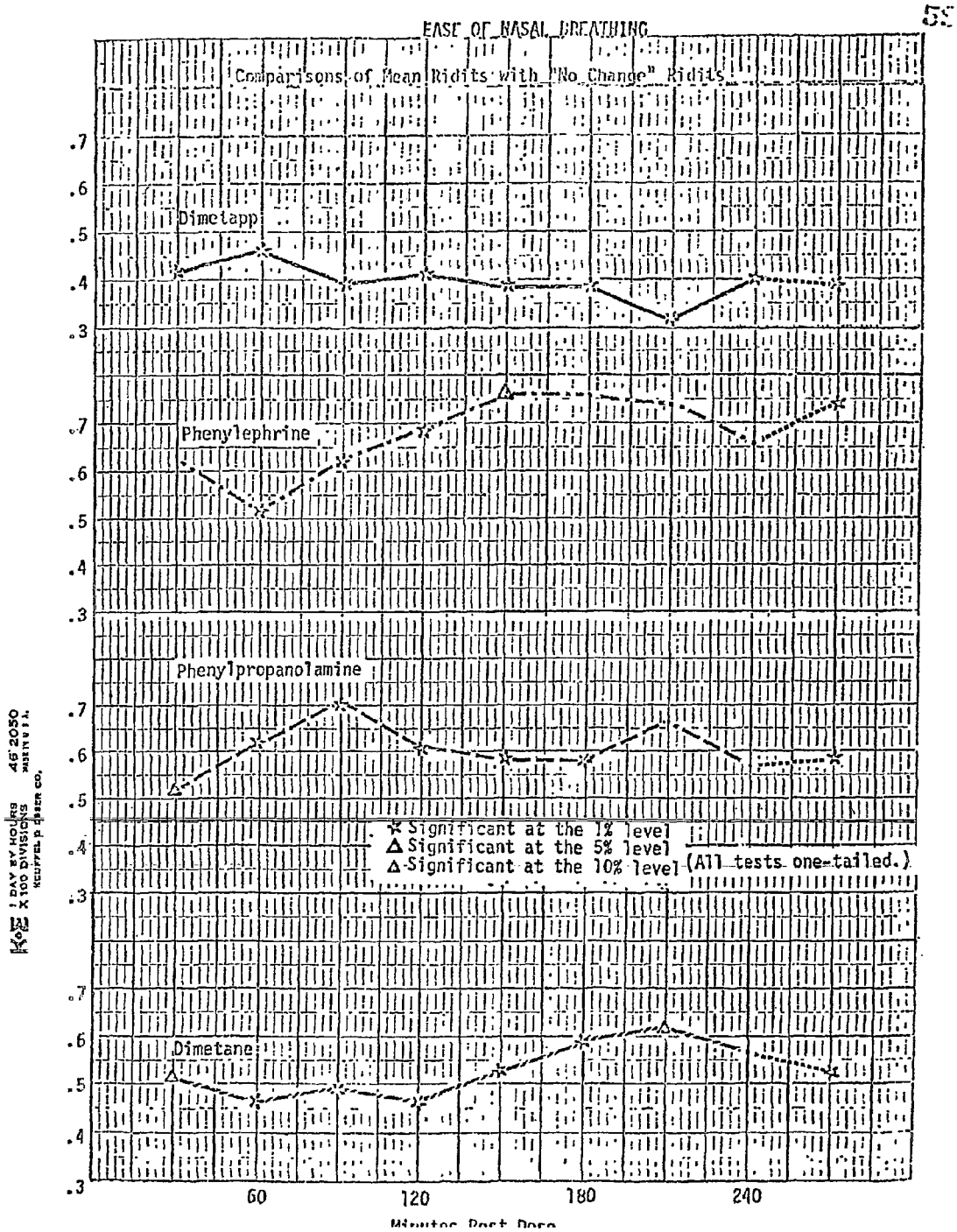
Comparison of Mean Ridits with "No Change" Ridits

Minutes Post Dose	Treatment Means (Ridits)		"No Change" Ridits	t	P +
30	Dimetapp	0.442	0.646	-4.212	<0.005
	PE	0.628		-0.214	NS
	PPA	0.524		-1.454	<0.10
	Dimetane	0.524		-1.454	<0.10
60	Dimetapp	0.464	0.917	-8.775	<0.005
	PE	0.521		-4.429	<0.005
	PPA	0.620		-3.322	<0.005
	Dimetane	0.469		-5.010	<0.005
90	Dimetapp	0.394	0.969	-11.434	<0.005
	PE	0.625		-3.949	<0.005
	PPA	0.707		-3.008	<0.005
	Dimetane	0.488		-5.522	<0.005
120	Dimetapp	0.412	0.969	-10.691	<0.005
	PE	0.685		-3.147	<0.005
	PPA	0.608		-4.000	<0.005
	Dimetane	0.470		-5.530	<0.005
150	Dimetapp	0.375	0.936	-11.387	<0.005
	PE	0.757		-2.143	<0.025
	PPA	0.577		-4.297	<0.005
	Dimetane	0.525		-4.920	<0.005
180	Dimetapp	0.357	0.854	-10.492	<0.005
	PE	0.763		-1.109	NS
	PPA	0.581		-3.328	<0.005
	Dimetane	0.586		-3.267	<0.005
210	Dimetapp	0.323	0.729	-9.946	<0.005
	PE	0.737		-0.113	NS
	PPA	0.674		-0.778	NS
	Dimetane	0.620		-1.542	<0.10
240	Dimetapp	0.403	0.625	-4.805	<0.005
	PE	0.656		0.387	NS
	PPA	0.568		-0.712	NS
	Dimetane	0.568		-0.712	NS
270	Dimetapp	0.382	0.990	-12.405	<0.005
	PE	0.740		-2.945	<0.005
	PPA	0.584		-4.782	<0.005
	Dimetane	0.531		-5.407	<0.005

+ One-tailed test

AHP2-REG-004-0044799

Figure 4.2.2-08



AHP2-REG-004-0044800

AHP2-REG-004-0044801

6. SAFETY FINDINGS

6.1 CLINICAL FINDINGS

6.1.1 Relationship of Drug to Adverse Effect

The relationship of the study medication to an adverse effect has been classified as (1) probable, (2) possible, or (3) unlikely. Judgements have been made primarily on the basis of information collected over the years the study medications have been marketed. An adverse effect has been declared probably or possibly related to study medication if the effect has been known to occur or has been reported in connection with the use of the drug. All other adverse effects have been judged unlikely to be related to the study medication.

6.1.2 Significance of an Adverse Effect

For this study no adverse effects have been categorized as "significant."

6.1.3 Listings of Adverse Reactions and Experiences

AHP2-REG-004-0044802

Table 6.1.3-01

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Dimetapp Elixir (single 10 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	5	64	F	VPC*	Cardio-vascular	No	Unlikely	No
		8	46	F	Drowsiness	CNS	No	Probably	No
		14	46	M	Drowsiness Dry mouth	CNS ANS	No No	Probably Probably	No No
		21	40	F	Drowsiness	CNS	No	Probably	No
		24	64	M	Frequent urination	Genito-urinary	No	Possibly	No
		35	23	F	Visual blurring	Ophthalmic	No	Probably	No
		44	40	F	Dryness of mouth and nose	ANS	No	Probably	No
		48	54	M	Light headed	CNS	No	Probably	No

Comments:

*Patient #5 had rare VPC prior to treatment and during study. The investigator did not consider this to be related to the test medication.

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044803

AHP2-REG-004-0044803

Table 6.1.3-02

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Dimetane Elixir (single 20 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	13	52	F	Circumoral numbness	ANS	No	Possibly	No
		20	51	M	Nervousness	CNS	No	Possibly	No
					Flatulence	Digestive	No	Unlikely	No
		27	46	F	Nervousness	CNS	No	Possibly	No
		36	39	M	Drowsiness	CNS	No	Probably	No

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044804

AHP2-REG-004-0044804

Table 6.1.3-03

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Propadrine Elixir (single 2.5 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	2	62	F	Dry mouth	ANS	No	Probably	No
		4	36	F	Drowsiness	CNS	No	Probably	No
		29	67	F	"Jittery"	CNS	No	Possibly	No

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044805

AHP2-REG-004-0044805

Table 6.1.3-04

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Neosynephrine Elixir (single 10 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	15	68	F	Nervousness	CNS	No	Possibly	No
					VPC's	Cardio-vascular	No	Possibly	No
		37	38	M	Headache	CNS	No	Possibly	No
					Visual blurring	CNS	No	Possibly	No
					Palpitations	Cardio-vascular	No	Probably	No

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044806

AHP2-REG-004-0044806

6.2 Measurements of Blood Pressures and Pulse Rates

A listing of the serial observations of blood pressures and pulse rates may be found in Appendix A6. Although rises in pulse rates from pre-drug values are occasionally noted, in no case, are these changes regarded as being clinically significant.

AHP2-REG-004-0044807

7. Overall Discussion and Concl.

AHP2-REG-004-0044808

7. OVERALL DISCUSSION AND CONCLUSIONS

On the basis of the data collected under the conditions of this study, one may conclude that the effects of Dimetapp Elixir on nasal airway resistances and on nasal mucosal characteristics are consistantly much better than those of any of its components.

AHP2-REG-004-0044809

APPENDICES

AHP2-REG-004-0044810

APPENDICES

AHP2-REG-004-0044811

A1. Study Protocol

AHP2-REG-004-0044812

A1.1 Study Protocol 01 (03/69)

AHP2-REG-004-0044813

3-6-67

FINAL

STUDY PROTOCOL

. H. ROBINS COMPANY
Medical Research Department
1407 Cummings Drive
Richmond, Virginia 23220

Name: Burton Marcus Cohen, M. D.

Address:

AHR Drug Number: G1 Drug Name: Dimetapp Elixir
Study Number: Protocol Number: 01

Study Type: Special X ; Dose-range
Controlled Therapeutic ; Uncontrolled Therapeutic

(Attach extra sheets, if necessary, and indicate by outline numbers shown below.)

A. OBJECTIVE(S): To compare the effect on nasal airway resistance and clinical observatio following a single dose of Dimetapp Elixir to that from a single dose of components.

B. PATIENTS or SUBJECTS: 1. Total number in study: 48 2. Number receiving "study" drug: 24

3. Disease(s) or symptoms being studied: Nasal congestion from URI

4. Age Range (yrs.) Adult 5. Male 24 (approx.) Female 24 (approx) Pregnant No

6. Hospitalized No ; Outpatients: Clinic No Office Yes

7. Other specific criteria for inclusion: Duration of URI not less than 24 hours, not more than 72 hours, at time of first test day.

8. Specific criteria for exclusion: Chronic pulmonary disease , allergic rhinitis

C. STUDY DESIGN

1. Open No Single-blind Yes (To physician and technician) Double-blind No

2. Continuous treatment Yes Crossover No 3. Randomized (yes or no) Yes

4. If this is a comparison study:
a. Comparison between subjects (yes or no): Yes ; if yes, will subjects be paired (yes or no): No

If paired, give basis of pairing:

b. Comparison within subjects (yes or no): Yes

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044814

TREATMENT: STUDY AND COMPARISON DRUG(S) INCLUDING PLACEBO

70

1. a.	Drug (include placebo)	Dimetapp Elixir	Neosynephrine Elixir	Propadrine Elixir	Dimetane Elixir
b.	No. of Subjects	24 5	8	8	8
c.	Route of Administration	Oral	Oral	Oral	Oral
d.	Single Dose (show unit size)	10 cc.	10 cc.	2.5 cc.	20 cc.
e.	Frequency of Administration (e.g., single dose, od, bid, tid, qid, etc.)	Single dose	Single dose	Single dose	Single dose
f.	Fixed or Variable Dosage (if variable, explain here or in Section K)	Fixed	Fixed	Fixed	Fixed
g.	Duration of Admin. (days)	1	1	1	1

2. If subjects are already on a drug with same general pharmacological action, for how long will they be taken off before being placed on the "study" or "comparison" drug? 48 hours

Given placebo during this "wash-out" period? No

3. What concomitant drug or other treatment will be given (or permitted) while subject is in this study? None

4. What concomitant drug or other treatment will be specifically excluded while subject is in this study?

Nasal decongestants (oral or topical)

E. CRITERIA FOR "EFFECTIVENESS" EVALUATION

~~1. Indicate specific clinical and/or laboratory parameters (and methods) to be used to evaluate drug effectiveness and~~ give schedule for these observations. For each lab test, show normal range of values for lab doing test:

OBSERVATION or TEST (and method)	SCHEDULE
A. Nasal airway resistance*	A. "0" time(drug given immediately thereafter), 30,60,90,120,180,240,270 minutes on each test day.
B. Observation of nasal mucosa	B. As above
*A.B. Craig., Jr., et.al: Resistanct to Airflow through the Nose. An. of ORL, 74:589, Sept., 1965	

(Continue in Section K or on extra page, if necessary)

AHP2-REG-004-0044815

Study Protocol

F. CRITERIA FOR "SAFETY" EVALUATION

1. Specific adverse clinical manifestations (i.e., "side effects") that warrant particular observation in connection with study drug: Nervousness, headache, nausea, dizziness or light-headed, drowsiness, dry mouth, urticaria, palpitation, blurred vision.

2. Laboratory determinations (for toxicity purposes) and schedule for these observations:

TEST	NORMAL RANGE OF VALUES FOR LAB. DOING TEST	SCHEDULE*
None		

*Pre-drug = within 3 days prior to drug initiation; interim = specify drug day(s); Post-drug = within 3 days following drug cessation.
Any abnormal test is to be repeated immediately, and supplemented by other tests considered desirable to assess situation.

3. Special Physical Examination:

PROCEDURE	SCHEDULE
BP (rt. arm sitting - 3 min)	0, 30, 60, 90, 120, 180, 240 and 270 minutes
Pulse (sitting 3 min)	

G. REPORTS

1. Attached is a copy of the special report form(s) to be used in this study. (An individual data sheet must be completed for each recipient of test drug or control medication. It must include patient's identification; symptom or diagnosis being treated; concurrent diagnosis; concurrent treatment; dosage of test drug administered; dates of drug administration; clinical observations and laboratory tests made to assess response or toxic effects; full statement of adverse effects noted and whether attributable to test drug; adequate statement of useful results observed and whether attributable to test drug; date of report and signature of investigator.)

H. ANALYSIS OF RESULTS

1. In addition to my own subjective evaluation of the over-all study, a statistical anaylsis will be performed by:

"Special" statistical techniques to be employed are:

2. Analysis will be performed by A.H. Robins statistician (yes or no): Yes

AHP2-REG-004-0044816

ADMINISTRATIVE ASPECTS

1. Study is contingent on approval by the following committee or panel (give name and address) (if none, please indicate

2. Name and address of hospital, clinic, institution or office where clinical work will be done: _____

3. Name and address of laboratory where laboratory work will be done: _____

4. Earliest date that study can start: _____

5. Estimated duration of the investigation as proposed: _____

6. First few reports will be submitted to A. H. Robins for checking:
Yes _____ No _____ ; then submitted: At end _____ Periodically _____

7. Comments: _____

J. LITERATURE REFERENCES

The following literature references are pertinent to this proposed study:
1. A. H. Robins Company Investigational Brochure

K. OTHER PERTINENT COMMENTS (e.g., general description of packaging and labeling of study medications, data forms, etc.) (attach supplemental page if needed):

SEE ATTACHED PAGE

TE: _____ INVESTIGATOR: _____

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044817

ADMINISTRATIVE ASPECTS

1. Study is contingent on approval by the following committee or panel (give name and address) (if none, please indicate):

2. Name and address of hospital, clinic, institution or office where clinical work will be done:

3. Name and address of laboratory where laboratory work will be done:

4. Earliest date that study can start:

5. Estimated duration of the investigation as proposed:

6. First few reports will be submitted to A. H. Robins for checking:
Yes _____ No _____ ; then submitted: At end _____ Periodically _____

7. Comments:

J. LITERATURE REFERENCES

The following literature references are pertinent to this proposed study:
1. A. H. Robins Company Investigational Brochure

K. OTHER PERTINENT COMMENTS (e.g., general description of packaging and labeling of study medications, data forms, etc.) (attach supplemental page if needed):
SEE ATTACHED PAGE

DATE: _____ INVESTIGATOR: _____

AHP2-REG-004-0044818

Section K - Protocol #01, Dimetapp Elixir

1. Each subject will have one test day. Drug combinations will be randomly assigned so that each subject will receive either Dimetapp Elixir, Dimetane, Neosynephrine or Propadrine.

2. Openly labeled commercial drugs will be used in this study. However, the randomization code will be kept, and the drugs will be administered, by someone other than the examining physician or the person conducting the airflow measurements.

3. Immediately after the 240 minute reading is taken, Afrin (oxymethazoline) nasal solution will be administered and a reading of nasal resistance will be taken 30 minutes later.

AHP2-REG-004-0044819

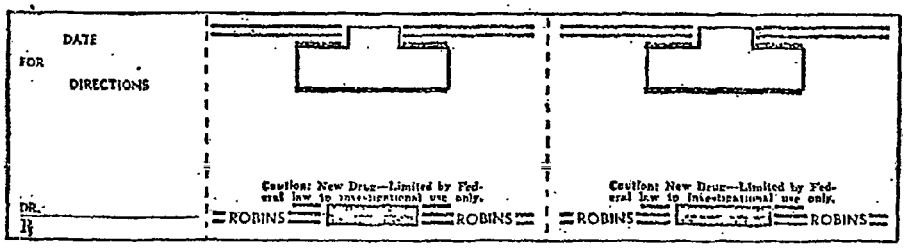
WORKSHEET FOR DETERMINING STUDY MEDICATION REQUIREMENTS AND PACKAGING INSTRUCTIONS

Investigator _____ Study Drug: Dimetapp Elixir Study No. _____ Protocol No. 01

DOSE FORM	UNIT SIZE	NUMBER DOSE UNITS PER PATIENT	NUMBER OF PATIENTS	TOTAL No. DOSE UNITS REQUIRED FOR ENTIRE STUDY
Dimetapp Elixir		10 cc.	24	240 cc.
(4 mg. bromphenirame, 5	mg.			
phenylephrine and 5 mg.				
phenylpropanolamin/5 cc.)				
Dimetane Elix. (2 mg. bron	/5 cc.)	20 cc.	8	160 cc.
Neosynephrine Elix. (1 mg.	PE/1 cc.)	10 cc.	8	80 cc.
Propadrine Elix. (4 mg. PE	/1 cc.)	2.5 cc.	8	20 cc.
Afrin Nasal Spray		4 drops each	24	
		nostril x 2		

PACKAGING: Commercial medication ____; special packaging required No; Number dose units per bottle _____ number bottles per patient _____; total number bottles required _____

LABELING (show): Single part label _____; double part label _____; triple part label _____.



(1st Part) (2nd Part) (3rd Part)

Randomization code required Yes. (If yes, attach to copy here and to completed protocol form.)

Additional instructions: _____

AHP2-REG-004-0044820

A1.2 Sample Data Sheet

AHP2-REG-004-0044821

CLINICAL DATA FORM
DIMETAPP ELIXIR

A.H. ROBINS COMPANY
Medical Department
1407 Cummings Drive
Richmond, Virginia 23220

Case Number _____
Study Number _____
Protocol Number _____

(Section I-IV to be completed at time of admission to study: date _____)

I. PATIENT IDENTIFICATION: Initials _____ Age _____ Sex _____ Race _____

Weight _____ Height _____ Pregnant-No

II. DIAGNOSIS OR CONDITION. Nasal mucosal congestion from URI.

Concurrent medical diagnosis or condition: _____

III. GENERAL HISTORY. Hepatic disease _____ renal disease _____

cardiac disease _____ hypertension _____ allergy _____ drug hypersensitivity _____ other _____

Give pertinent details of above (dates, severity, treatment, etc.) _____

_____

_____

IV. SPECIAL HISTORY. Date of onset of symptoms of URI _____ Symptoms present

cough _____ fever _____ sore throat _____ nasal stuffiness _____

headache _____ nasal secretion _____ muscular aching _____

weakness _____ other _____

V. DOSAGE AND SCHEDULE

Test Drug	Date	Time	Drug	Lot #	Dose
1st test day					
2nd test day					

VI. OBSERVATIONS AND ADVERSE EFFECTS (Record on other side).

AHP2-REG-004-0044822

CONFIDENTIAL / TRADE SECRET

te _____

VI. OBSERVATIONS AND ADVERSE EFFECTS (Drug Given Immediately After Making the "0" Minute Observation)

Case Number _____

st Day	Clinical Observation*					Ease**	Peak (V) L/minute		Pressure (cm H_2O) at 30 L/minute			Adverse Effects (see Protocol Fi, name at top of column and indicate severity *** in time block			
	PR	BP	MC	MH	SS		Insp.	Expir.	Insp.	Expir.	Total				
" time															
0 min.															
0 min.															
0 min.															
0 min.															
0 min.															
0 min															
0 min .															
0 min.															
70 min.															

* PR = pulse rate (give figures beats/min); BP = blood pressure (give figures mmHg); MC = Nasal mucosal congestion; MH = nasal mucosal hyperemia; SS = nasal secretion grade all as 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

** Ease of nasal breathing: 0 = normal; 1 = only mildly impaired; 2 = moderately impaired; 3 = severely impaired; 4 = total obstruction.

*** 1 = Did not significantly interfere with patient's functioning; 2 = significantly interfered with patient's functioning; 3 = nullified therapeutic effect; 4 = required withdrawal from study.

AHP2-REG-004-0044823

AHP2-REG-004-0044823

VII. COMMENT (e.g., if prematurely dropped from study, give reason; etc): _____

_____

_____

_____

_____

_____ Date of Report

_____ Signature of Investigator

AHP2-REG-004-0044824

A1.3 Randomization Schedule

The randomization code may be broken as follows:

A - Dimetapp Elixir

B - Neosynephrine Elixir

C - Propadrine Elixir

D - Dimetane Elixir

AHP2-REG-004-0044825

Randomization Schedule

Diseases Study Protocol #01

Investigator: Burton M. Cohen, M.D.

Pat. #	Drug	Pat. #	Drug
1	A	25	A
2	C	26	A
3	A	27	D
4	C	28	A
5	A	29	C
6	C	30	C
7	B	31	D
8	A	32	A
9	A	33	C
10	C	34	A
11	A	35	A
12	A	36	D
13	D	37	B
14	A	38	A
15	B	39	A
~~16~~	~~A~~	~~40~~	~~B~~
17	D	41	A
18	B	42	B
19	B	43	A
20	D	44	A
21	A	45	D
22	D	46	B
23	A	47	C
24	A	48	A

AHP2-REG-004-0044826

A4. Special Findings

AHP2-REG-004-0044827

APPENDIX A4. SPECIAL FINDINGS

A4.1 Listing of Measurements of Nasal Airway Resistance

AHP2-REG-004-0044828

Table A4.1-01

MEASUREMENTS OF NASAL INSPIRATORY RESISTANCE*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	3.00	2.75	2.50	2.35	2.70	2.35	2.70	3.05	3.15	2.05
3	3.75	3.80	2.75	2.40	1.95	2.15	2.30	3.10	2.95	1.75
5	3.80	4.05	2.95	2.45	2.30	2.65	3.10	3.85	4.10	2.65
8	4.55	4.40	2.95	2.55	2.35	2.60	3.10	2.85	3.10	2.45
9	5.00	4.80	3.75	3.10	2.80	3.05	3.60	4.70	4.55	3.05
11	3.60	3.20	3.00	1.75	1.80	1.75	1.80	1.90	2.05	1.45
12	4.05	3.60	2.90	3.00	1.90	1.65	1.55	2.05	1.75	1.65
14	4.40	3.85	2.40	2.35	2.40	2.70	1.90	2.60	2.75	1.55
16	3.85	3.75	3.60	2.10	2.15	2.00	2.55	2.65	2.75	2.10
21	3.85	3.65	2.05	2.35	2.40	2.25	3.00	3.40	3.65	2.05
23	3.70	3.90	2.10	1.90	2.10	1.85	2.60	2.60	3.15	1.80
24	3.70	3.85	3.55	2.55	2.35	2.40	2.30	3.15	4.10	2.10
25	4.00	3.80	3.65	2.10	2.60	2.70	2.65	3.65	3.95	3.10
26	4.40	3.80	2.55	2.15	2.70	2.40	2.65	3.00	2.95	2.40
28	4.00	3.50	4.00	2.60	2.40	2.75	2.65	3.55	4.10	2.60
32	3.75	3.80	3.55	3.05	2.60	2.40	2.15	2.65	3.75	2.10
34	3.65	3.50	3.40	3.60	2.80		3.10	2.95	3.75	2.60
35	4.40	4.00	4.10	3.10	2.80	2.40	2.70	2.90	2.75	2.40
38	3.65	3.00	2.60	2.55	2.30	2.15	2.40	2.80	2.75	2.15
39	4.40	3.80	2.25	1.95	2.40	2.05	2.35	2.75	3.10	2.25
41	4.15	3.70	3.30	4.10	3.85	4.20	3.95	4.50	3.75	2.60
43	5.15	4.15	3.95	3.40	3.30	2.95	3.55	4.15	4.40	3.10
44	4.35	4.60	3.50	3.65	2.80	2.10	3.60	2.55	4.05	3.80
48	4.60	3.80	4.35	2.60	2.40	2.70	2.65	3.15	3.80	2.90
MEANS	4.07	3.78	3.15	2.65	2.51	2.42	2.70	3.10	3.38	2.38

* Pressure (cm H_2O) at 0.5 L/sec

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

(Continued)

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044829

AHP2-REG-004-0044829

Table A4. (Continued)

MEASUREMENTS OF NASAL INSPIRATORY RESISTANCE*

TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	3.10	3.25	2.75	2.65	2.55	2.75	3.05	2.85	3.15	1.95
15	3.75	3.80	3.60	3.40	2.70	2.95	2.90	3.05	3.55	2.65
18	4.55	4.30	2.80	2.70	3.10	2.90	3.75	4.15	3.95	3.00
19	4.45	4.40	3.70	3.65	3.80	3.45	4.10	3.95	4.10	2.90
37	3.85	3.55	3.40	2.60	2.40	2.75	3.60	3.55	3.60	2.60
40	3.75	3.40	3.30	2.60	3.10	3.00	4.15	3.35	4.05	3.00
42	4.15	3.95	3.50	4.25	3.70	4.10	4.25	4.15	3.95	2.65
46	3.85	3.75	3.80	2.75	3.40	3.75	3.80	4.25	4.00	3.10
MEANS	3.93	3.80	3.36	3.07	3.09	3.31	3.69	3.66	3.79	2.73

TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	4.25	4.30	3.95	4.10	2.75	3.10	3.75	3.40	4.55	3.10
4	3.75	3.60	3.50	2.75	3.05	3.30	4.10	3.95	3.05	2.55
6	4.20	3.95	3.45	3.10	2.10	3.00	2.95	3.85	3.75	2.75
10	4.80	4.55	4.40	3.65	2.80	2.60	2.55	3.80	3.75	3.10
29	2.60	2.55	2.40	2.10	2.40	2.65	2.70	2.65	3.05	2.75
30	3.80	3.75	3.20	2.80	2.60	3.10	3.40	3.20	3.60	2.60
33	4.05	3.75	3.50	3.00	3.15	3.00	2.85	3.75	3.60	2.80
47	3.95	4.10	2.95	3.10	3.00	2.60	2.80	2.70	2.65	2.55
MEANS	3.92	3.82	3.42	3.07	2.73	2.92	3.14	3.41	3.50	2.71

TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	4.00	3.85	4.05	3.75	2.45	2.75	2.35	2.55	3.05	1.95
17	3.55	3.40	2.90	2.40	2.60	3.15	2.65	3.65	3.40	2.60
20	3.80	3.90	3.45	2.40	3.60	2.80	2.75	2.90	3.60	2.10
22	4.40	3.90	3.40	2.65	2.50	2.40	2.95	3.70	2.90	2.60
27	4.60	3.80	2.90	2.70	2.60	2.70	3.10	3.40	3.90	2.60
31	2.95	2.80	2.30	2.60	2.20	2.60	2.70	2.60	2.30	2.00
36	4.40	3.95	3.50	3.60	3.20	2.80	4.10	3.85	4.15	3.00
45	4.35	4.10	4.40	3.75	4.20	3.75	3.80	2.90	3.75	2.90
MEANS	4.01	3.71	3.36	2.98	2.97	2.87	3.05	3.21	3.30	2.47

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044830

AHP2-REG-004-0044830

Table 4.1-02

MEASUREMENTS OF NASAL EXPIRATORY RESISTANCE*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	2.95	2.50	2.50	2.25	2.40	2.25	3.00	2.15	2.40	2.80
3	2.50	2.15	2.00	2.05	1.75	1.75	2.15	2.65	2.40	1.50
5	3.50	3.45	2.10	1.95	1.75	1.90	2.10	2.10	3.10	2.10
8	3.25	3.20	2.70	2.10	2.25	1.90	2.15	2.65	3.05	2.30
9	3.75	3.45	3.50	2.85	1.80	1.75	1.90	2.65	3.35	2.80
11	3.55	2.80	1.90	1.60	1.50	1.25	1.75	1.60	1.90	1.25
12	3.20	1.90	1.90	2.70	1.60	1.50	1.40	2.00	1.80	1.30
14	3.60	3.40	2.40	2.30	2.20	1.80	1.60	1.85	2.10	1.40
16	3.00	2.85	3.40	1.80	1.65	1.75	2.00	2.45	2.45	2.00
21	2.60	2.60	1.80	1.90	1.70	1.90	1.95	2.20	3.60	1.35
23	2.60	2.15	1.90	1.75	2.00	1.80	2.40	2.55	2.95	1.35
24	3.25	3.25	2.10	2.00	2.30	2.15	2.25	2.40	2.60	1.70
25	2.90	3.70	3.50	2.00	2.30	1.40	2.50	3.50	3.80	2.10
26	2.80	2.60	2.15	1.80	2.45	1.80	1.90	2.05	2.00	1.90
28	3.40	3.20	1.90	2.30	2.35	2.60	2.15	3.10	3.70	2.50
32	3.60	3.30	3.10	1.80	1.80	2.05	1.95	2.50	3.10	1.45
34	3.50	3.20	2.05	3.10	1.35		2.10	2.80	2.40	2.20
35	2.90	2.70	2.10	1.75	2.15	2.30	2.65	2.90	2.55	1.80
38	2.10	1.85	1.30	2.10	1.35	1.40	1.50	2.40	2.10	1.60
39	2.65	2.00	1.80	1.75	2.30	1.65	2.15	2.60	2.80	1.75
41	3.80	3.10	3.10	3.80	3.50	3.70	3.50	3.75	3.50	2.50
43	3.60	3.75	3.10	2.70	2.60	2.40	3.30	2.60	3.00	2.95
44	3.10	2.40	2.00	2.00	2.10	1.80	2.05	2.50	2.65	1.75
48	2.95	3.10	2.65	2.50	2.30	2.60	2.50	3.00	3.00	2.85
MEANS	3.13	2.86	2.37	2.20	2.07	1.97	2.20	2.54	2.76	1.97

*Pressure (cm H_2O) at 0.5 L/sec

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044831

AHP2-REG-004-0044831

Tab I-02 (Continued)

MEASUREMENTS OF NASAL EXPIRATORY RESISTANCE*

TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	0	30	60	90	120	150	180	210	240	270
	MINUTES AFTER DOSE									
7	2.95	2.65	2.65	2.55	2.20	2.60	2.85	2.60	2.95	1.40
15	3.75	3.35	2.95	3.35	2.65	2.80	2.40	3.00	3.40	2.15
18	4.00	3.60	2.60	2.50	2.60	2.35	3.40	3.50	3.85	2.10
19	4.10	3.95	3.45	3.10	3.10	3.30	3.45	3.70	3.00	2.80
37	3.60	3.20	2.60	2.60	2.30	2.55	3.10	3.10	3.20	2.10
40	3.25	3.10	2.80	2.10	2.95	2.00	3.10	2.60	3.80	2.75
42	2.80	3.00	2.80	3.10	2.40	2.40	4.00	3.15	3.40	2.55
46	3.00	3.50	3.10	2.60	2.60	2.50	3.40	2.80	3.15	3.00
MEANS	3.52	3.29	2.87	2.74	2.60	2.56	3.21	3.06	3.34	2.36

TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	0	30	60	90	120	150	180	210	240	270
	MINUTES AFTER DOSE									
2	3.15	3.20	3.30	3.10	2.40	2.15	2.20	3.15	3.65	2.10
4	3.60	3.55	3.45	2.65	2.55	2.10	2.15	3.25	2.90	2.25
6	3.10	2.95	3.10	2.65	2.00	2.35	2.85	3.55	2.80	2.05
10	3.90	3.85	3.75	3.35	2.60	1.80	2.40	3.70	3.60	2.15
29	2.40	2.30	2.10	1.60	1.75	1.85	2.40	2.20	3.00	1.95
30	2.20	2.15	1.90	2.70	2.50	2.90	2.40	2.60	2.70	2.10
33	2.80	3.40	3.30	2.15	2.15	2.40	2.50	3.00	2.80	2.70
47	3.80	2.75	2.60	2.00	2.40	2.10	2.20	2.30	2.55	2.00
MEANS	3.12	3.02	2.94	2.52	2.27	2.21	2.39	2.97	3.00	2.16

TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	0	30	60	90	120	150	180	210	240	270
	MINUTES AFTER DOSE									
13	3.65	3.50	2.45	3.00	2.10	2.25	2.05	2.15	3.00	1.75
17	3.60	3.10	2.85	1.90	1.90	2.05	2.55	2.75	2.60	1.85
20	3.10	3.20	3.55	1.80	2.30	2.65	2.75	2.65	2.80	2.05
22	2.05	3.40	3.20	2.50	2.45	2.30	2.80	3.40	2.90	2.50
27	3.70	3.60	2.60	2.50	2.30	2.05	2.60	2.20	3.00	2.20
31	2.60	2.60	2.25	2.40	1.95	2.05	2.75	2.15	2.40	1.60
36	3.60	3.40	3.00	2.60	2.40	2.10	2.40	3.00	3.75	2.45
45	2.80	2.75	2.20	2.15	2.60	3.00	2.55	2.60	3.35	2.50
MEANS	3.21	3.19	2.76	2.36	2.22	2.31	2.56	2.61	2.97	2.11

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044832

AHP2-REG-004-0044832

A4.2 Listings of Ratings for Nasal Mucosal Characteristics

AHP2-REG-004-0044833

Table A4.2-01

RATINGS OF NASAL MUCOSAL CONGESTION*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	3	3	2	2	3	3	2	3	3	3
3	4	4	2	1	2	2	3	2	3	1
5	3	3	2	2	2	3	2	3	4	2
8	3	3	3	2	2	3	2	3	3	2
9	3	4	3	2	2	2	2	3	3	2
11	3	3	3	2	2	2	2	3	3	2
12	3	3	2	2	2	2	2	3	3	2
14	3	3	2	2	2	2	2	2	2	2
16	4	3	4	2	2	2	2	2	2	2
21	3	3	2	2	2	2	2	3	3	2
23	4	3	2	2	2	2	2	3	2	2
24	4	4	3	3	2	2	2	2	2	2
25	3	3	3	3	3	3	3	3	3	2
26	3	3	2	2	2	2	2	3	3	2
28	4	4	3	3	2	2	3	3	3	2
32	4	3	4	2	2	2	2	3	3	2
34	4	3	3	2	2	2	2	3	3	2
35	3	2	2	2	2	3	3	3	3	2
38	3	2	3	2	2	2	2	3	3	2
39	3	3	3	2	2	2	2	2	3	2
41	4	4	3	3	4	4	4	3	4	2
43	4	3	3	3	2	3	2	3	3	2
44	4	4	3	2	2	2	3	2	3	2
48	4	4	3	2	2	2	3	3	3	2

*Rated on a five point scale: 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044834

AHP2-REG-004-0044834

Table A4.2-01 (Cont'd.)

RATINGS OF NASAL MUCOSAL CONGESTION*

2 3 TREATMENT GROUP: Nepsynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	3	3	2	3	3	3	3	4	3	2
15	3	3	3	3	2	2	2	3	3	2
18	3	3	2	2	2	3	3	3	3	3
19	4	3	3	3	3	3	4	3	4	3
37	4	4	2	2	3	3	3	3	4	2
40	4	4	3	3	3	4	4	4	4	3
42	3	3	3	3	3	3	3	4	3	2
46	3	3	2	3	3	3	3	3	3	2

3 3 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	4	4	4	3	2	3	3	4	4	3
4	4	4	4	3	3	3	3	3	4	3
6	3	3	2	2	2	3	2	3	3	2
10	3	3	3	3	3	3	2	3	3	2
29	3	3	3	2	2	3	3	3	4	2
30	3	3	2	2	2	2	2	3	3	2
33	3	3	3	2	3	2	3	3	3	2
47	3	3	2	3	2	2	3	3	3	2

4 3 TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	3	3	2	2	2	2	2	3	3	2
17	4	3	2	2	2	3	3	4	3	2
20	3	3	2	2	2	3	3	3	3	2
22	3	3	2	2	2	2	2	3	2	3
27	4	3	3	2	2	2	2	3	4	2
31	3	3	2	2	3	3	3	3	3	2
36	4	3	3	2	2	2	3	3	3	2
45	3	3	2	2	2	2	2	3	4	2

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044835

AHP2-REG-004-0044835

Table A4.2-02

RATINGS ON NASAL MUCOSAL HYPEREMIA *

1 4. TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	3	2	2	2	2	2	2	3	3	3
3	3	3	2	2	2	2	2	3	3	1
5	3	3	2	2	2	2	2	3	3	2
8	3	3	2	2	2	2	3	3	3	2
9	3	3	2	2	2	2	2	3	3	2
11	3	2	3	2	2	2	2	2	2	1
12	3	2	2	2	2	2	3	2	2	2
14	3	3	2	2	2	2	2	2	2	2
16	4	3	3	2	2	2	2	2	3	2
21	3	3	2	2	2	2	2	3	3	2
23	4	4	2	2	2	2	2	3	2	2
24	4	3	2	2	2	2	2	3	3	2
25	3	3	3	2	2	3	2	2	2	2
26	3	3	2	2	2	2	2	2	3	2
28	4	3	3	3	2	2	3	3	3	2
32	4	3	3	2	2	2	2	2	3	2
34	4	3	3	2	2		3	3	3	2
35	3	2	2	2	2	3	3	3	3	2
38	3	2	2	2	2	2	2	3	3	2
39	3	3	3	2	2	2	2	2	3	2
41	4	3	3	3	3	3	3	3	4	2
43	4	3	3	3	2	3	2	3	3	2
44	4	4	3	2	2	2	3	3	3	2
48	4	2	2	2	2	2	3	3	3	2

*Rated on a five point scale: 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044836

Table A4.2-02 (Cont'd.)

RATINGS ON NASAL MUCOSAL HYPEREMIA *

2 4 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	3	3	2	2	3	3	3	3	3	2
15	3	3	2	2	2	2	2	3	3	2
18	3	2	2	2	3	3	3	3	3	3
19	4	3	3	3	3	4	4	4	4	3
37	4	4	2	2	3	3	3	3	3	2
40	4	4	3	2	2	3	3	3	3	2
42	3	2	3	2	3	3	3	4	3	2
46	3	3	2	3	3	3	3	3	4	2

3 4 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	4	4	3	3	3	3	3	4	4	3
4	4	4	3	3	3	2	4	3	3	2
6	3	3	2	2	2	2	2	3	3	2
10	3	3	3	2	2	2	2	3	3	2
29	3	3	3	2	2	3	3	3	3	2
30	3	3	2	2	2	2	2	3	3	2
33	3	2	2	2	3	2	3	3	3	2
47	3	3	2	3	2	2	2	3	3	2

4 4 TREATMENT GROUP: Dimetane Elixir (8 mg. brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	3	3	2	2	2	2	3	3	3	2
17	4	4	3	3	3	3	3	3	3	3
20	3	3	2	2	2	2	2	2	3	2
22	3	3	3	2	2	3	3	3	3	2
27	4	3	3	2	2	2	2	3	4	2
31	3	2	2	2	2	3	3	3	3	2
36	4	3	3	2	2	2	3	3	3	2
45	3	3	2	2	2	2	2	3	3	2

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044837
AHP2-REG-004-0044837

Table A4.2-03

RATINGS OF NASAL SEROUS SECRETIONS *

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	3	2	2	2	2	2	2	3	3	3
3	3	3	2	1	2	2	2	2	3	1
5	3	3	2	2	2	2	2	3	3	2
8	4	3	2	2	2	2	2	3	3	2
9	4	3	2	2	2	2	2	2	2	2
11	3	3	2	2	1	1	2	2	2	1
12	3	3	2	1	1	0	1	2	2	0
14	2	2	1	0	1	1	1	1	2	0
16	3	3	3	0	1	1	1	2	2	0
21	3	2	1	1	1	1	2	2	3	0
23	3	3	2	0	0	1	1	2	3	0
24	3	3	2	0	0	0	1	1	1	1
25	2	2	1	1	0	1	1	2	2	1
26	3	2	1	0	0	0	0	2	2	0
28	3	2	2	1	1	1	2	2	2	2
32	3	3	3	1	0	1	2	2	3	1
34	3	3	2	1	0		2	3	3	2
35	3	3	2	2	2	2	3	2	3	1
38	3	2	2	1	0	1	1	3	3	1
39	3	2	2	2	0	0	2	2	3	1
41	3	3	3	3	3	3	4	4	3	2
43	3	3	2	2	2	2	2	2	2	2
44	3	3	2	2	1	2	3	3	3	1
48	3	2	2	2	1	2	2	3	3	1

*Rated on a five point scale: 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044838

A4.2-03 (Cont'd.)

RATINGS OF NASAL SEROUS SECRETIONS*

2 5 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	3	3	2	2	2	3	3	4	3	1
15	3	3	2	2	2	2	2	3	3	2
18	3	2	1	1	1	2	3	3	3	2
19	4	3	3	2	2	4	4	4	4	2
37	3	3	2	1	1	2	2	3	3	2
40	3	2	2	2	2	3	3	3	3	2
42	3	2	2	2	3	3	3	3	3	2
46	3	2	2	2	2	1	2	3	3	2

3 5 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	4	4	3	3	3	2	3	4	4	3
4	4	4	3	3	2	2	4	4	4	2
6	3	3	2	2	2	2	2	3	3	2
10	3	3	3	2	2	2	2	3	3	2
29	3	2	2	2	2	2	3	3	3	2
30	3	2	2	2	1	2	2	3	3	2
33	2	2	2	2	2	2	3	2	3	2
47	3	2	2	2	2	2	2	3	2	2

4 5 TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	2	2	2	0	0	1	2	2	3	1
17	3	3	3	3	2	3	3	3	3	2
20	2	2	2	1	1	1	2	3	3	1
22	2	2	2	2	1	2	2	3	3	1
27	3	3	3	2	1	2	2	3	4	2
31	3	3	2	2	2	2	2	3	3	1
36	3	3	2	1	1	2	3	4	3	2
45	3	3	2	2	2	2	2	3	3	2

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044839

AHP2-REG-004-0044839

Table A4.2-04

RATINGS OF EASE OF NASAL BREATHING*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	2	2	2	2	2	2	2	2	2	2
3	3	3	3	2	2	1	1	2	3	1
5	4	3	2	2	1	2	1	3	3	1
8	3	3	2	1	2	2	2	3	3	1
9	4	3	2	2	2	2	2	2	3	2
11	3	3	3	1	1	1	2	2	2	1
12	3	3	1	1	0	0	0	1	1	0
14	3	3	1	0	1	1	1	1	2	0
16	3	3	3	2	1	1	1	2	2	0
21	3	2	1	1	1	1	2	2	3	1
23	3	3	2	0	0	0	0	2	3	0
24	3	3	2	1	1	1	1	2	1	1
25	3	2	1	1	1	1	1	2	2	1
26	3	2	1	0	1	1	1	2	2	0
28	3	2	2	1	1	1	2	2	2	2
32	3	3	3	0	0	1	2	2	3	1
34	3	3	2	1	1		2	2	3	2
35	3	2	1	1	2	2	3	2	3	1
38	3	2	2	1	1	1	1	2	3	1
39	3	3	2	1	1	1	1	2	3	1
41	3	3	3	3	3	3	3	3	3	2
43	3	3	2	2	2	2	2	2	3	2
44	4	3	2	2	1	2	3	2	3	1
48	3	3	2	2	1	2	2	3	3	1

*Rated on a five point scale: 0=normal; 1=only mildly impaired; 2=moderately impaired; 3=severely impaired; 4=total obstruction.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044840

Table A4.2-04 (Cont'd.)

RATINGS OF EASE OF NASAL BREATHING*

2 6 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	3	2	2	2	2	3	3	4	3	2
15	3	4	2	2	2	2	2	2	4	2
18	3	3	2	1	1	1	3	4	4	2
19	4	4	3	3	3	4	4	4	4	2
37	3	3	2	1	1	3	2	3	3	2
40	3	2	2	2	2	2	3	3	3	2
42	3	2	2	2	3	3	3	3	2	2
46	3	2	2	2	2	2	3	3	3	2

3 6 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	3	3	3	3	2	2	2	3	3	2
4	4	4	3	3	3	2	3	4	4	2
6	3	3	2	1	1	2	2	3	3	1
10	3	3	3	2	1	2	2	3	3	1
29	3	2	2	2	2	2	3	3	3	2
30	3	3	2	2	1	2	2	3	2	2
33	3	3	2	2	2	1	3	2	3	1
47	3	2	2	2	2	2	2	3	3	2

4 6 TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	3	3	2	1	1	1	2	2	3	1
17	4	4	3	3	2	3	4	4	4	3
20	3	3	2	1	1	1	2	3	2	1
22	3	3	2	2	2	2	2	3	3	2
27	4	3	2	1	1	2	2	3	4	2
31	3	3	2	2	2	2	3	3	3	1
36	3	3	2	1	1	2	3	3	3	1
45	3	2	2	2	2	2	2	3	3	2

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044841
AHP2-REG-004-0044841

A4.3 Analyses of Covariance - Nasal Inspiratory and Expiratory Resistances

Treatment 1 = Dimetapp

Treatment 2 = Neosynephrine (10 mg phenylephrine hydrochloride)

Treatment 3 = Propadrine (10 mg phenylpropanolamine hydrochloride)

Treatment 4 = Dimetane (8 mg brompheniramine maleate)

AHP2-REG-004-0044842

NASAL INSPIRATORY RESISTANCE - 30 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	0.03490	0.05167	3			0.22668	3	0.075559	1.36449
ERROR	11.82177	9.24594	9.61250	44	0.78211	7.23135	2.38115	43	0.055376	
TRT 1	5.43990	4.06031	4.68906	23	0.74640	3.03060	1.65846	22		
TRT 2	1.46949	1.20750	1.16000	7	0.82160	0.99209	0.16791	6		
TRT 3	2.76500	2.55875	2.52969	7	0.92541	2.36788	0.16180	6		
TRT 4	2.14719	1.41938	1.23375	7	0.66104	0.93826	0.29549	6		
TOTAL	12.02370	9.21104	9.66417	47	0.76607	7.05634	2.60783			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.7812	3.7348
TRT 2	3.9312	3.8000	3.8644
TRT 3	3.9250	3.8187	3.8880
TRT 4	4.0062	3.7125	3.7182

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 0.412 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 3.269 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 0.946 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.3692 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 176.6620 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.7792

DISREGARDING COVARIATE, F IS 0.0788

COVARIATE = 0 MIN

OBSERVATION = 30 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044843

AHP2-REG-004-0044843

NASAL INSPIRATORY RESISTANCE - 60 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.33060	0.62646	3			1.07129	3	0.359095	1.21346
ERROR	11.82177	7.04177	16.91521	44	0.59566	4.19451	12.72070	43	0.295830	
TRT 1	5.43990	2.88271	10.13958	23	0.52992	1.52760	8.61198	22		
TRT 2	1.46949	0.29594	1.07719	7	0.20136	0.05959	1.01760	6		
TRT 3	2.76500	2.40125	2.56469	7	0.86844	2.08535	0.47933	6		
TRT 4	2.14719	1.48188	3.13375	7	0.68083	0.99529	2.13846	6		
TOTAL	12.02370	6.70917	17.54167	47	0.55800	3.74368	13.79798			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.1542	3.1188
TRT 2	3.9312	3.3562	3.4053
TRT 3	3.9250	3.4187	3.4715
TRT 4	4.0062	3.3625	3.3668

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.133 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 3.376 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 0.844 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.5153 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 13.6993 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.2667

DISREGARDING COVARIATE, F IS 0.5432

COVARIATE = 0 MIN

OBSERVATION = 60 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044844

AHP2-REG-004-0044844

NASAL INSPIRATORY RESISTANCE - 90 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.59622	1.86818	3			2.49604	3	0.832014	2.75017
ERROR	11.82177	6.11240	16.16927	44	0.51705	3.16039	13.00888	43	0.302532	
TRT 1	5.43990	2.13271	8.37958	23	0.39205	0.83613	7.54346	22		
TRT 2	1.46969	0.78075	2.69500	7	0.52307	0.40211	2.29289	6		
TRT 3	2.76500	2.21750	2.52000	7	0.80199	1.77841	0.74159	6		
TRT 4	2.14719	0.99344	2.57469	7	0.46267	0.45963	2.11505	6		
TOTAL	12.02370	5.51818	18.03745	47	0.45896	2.53252	15.50493			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	2.6542	2.6235
TRT 2	3.9312	3.0750	3.1175
TRT 3	3.9250	3.0750	3.1208
TRT 4	4.0062	2.9817	2.9850

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.198 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 7.855 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.477 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.5318 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 9.9595 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.8490

DISREGARDING COVARIATE, F IS 1.6946

COVARIATE = 0 MIN

OBSERVATION = 90 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044845

AHP2-REG-004-0044845

NASAL INSPIRATORY RESISTANCE - 120 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.57021	2.52667	3			2.93009	3	0.976697	4.63362
ERROR	11.82177	4.26594	10.60313	44	0.36085	1.53938	9.06374	43	0.210785	
TRT 1	5.43990	1.89406	4.53156	23	0.34818	0.65947	3.87209	22		
TRT 2	1.46969	1.05656	1.89219	7	0.71890	0.75957	1.13262	6		
TRT 3	2.76500	0.35125	0.87969	7	0.12703	0.04462	0.83507	6		
TRT 4	2.14719	0.96406	3.29969	7	0.44899	0.43285	2.85683	6		
TOTAL	12.02370	3.69573	13.12979	47	0.30737	1.13596	11.99383			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	2.5062	2.4848
TRT 2	3.9312	3.0937	3.1234
TRT 3	3.9250	2.7312	2.7632
TRT 4	4.0062	2.9187	2.9214

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 2.174 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 9.553 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 2.517 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.1469 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 7.0722 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.7104

DISREGARDING COVARIATE, F IS 3.4950

COVARIATE = 0 MIN

OBSERVATION = 120 MIN

AHP2-REG-004-0044846

NASAL INSPIRATORY RESISTANCE | 150 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.25359	-1.307358	5.28069	3			5.69172	3	1.899240	8.62158
ERROR	11.63514	2.76810	9.91069	43	0.23791	0.65855	9.25214	42	0.220269	
TRT 1	5.25326	2.09185	6.20913	22	0.39820	0.03297	5.37616	21		
TRT 2	1.46969	0.44340	2.00219	7	0.30172	0.13379	1.86839	6		
TRT 3	2.76500	0.07125	0.49989	7	0.02577	0.00186	0.49785	6		
TRT 4	7.14719	0.14156	1.19969	7	0.07524	0.01216	1.18753	6		
TOTAL	11.88872	1.69452	15.19138	46	0.14253	0.24152	14.94986			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0915	2.4217	2.4051
TRT 2	3.9317	3.3062	3.3277
TRT 3	3.9250	2.9187	2.9417
TRT 4	4.0062	2.8687	2.8729

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 1.670 WITH 7 AND 47 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 72.525 WITH 1 AND 42 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 4.382 WITH 6 AND 39 DF

TEST FOR EQUAL BETAS F IS 0.4691 WITH 3 AND 39 DF

TEST BETA BAR IS ZERO F IS 2.8761 WITH 1 AND 39 DF

OVERALL X MEAN 4.0213

OVERALL Y MEAN 2.7330

DISREGARDING COVARIATE, F IS 7.6372

COVARIATE = 0 MIN

OBSERVATION = 150 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044847

AHP2-REG-004-0044847

NASAL INSPIRATORY RESISTANCE - 180 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.07448	6.05271	3			6.79564	3	2.265214	7.69474
ERROR	11.82177	4.86333	14.72208	44	0.41139	2.00072	12.72137	43	0.295846	
TRT 1	5.43990	2.83521	8.12458	23	0.48442	1.27655	6.84803	22		
TRT 2	1.46969	0.98063	1.91875	7	0.66723	0.65431	1.26444	6		
TRT 3	2.74500	-0.03250	2.13875	7	-0.01175	0.00038	2.13837	6		
TRT 4	2.14719	1.28000	2.54000	7	0.59613	0.76304	1.77696	6		
TOTAL	12.02370	3.88885	20.77479	47	0.32343	1.25778	19.51701			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	2.7042	2.6797
TRT 2	3.9312	3.6875	3.7214
TRT 3	3.9250	3.1375	3.1739
TRT 4	4.0062	3.0500	3.0530

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 2.282 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 18.407 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 4.151 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.7689 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 6.6536 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.9979

DISREGARDING COVARIATE, F IS 6.0299

COVARIATE = 0 MIN

OBSERVATION = 180 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044848

AHP2-REG-004-0044848

NASAL INSPIRATORY RESISTANCE - 210 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.59193	2.08651	3			2.79162	3	0.9305539	3.09525
ERROR	11.82177	6.79177	16.82927	44	0.57451	3.90197	12.92730	43	0.300635	
TRT 1	5.43990	3.00521	10.88458	23	0.55244	1.66019	9.22439	22		
TRT 2	1.46969	1.36188	2.04875	7	0.92664	1.26197	0.78678	6		
TRT 3	2.76500	1.42250	1.87875	7	0.51447	0.73183	1.14692	6		
TRT 4	2.14719	1.00219	2.01719	7	0.46674	0.46777	1.54942	6		
TOTAL	12.02370	6.19984	18.91578	47	0.51564	3.19686	15.71892			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.1042	3.0701
TRT 2	3.9312	3.4625	3.7098
TRT 3	3.9250	3.4125	3.4634
TRT 4	4.0062	3.2062	3.2104

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.584 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 8.117 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.580 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.2306 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 12.2874 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.2656

DISREGARDING COVARIATE, F IS 1.8184

COVARIATE = 0 MIN

OBSERVATION = 210 MIN

102

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044849

NASAL INSPIRATORY RESISTANCE - 240 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.35568	1.09776	3			1.51118	3	0.503726	1.49900
ERROR	11.82177	6.23281	17.73594	44	0.52723	3.28614	14.44980	43	0.336042	
TRT 1	5.43990	2.49031	12.04406	23	0.45779	1.14003	10.90403	22		
TRT 2	1.46969	0.82156	0.76219	7	0.55900	0.45926	0.30293	6		
TRT 3	2.76500	1.28250	2.37500	7	0.46363	0.59487	1.78013	6		
TRT 4	2.14719	1.63844	2.55469	7	0.76306	1.25023	1.30446	6		
TOTAL	12.02370	5.87714	18.83370	47	0.48840	2.87272	15.96098			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.3812	3.3499
TRT 2	3.9312	3.7937	3.8371
TRT 3	3.9250	3.5000	3.5467
TRT 4	4.0062	3.3812	3.3851

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 9.701 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 3.095 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 0.779 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.1476 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 9.1974 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.4698

DISREGARDING COVARIATE, F IS 0.0078

COVARIATE = 0 MIN

OBSERVATION = 240 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044850

AHP2-REG-004-0044850

NASAL INSPIRATORY RESISTANCE - 270 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.47016	1.13109	3			1.57005	3	0.523349	2.77222
ERROR	11.82177	5.33156	10.52219	44	0.45100	2.40451	8.11768	43	0.188783	
TRT 1	5.43990	2.36831	7.83906	23	0.43389	1.02411	6.81495	22		
TRT 2	1.46969	0.83219	0.94969	7	0.56623	0.47121	0.47847	6		
TRT 3	2.76900	1.13750	0.58875	7	0.41139	0.26796	0.12079	6		
TRT 4	2.14719	1.00155	1.14469	7	0.46645	0.46718	0.67751	6		
TOTAL	12.02370	4.86141	11.65328	47	0.40432	1.96556	9.68772			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0749	2.3812	2.3545
TRT 2	3.9312	2.7312	2.7684
TRT 3	3.9250	2.7125	2.7524
TRT 4	4.0062	2.4687	2.4720

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.096 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 8.124 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.319 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.0428 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 11.8863 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.5094

DISREGARDING COVARIATE, F IS 1.5766

COVARIATE = 0 MIN

OBSERVATION = 270 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044851

AHP2-REG-004-0044851

NASAL EXPIRATORY RESISTANCE, 30 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.00078	1.46630	3			0.49373	3	0.164577	1.30721
ERROR	10.08802	8.15583	12.00740	44	0.80847	6.59372	5.41367	43	0.125899	
TRT 1	4.59990	4.21708	7.48833	23	0.91678	3.86613	3.62220	22		
TRT 2	1.41469	1.15094	1.11719	7	0.81356	0.93636	0.18083	6		
TRT 3	2.76969	1.92219	2.49969	7	0.69401	1.33402	1.16567	6		
TRT 4	1.30375	0.86563	0.90219	7	0.66345	0.57473	0.32746	6		
TOTAL	11.08120	9.15661	13.47370	47	0.82632	7.56629	5.90740			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.8583	2.9215
TRT 2	3.5187	3.2937	3.0403
TRT 3	3.1187	3.0187	3.0886
TRT 4	3.7125	3.1937	3.1879

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 1.818 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 0.285 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 0.769 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.2958 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 47.8000 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 3.0135

DISREGARDING COVARIATE, F IS 1.7910

COVARIATE = 0 MIN

OBSERVATION = 30 MIN

105

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044852

NASAL EXPIRATORY RESISTANCE - 60 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	0.87594	2.92771	3			2.23710	3	0.745701	3.02000
ERROR	10.08802	5.26042	14.02208	44	0.58093	3.40448	10.61760	43	0.246921	
TRT 1	4.59990	3.16010	8.73990	23	0.68699	2.17097	6.56892	22		
TRT 2	1.41469	0.40969	0.59969	7	0.28960	0.11864	0.48104	6		
TRT 3	2.76969	2.09938	3.10375	7	0.75798	1.59129	1.51246	6		
TRT 4	1.30375	0.79125	1.57875	7	0.14659	0.02805	1.55070	6		
TOTAL	11.08120	6.13635	16.94979	47	0.60791	4.09509	12.85470			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.3729	2.4183
TRT 2	3.5187	2.8687	2.8866
TRT 3	3.1187	2.9375	2.9677
TRT 4	3.2125	2.7625	2.7583

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 4.364 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 0.332 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 1.807 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.6651 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 13.4656 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.6146

DISREGARDING COVARIATE, F IS 3.0623

COVARIATE = 0 MIN

OBSERVATION = 60 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044853

AHP2-REG-004-0044853

NASAL EXPIRATORY RESISTANCE - 90 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.12865	1.95083	3			1.11710	3	0.372388	1.80267
ERROR	10.08802	4.35615	10.76333	44	0.43131	1.88104	8.88229	43	0.206565	
TRT 1	4.59990	2.07115	6.16740	23	0.58070	1.55113	4.61627	22		
TRT 2	1.41469	0.26938	1.17375	7	0.19041	0.05129	1.12246	6		
TRT 3	2.74969	0.98625	2.34500	7	0.35609	0.35119	1.99381	6		
TRT 4	1.30375	0.42938	1.07719	7	0.32934	0.14141	0.93578	6		
TOTAL	11.08120	5.48479	12.71417	47	0.49496	2.71477	9.99939			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.2021	2.2358
TRT 2	3.5187	2.7375	2.6021
TRT 3	3.1187	2.5250	2.5623
TRT 4	3.2125	2.3562	2.3531

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 1.618 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 2.173 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 1.024 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.3291 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 8.6801 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.3708

DISREGARDING COVARIATE, F IS 2.6583

COVARIATE = 0 MIN

OBSERVATION = 90 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044854

NASAL EXPIRATORY RESISTANCE - 120 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.20333	1.72292	3			1.13928	3	0.379759	2.69991
ERROR	10.08802	2.30250	6.57375	44	0.22824	0.52552	6.04823	43	0.140656	
TRT 1	4.59990	1.23781	5.04906	23	0.26910	0.33309	4.71597	22		
TRT 2	1.41469	0.53500	0.66500	7	0.37818	0.20232	0.46268	6		
TRT 3	2.76969	0.53469	0.53969	7	0.19305	0.10322	0.43647	6		
TRT 4	1.30375	-0.00500	0.32000	7	-0.00384	0.00002	0.31998	6		
TOTAL	11.08120	3.50583	8.29667	47	0.31638	1.10916	7.18750			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.0687	2.0866
TRT 2	3.5187	2.6000	2.5284
TRT 3	3.1187	2.2687	2.2885
TRT 4	3.2125	2.2250	2.2233

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.942 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 6.216 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.407 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.2541 WITH 3 AND 40 DF

TEST BETA HAT IS ZERO F IS 3.5418 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.2167

DISREGARDING COVARIATE, F IS 3.8440

COVARIATE = 0 MIN

OBSERVATION = 120 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044855

AHP2-REG-004-0044855

NASAL EXPIRATORY RESISTANCE - 150 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	1.04964	1.39293	2.27583	3			1.79338	3	0.597795	2.95529
ERROR	9.94291	1.26808	8.65747	43	0.12754	0.16173	8.49575	42	0.202280	
TRT 1	4.45478	1.99402	5.96435	22	0.44761	0.89255	5.07180	21		
TRT 2	1.41469	0.40563	0.99375	7	0.42810	0.25927	0.73448	6		
TRT 3	2.76969	-0.88844	0.85719	7	-0.32077	0.28499	0.57220	6		
TRT 4	1.30375	-0.44312	0.84219	7	-0.33988	0.15061	0.69158	6		
TOTAL	10.99245	2.66101	10.93330	46	0.24208	0.64417	10.28913			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1109	1.9739	1.9851
TRT 2	3.5187	2.5625	2.5217
TRT 3	3.1187	2.2062	2.2165
TRT 4	3.2125	2.3062	2.3045

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 1.056 WITH 2 AND 42 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 6.754 WITH 1 AND 42 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 2.960 WITH 6 AND 39 DF

TEST FOR EQUAL BETAS — F IS 2.6215 WITH 3 AND 39 DF

TEST BETA BAR IS ZERO — F IS 0.8921 WITH 1 AND 39 DF

OVERALL X MEAN 3.1989

OVERALL Y MEAN 2.1702

DISREGARDING COVARIATE, F IS 3.7679

COVARIATE = 0 MIN

OBSERVATION = 150 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044856

NASAL EXPIRATORY RESISTANCE - 180 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	2.42297	6.21693	3			5.67111	3	1.890369	9.69942
ERROR	10.08802	0.03667	8.38927	44	0.00363	0.00013	8.38914	43	0.195096	
TRT 1	4.59990	1.03229	6.05458	23	0.22442	0.23166	5.82292	22		
TRT 2	1.41469	-0.20437	1.56375	7	-0.14447	0.02953	1.55422	6		
TRT 3	2.10069	-0.30312	0.35375	7	-0.10944	0.03318	0.32057	6		
TRT 4	1.30375	-0.48812	0.41719	7	-0.37440	0.18275	0.23443	6		
TOTAL	11.08120	2.45964	14.60620	47	0.22196	0.54595	14.06025			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.2042	2.2045
TRT 2	3.5187	3.2125	3.2114
TRT 3	3.1187	2.3875	2.3878
TRT 4	3.2125	2.5562	2.5562

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 0.784 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 27.501 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 5.180 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.8038 WITH 3 AND 40 DF

TEST BETA HAS IS ZERO — F IS 0.0007 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.4615

DISREGARDING COVARIATE, F IS 10.8688

COVARIATE = 0 MIN

OBSERVATION = 180 MIN

110

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044857

NASAL EXPIRATORY RESISTANCE - 210 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	0.99557	2.23401	3			1.80369	3	0.601231	2.69266
ERROR	10.08802	2.11906	10.08219	44	0.21006	0.44512	9.63706	43	0.224118	
TRT 1	4.59990	0.33906	5.42656	23	0.07371	0.02499	5.40157	22		
TRT 2	1.41469	0.88156	1.10719	7	0.62315	0.54935	0.55784	6		
TRT 3	2.76969	1.12719	2.15969	7	0.40697	0.45873	1.70095	6		
TRT 4	1.30375	-0.22875	1.38875	7	-0.17546	0.04014	1.34861	6		
TOTAL	11.08120	3.11464	12.31620	47	0.28107	0.87544	11.44076			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.5437	2.5602
TRT 2	3.5187	3.0562	2.9904
TRT 3	3.1187	2.9687	2.9869
TRT 4	3.2125	2.6125	2.6110

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 2.758 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 2.533 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.800 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.9296 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 1.9764 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.7115

DISREGARDING COVARIATE, F IS 3.2498

COVARIATE = 0 MIN

OBSERVATION = 210 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044858

NASAL EXPIRATORY RESISTANCE - 240 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.30609	2.09734	3			1.46871	3	0.489571	2.01437
ERROR	10.08802	2.19531	10.92844	44	0.21762	0.47773	10.45070	43	0.243040	
TRT 1	4.59990	1.12438	7.71125	23	0.24443	0.27484	7.43641	22		
TRT 2	1.41469	0.09596	0.80219	7	0.06782	0.00651	0.79568	6		
TRT 3	2.76969	0.47750	1.16500	7	0.17240	0.08232	1.08268	6		
TRT 4	1.30375	0.49750	1.25000	7	0.38159	0.18984	1.06016	6		
TOTAL	11.08120	3.50141	13.02578	47	0.31598	1.10636	11.91942			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.7625	2.7795
TRT 2	3.5187	3.3437	3.2755
TRT 3	3.1187	3.0000	3.0188
TRT 4	3.2125	2.9750	2.9734

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.781 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 4.481 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 0.992 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.0974 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 1.8419 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.9344

DISREGARDING COVARIATE, F IS 2.8148

COVARIATE = 0 MIN

OBSERVATION = 240 MIN

112

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044859

NASAL EXPIRATORY RESISTANCE - 270 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	0.83464	0.93026	3			0.57930	3	0.193101	0.89803
ERROR	10.08802	2.19719	9.72469	44	0.21780	0.47855	9.24614	43	0.215026	
TRT 1	4.59990	1.81375	6.55500	23	0.39430	0.71517	5.83983	22		
TRT 2	1.41469	0.43656	1.89219	7	0.30859	0.13472	1.75747	6		
TRT 3	2.76969	-0.03937	0.38875	7	-0.01422	0.00056	0.38819	6		
TRT 4	1.30375	-0.01375	0.88875	7	-0.01055	0.00015	0.88860	6		
TOTAL	11.08120	3.03182	10.65495	47	0.27360	0.82951	9.82544			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	1.9750	1.9920
TRT 2	3.5187	2.3562	2.2880
TRT 3	3.1187	2.1625	2.1813
TRT 4	3.2125	2.1125	2.1109

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.532 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 1.630 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 0.715 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.5590 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 2.1571 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.0927

DISREGARDING COVARIATE, F IS 1.4030

COVARIATE = 0 MIN

OBSERVATION = 270 MIN

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044860

A4.4 Analyses of Variance - Nasal Mucosal Characteristics

AHP2-REG-004-0044861

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.39583	3	0.13194	2.55657
ERROR	2.27083	44	0.05161	
TOTAL	2.66667	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22718

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044862
AHP2-REG-004-0044862

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS = 60 MIN.

	SS	DF	MS	F
TREATMENT	0.61935	3	0.20645	4.44940
ERROR	2.04157	44	0.04640	
TOTAL	2.66091	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.21540

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044863

AHP2-REG-004-0044863

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.83069	3	0.27690	5.01418
ERROR	2.42981	44	0.05522	
TOTAL	3.26050	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23500

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044864

AHP2-REG-004-0044864

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.68473	3	0.22824	3.58379
ERROR	2.80227	44	0.06369	
TOTAL	3.48701	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25236

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044865
AHP2-REG-004-0044865

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 150 MIN.

	SS	DF	MS	F
TREATMENT	1.01848	3	0.33949	6.21379
ERROR	2.34932	43	0.05464	
TOTAL	3.36780	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23374

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044866

AHP2-REG-004-0044866

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 180 MIN.

	SS	DF	MS	F
TREATMENT	0.94787	3	0.31596	5.69326
ERROR	2.44186	44	0.05550	
TOTAL	3.38973	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23558

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044867

AHP2-REG-004-0044867

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 210 MIN.

	SS	DF	MS	F
TREATMENT	1.35839	3	0.45280	11.45093
ERROR	1.73986	44	0.03954	
TOTAL	3.09825	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.19885

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044868

AHP2-REG-004-0044868

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.86753	3	0.28918	7.03316
ERROR	1.80911	44	0.04112	
TOTAL	2.67663	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.20277

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044869
AHP2-REG-004-0044869

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.95197	3	0.31732	5.99341
ERROR	2.32959	44	0.05295	
TOTAL	3.28156	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23010

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044870

AHP2-REG-004-0044870

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.26773	3	0.08924	1.84986
ERROR	2.12274	44	0.04824	
TOTAL	2.39047	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.21965

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044871

AHP2-REG-004-0044871

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 60 MIN.

	SS	DF	MS	F
TREATMENT	0.45273	3	0.15091	2.60916
ERROR	2.54489	44	0.05784	
TOTAL	2.99762	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24050

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044872
AHP2-REG-004-0044872

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.63584	3	0.21195	3.98581
ERROR	2.33973	44	0.05318	
TOTAL	2.97557	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23060

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044873

AHP2-REG-004-0044873

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.49019	3	0.16340	2.55367
ERROR	2.81535	44	0.06399	
TOTAL	3.30555	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25295

127

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044874

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 150 MIN.

	SS	DF	MS	F
TREATMENT	0.47311	3	0.15770	2.33221
ERROR	2.90766	43	0.06762	
TOTAL	3.38078	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.26004

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044875

AHP2-REG-004-0044875

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 180 MIN.

	SS	DF	MS	F
TREATMENT	0.83125	3	0.27708	5.20267
ERROR	2.34336	44	0.05326	
TOTAL	3.17461	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23078

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044876
AHP2-REG-004-0044876

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 210 MIN.

	SS	DF	MS	F
TREATMENT	0.51032	3	0.17011	2.81823
ERROR	2.65581	44	0.06036	
TOTAL	3.16613	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24568

130

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044877

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.49409	3	0.16470	3.06373
ERROR	2.36531	44	0.05376	
TOTAL	2.85940	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23186

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044878

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.36599	3	0.12200	2.10080
ERROR	2.55518	44	0.05807	
TOTAL	2.92118	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24098

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044879
AHP2-REG-004-0044879

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.28551	3	0.09517	1.57054
ERROR	2.66624	44	0.06060	
TOTAL	2.95175	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24616

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044880
AHP2-REG-004-0044880

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 60 MIN.

	SS	DF	MS	F
TREATMENT	0.08483	3	0.02828	0.60221
ERROR	2.06608	44	0.04696	
TOTAL	2.15091	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.21669

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044881

AHP2-REG-004-0044881

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.22104	3	0.07368	1.48881
ERROR	2.17757	44	0.04949	
TOTAL	2.39861	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22246

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044882
AHP2-REG-004-0044882

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.67829	3	0.22610	4.56776
ERROR	2.17793	44	0.04950	
TOTAL	2.85622	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22248

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044883

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 150 MIN.

	SS	DF	MS	F
TREATMENT	0.65385	3	0.21795	3.82387
ERROR	2.45087	43	0.05700	
TOTAL	3.10472	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23874

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044884
AHP2-REG-004-0044884

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 180 MIN.

	SS	DF	MS	F
TREATMENT	0.60254	3	0.20085	3.54829
ERROR	2.49058	44	0.05660	
TOTAL	3.09313	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23792

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044885

AHP2-REG-004-0044885

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 210 MIN.

	SS	DF	MS	F
TREATMENT	0.65672	3	0.21891	3.83674
ERROR	2.51044	44	0.05706	
TOTAL	3.16716	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23886

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044886

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.40593	3	0.13531	2.35020
ERROR	2.53328	44	0.05757	
TOTAL	2.93921	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23995

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044887

AHP2-REG-004-0044887

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.24914	3	0.08305	1.35886
ERROR	2.68908	44	0.06112	
TOTAL	2.93822	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24722

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044888

AHP2-REG-004-0044888

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.22060	3	0.07353	1.30637
ERROR	2.47665	44	0.05629	
TOTAL	2.69725	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23725

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044889

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 60 MIN.

	SS	DF	MS	F
TREATMENT	0.15823	3	0.05274	0.82464
ERROR	2.81427	44	0.06396	
TOTAL	2.97250	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25290

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044890

AHP2-REG-004-0044890

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.74109	3	0.24703	4.07010
ERROR	2.67052	44	0.06069	
TOTAL	3.41160	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24636

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044891

AHP2-REG-004-0044891

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.55746	3	0.18582	2.85238
ERROR	2.86639	44	0.06515	
TOTAL	3.42385	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25524

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044892

AHP2-REG-004-0044892

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 150 MIN.

	SS	DF	MS	F
TREATMENT	0.93837	3	0.31279	5.60259
ERROR	2.40066	43	0.05583	
TOTAL	3.33903	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23628

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044893
AHP2-REG-004-0044893

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 180 MIN.

	SS	DF	MS	F
TREATMENT	1.15595	3	0.38532	7.15558
ERROR	2.36934	44	0.05385	
TOTAL	3.52530	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23205

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044894

AHP2-REG-004-0044894

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 210 MIN.

	SS	DF	MS	F
TREATMENT	1.55733	3	0.51911	12.98081
ERROR	1.75959	44	0.03999	
TOTAL	3.31692	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.19998

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044895

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.49496	3	0.16499	3.22141
ERROR	2.25347	44	0.05122	
TOTAL	2.74843	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22631

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044896

AHP2-REG-004-0044896

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.85791	3	0.28597	4.95970
ERROR	2.53699	44	0.05766	
TOTAL	3.39490	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24012

CONFIDENTIAL / TRADE SECRET
AHP2-REG-004-0044897
AHP2-REG-004-0044897

A4.5 Reference on Respiron Methodology

Cohen, Burton M., "Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders." *Respiration* 26:35-46, 1969.

AHP2-REG-004-0044898

Respiration
Editor: H. HERZOG, Basel
S. KARGER - BASEL/NEW YORK (Printed in Switzerland)
SEPARATUM

Respiration 26: 35–46 (1969)

Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders[1]

BURTON M. COHEN[2]

Analysis of pressure, volume and flow characteristics has supplanted conventional spirometry for critical estimation of lower airway resistance and responsiveness [1–6] and determination of the locus of drug action [6] in critical trials. Parallel observations have defined the significant contribution of the upper airways, principally the nasal component, to total respiratory work and resistance [7–15], implying that the relationship between upper and lower airways dynamics and the effects of therapy is not simple [16–19]. Because these measurements have been made principally in normal, often trained, individuals, it seemed pertinent to determine respiratory partitioning in patients with expiratory airflow disorders and the possible influence of drugs directed at various sites on the resistance compartments.

Materials and Methods

Twenty-five normal adults were matched to 25 patients with chronic bronchitis or diffuse obstructive pulmonary emphysema [20] who were free of known nasal disease or anatomic obstruction. All of the latter had demonstrated the presence of a partial potentially reversible physiologic defect on prior isoproterenol aerosol testing [21]. None had received steroids, xanthine derivatives or sympathomimetic agents for at least two weeks prior to study.

[1] Presented at the Fifth Annual Meeting, The American College of Clinical Pharmacology and Chemotherapy, Atlantic City, N.J., May 2–4, 1968.

[2] Attending Physician, Elizabeth General Hospital; Associate Clinical Professor of Medicine, The New Jersey College of Medicine.

Received: June 5, 1968.

NOV 30 1971

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044899

AHP2-REG-004-0044899

The body volume plethysmograph used was a modification of Mead's adaptation [22] of the design of DuBois, Cowan, and associates [23]. The volume-flow and pressure-volume oscilloscopic loops inscribed were read directly with the calibrated disc attachment for the tube face described by BURNICK [23] and were photographed. Nasal resistance (R_n) was calculated from these plots as the difference between the values recorded during nasal ($R_n + R_o$) and oral (R_o) breathing. Nasal resistance was also determined with the subjects outside the chamber by posterior electronic rhinometry (fig. 1). A clinical pneumotachograph[3] was inserted in the outlet of a B-L-B rebreathing pressure mask; the pressure drop across the wire mesh screen was measured with a bidirectional gas pressure transducer[4] which generated the flow signal. Two polyethylene tubes were sealed into separate perforations made in the body of the mask, so that one ended just inside the mask, while the other was positioned to pass between the closed lips of the subject to lie on the tongue, its open end sensing pressure changes in the posterior buccal cavity and in the oral pharynx. These tubes were connected to a physiologic pressure transducer[5] which generated a signal proportionate to the pressure difference between the oral pharynx and the point in the mask external to the nose but before the low resistance pneumotachograph. The flow and pressure signals were amplified[6] and displayed on the precalibrated axes of the oscilloscope and were photographed. Flow was displayed on the vertical axis and pressure on the horizontal axis, so that expiration occupied the right upper quadrant and inspiration the left lower quadrant (fig. 2). Increased flow resistance rotated the expiratory curve clockwise, whereas a decreased resistance induced a counter-clockwise displacement. Inspiratory and expiratory resistance were read at the reference flow rate of 0.5 l/sec.

Following calculation of resistance compartments for the 50 subjects, 10 patients with obstructive lung disease entered a double-blind, crossover protocol including isoproterenol aerosolized from a metered hand device[7], phenylephrine nasal drops[8] and their matched placebos, in four combinations for each subject (isoproterenol aerosol + placebo drops; isoproterenol aerosol + phenylephrine drops; placebo aerosol + phenylephrine drops and placebo aerosol + placebo drops). On each of four consecutive days, after three determinations each of R_n and R_o with the plethysmograph and three recordings of R_n rhinometrically, two inhalations of the aerosol were given and two drops of the nasal solution instilled in each nostril according to a randomized code; the tests were repeated in like order 5, 15, 30, 60 and 90 min after medication.

[3] Fleisch No. 3 Pneumotachograph, Instrumentation Associates, New York, N. Y.

[4] No. 270B Bidirectional Gas Pressure Transducer, Hewlett-Packard Medical Division, Waltham, Mass.

~~[5] No. 268B Physiologic Differential Pressure Transducer, Hewlett-Packard.~~

[6] No. 760-3000 Carrier Pre-Amplifiers, Hewlett-Packard.

[7] Isoproterenol was given as Iso-Mediihaler®, Riker Laboratories, Northridge, California. Each cc. of this dry micronized suspension contains 2.0 mg. of isoproterenol sulfate; 0.075 mg. of drug is delivered at each valve depression.

[8] Phenylephrine was given as Neo-Synephrine Hydrochloride Plain (intranasal) 0.25 % Solution®, Winthrop Laboratories, New York, N. Y.

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044900

AHP2-REG-004-0044900

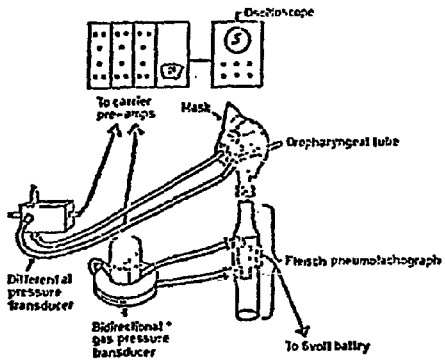


Fig. 1. Apparatus for measuring nasal air flow resistance by posterior rhinometry.

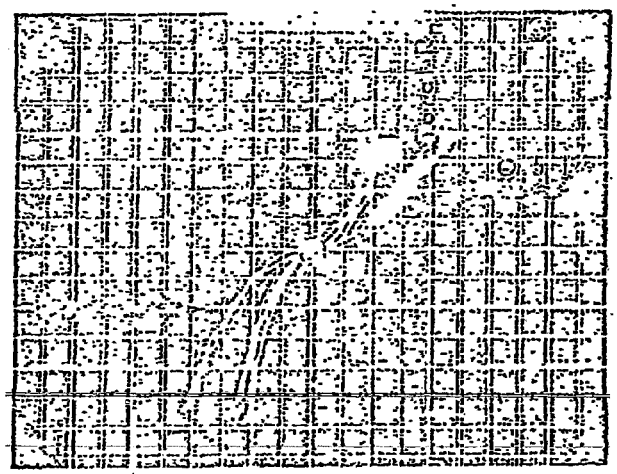


Fig. 2. Oscilloscope camera photograph demonstrating pressure-flow curves for both nasal passages and for each nasal passage, determined separately, in one normal subject.

AHP2-REG-004-0044901

Table I. Respiratory flow partitioning in normal subjects and patients with expiratory airflow disorders

Subjects	Flow Resistances (cm H2O/l/sec)		
	Lower Airways (R_L)	Nasal Airways (R_N)	Total Airways ($R_N + R_L$)
Normals (25)	1.49±0.14	2.47±0.41	3.96±0.
Expiratory Airflow Obstruction (25)	3.06±0.91	3.99±0.72	7.05±0.64
Intergroup Differences			
t	2.75	2.23	2.46
P	0.01–0.005	0.05–0.025	0.02–0.01
Significance at 0.05 level	Sig.	Sig.	Sig.

Results

A. Comparison of normal subjects and patients. Table I presents the values for resistances in the 25 patients with obstructive lung disorders and the 25 matched normal subjects. Mean values for lower airway, nasal and total resistances were 1.49, 2.47 and 3.96 cm H2O/l/sec for the normal individuals, and 3.06, 3.99 and 7.05 cm H2O/l/sec for the 25 patients, respectively. The differences between the three flow resistance indices were significant at the 0.05 level or better in distinguishing the two groups. Values for R_N obtained rhinometrically were in good general agreement with those calculated by plethsymographic subtraction. Mean R_N accounted for 56.5% of total airways resistance for patients with breathing handicaps, and 62.3% of the total for normal subjects during nasal breathing.

B. Behaviour of resistance indices in the clinical drug trial. Drug combinations including phenylephrine drops led to falls in mean R_N, while isoproterenol aerosol + placebo nose drops and the combination of two placebos did not alter this index (fig. 3). Mean R_N fell after isoproterenol aerosol + phenylephrine drops, isoproterenol aerosol + placebo drops and placebo aerosol + phenylephrine drops, in descending order of effectiveness, with a slight rise following the combined placebo (fig. 4). The greatest decline in total resistance ($[R_N + R_L]$) occurred with the two

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044902

AHP2-REG-004-0044902

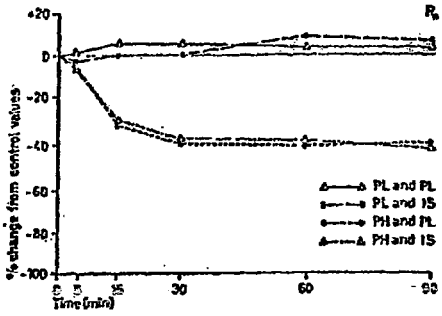


Fig. 3. Behaviour of mean nasal resistance (R_n) following the use of four nasal drops – aerosol combinations by 10 patients with obstructive ventilatory disease. (PL & PL represents placebo nose drops and placebo aerosol; PL & IS represents placebo nose drops and isoproterenol aerosol; PH & PL represents phenylephrine nose drops and placebo aerosol; PH & IS represents phenylephrine nose drops and isoproterenol aerosol).

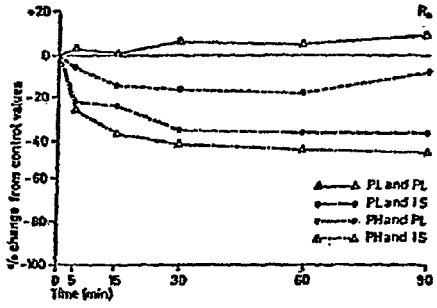


Fig. 4. Behaviour of mean lower airways resistance (R_L) following the use of four nasal-drops-aerosol combinations by 10 patients with obstructive ventilatory disease. The caption is described in the legend of figure 3.

active medications, placebo aerosol + phenylephrine drops was intermediate, and isoproterenol aerosol + placebo drops followed in effectiveness (fig. 5). Table II lists the ranking for each of the respiratory resist-

AHP2-REG-004-0044903

Comm Nasal Airway Resistance and the Effects

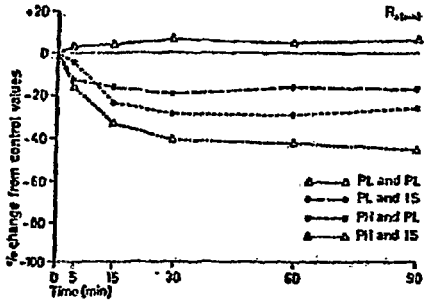


Fig. 5. Behaviour of total airways resistance ($R_a + R_e$) following the use of four nasal drops-aerosol combinations by 10 patients with obstructive ventilatory disease. The caption is described in the legend of figure 3.

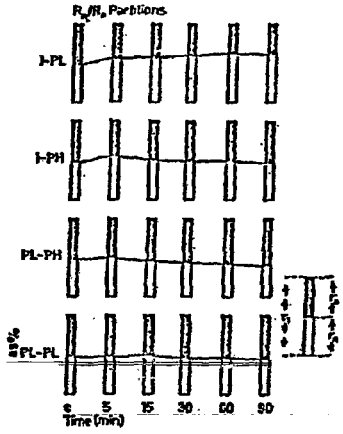


Fig. 6. Changes in R_a/R_e partitioning for 10 patients with chronic obstructive lung diseases, presented as per cents of total airways resistance, following the use of four nasal drops-aerosol combinations. The drug schedules are captioned as in the legends of figures 3, 4 and 5.

AHP2-REG-004-0044904

Table II. Relative ranking of aerosol-nasal drop-combinations for airways resistance effects

Airways Resistance	Relative Ranking of Combinations[1]
Lower airways	Ph. + I. > Pl. + I. > Ph. + Pl. > Pl. + Pl.
Nasal airways	Ph. + Pl. = Ph. + I. > Pl. + I. = Pl. + Pl.
Total	Ph. + I. > Ph. + Pl. > Pl. + I. > Pl. + Pl.

[1] Ph. + I. = Phenylephrine drops and isoproterenol aerosol.
Pl. + I. = Placebo drops and isoproterenol aerosol.
Ph. + Pl. = Phenylephrine drops and aerosol placebo.
Pl. + Pl. = Placebo drops and aerosol placebo.

ances of the four combinations, which were significant at the 0.05 level or beter for the differences observed. Figure 6 presents the response to the various therapies as changes in the $\frac{R_n}{(R_n+R_o)}$ partitioning. Table III summarizes the mean values and standard deviations for the resistance indices, their per cent changes from control and their statistical significance at the 0.01 level, using Oldham's method [24] for t-test interpretation of repeated measurements made on the same subjects.

Discussion

Although the relationships of the respiratory functions of the nasal passages and the lower airway hinted at in antiquity were explored during the last century, it has only been within the past decade that acceptable methods have become available for critical assessment [25]. Electronic presentation of nasal ventilation now offers a practical, highly sensitive and reproducible approach to clinical drug studies yielding serial observations free of subjective bias or patient inconvenience. Because the nasal pressure-flow curve is essentially non-linear, protocols relating inspiratory and expiratory pressures to a uniform, specified rate of flow appear to be the most valid reflections of these changes [12,26–27]. At the lower flow rates during the initial inscription of the curves, when linearity is approached, resistance changes provide sensitive and objective measures of nasal patency and the impact of allergic, infectious and other influences, as well as therapy [26–29].

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044905

AHP2-REG-004-0044905

Table III
Airways resistance behaviour of 10 patients with obstructive ventilatory

Medication and Indices	Mean Respiratory Resistances							
	Control			5 min			15 min	
	R_t	R_n	R_o	R_t	R_n	R_o	R_t	R_n
Isoproterenol aerosol and placebo drops								
mean	8.25	3.85	4.40	7.23	3.82	3.41	6.94	3.85
S.D.	1.04	0.76	0.93	1.07	0.79	0.66	0.98	0.82
% change	–	–	–	–12.3	–0.7	–22.5	–15.8	0
significance[1]				S	NS	S	S	NS
Isoproterenol aerosol and phenylephrine drops								
mean	8.36	3.92	4.44	7.06	3.72	3.34	5.54	2.75
S.D.	1.02	0.87	0.79	0.97	0.86	0.75	0.93	0.68
% change	–	–	–	–15.5	–5.1	–25.0	–33.7	–29.8
significance[1]				S	NS	S	S	S
Placebo aerosol and phenylephrine drops								
mean	8.41	4.05	4.36	8.03	3.89	4.14	6.50	2.78
S.D.	0.74	0.45	0.78	0.91	0.50	0.73	0.81	0.18
% change	–	–	–	–4.5	–3.9	–5.0	–22.7	–31.3
significance[1]				NS	NS	NS	S	S
Placebo aerosol and placebo drops								
mean	8.52	4.00	4.52	8.71	4.04	4.67	8.80	4.23
S.D.	1.00	0.54	0.84	1.01	0.32	0.94	0.96	0.27
% change	–	–	–	2.2	0.1	3.0	3.2	5.7
significance[1]				NS	NS	NS	NS	NS

[1] Significant at the 0.01 level or better, calculated by the method of Oldham for analysis of non-independent samples.

The physiology of the upper airway and the importance of nasal airflow and nasal respiratory reflexes in total ventilation have been authoritatively reviewed [30]. Nasal stenosis may be compensated for by an unusually powerful pulmonary action, but mouth breathing may occur, even with a normal nasal passage, if lung function is reduced by respiratory or

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044906

AHP2-REG-004-0044906

diseases following treatment with combinations of aerosols and nasal drops

[cm H_2O/l/sec][a]									
	30 min			60 min			90 min		
R_s	R_t	R_n	R_s	R_t	R_n	R_s	R_t	R_n	R_n
3.09	6.67	3.85	2.82	6.91	4.18	2.73	6.81	4.09	2.72
0.61	1.07	0.84	0.53	1.06	1.18	0.48	1.05	0.91	0.47
-29.7	-19.1	0	-35.9	-16.2	8.5	-37.9	-17.4	6.2	-38.1
S	S	NS	S	S	NS	S	S	NS	S
2.79	4.96	2.42	2.54	4.82	2.40	2.42	4.55	2.22	2.33
0.38	0.94	0.53	0.36	1.01	0.40	0.30	0.85	0.44	0.22
-37.1	-40.6	-38.2	-32.7	-42.3	-38.7	-45.4	-45.5	-43.3	-47.5
S	S	S	S	S	S	S	S	S	S
3.72	6.05	2.30	3.55	5.93	2.40	3.53	6.26	2.30	3.96
0.75	0.65	0.54	0.73	0.81	0.48	0.68	0.79	0.81	0.64
-14.7	-28.0	-38.2	-16.2	-29.4	-40.7	-19.0	-25.5	-43.2	-9.1
S	S	S	S	S	S	S	S	S	NS
4.57	9.01	4.20	4.81	8.88	4.14	4.74	9.04	4.13	4.91
0.73	1.02	0.36	0.79	1.17	0.33	0.72	0.91	0.39	0.73
0.1	5.7	5.0	6.4	4.2	3.5	4.8	6.1	3.2	8.6
NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

[a] R_t represents the sum of the resistance for the lower airways and the nasal airways;
R_n represents the resistance of the nasal airways;
R_s represents the resistance of the lower airways.

cardiac disease [7, 18, 19, 31]. Ogura describes the high nasal resistance of nasal obstruction as responsible for reductions in spirographic indices and compliance, increases in pulmonary resistance measured through the nose or mouth and in ventilatory work, variables significantly bettered by successful medical or surgical treatment [18, 19]. The lack of correlation

AHP2-REG-004-0044907

between the degree of nasal obstruction relieved and the magnitude of improved lung function suggested that the stimulus response was mediated through a reflex arc [19]. Alveolar hypoventilation, hypoxia and hypercapnia have been incriminated in the genesis of pulmonary hypertension and cor pulmonale from obstructive lesions of the nasal passages [32].

Unlike our subjects, Ogura's five individuals with acute or chronic bronchopulmonary disorders had abnormal noses. In the only evaluation of subjects comparable to our own, NOLTE and ULMER reported an average R_n of 4.72 cm H_2O/l/sec for 29 patients with 'chronic obstructive bronchitis', and an average of 3.74 cm H_2O/l/sec for 43 persons with healthy lungs, data not dissimilar from the present estimates [13]. Our experience reinforces the data of NOLTE and ULMER in suggesting that nasal airflow resistance is frequently elevated in the presence of chronic obstructive lung disorders, making an important contribution to the total breathing handicap of these patients; although absolute values for R_n and R_a rise, respiratory resistance partitioning resembles that of subjects without upper or lower airways diseases. Although the absence of significant distant effects from systemic absorption from the medication instilled in the nasal passages cannot be excluded without definitive pharmacologic support* [33], analysis of the clinical drug trial suggests that this local therapy of the nasal airways was responsible for reduction in R_n, as well as R_a, and that the combination of such medication with an aerosol of isoproterenol, a sympathomimetic amine bronchodilator, was superior in its effects on these indices and total respiratory resistance, than either drug alone. Description of changes in nasal flow and lower respiratory tract resistances may be more informative and precise than reliance upon the latter only in judging the efficacy and site of action of drugs directed to the relief of airway obstruction.

Summary

Nasal resistance was calculated with the whole-body, volume displacement plethysmograph, and by electronic posterior rhinometry, for 25 patients with chronic bronchitis or pulmonary emphysema and 25 matched normal subjects. Ten patients entered a double-blind crossover protocol

*...studies of either its absorption or fate have failed to come to my attention [Beckman, 33].

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044908

in which isoproterenol aerosol, phenylephrine nasal drops and their respective placebos were given in four therapeutic combinations.

Mean values for lower airways, nasal airways and total resistances were significantly higher for the patient group, although respiratory partitioning was unchanged. Therapy directed to the nasal passages alone had helpful effects in lowering the abnormal lower and nasal airway resistances. Nasal respiratory dynamics can not be disregarded in the consideration of breathing handicaps nor in the therapy of airways disorders.

References

1. Ruth, W. I. and Andrews, C. E.: Airway resistance studies in bronchial asthma. J. lab. clin. Med. *54:* 889 (1959).
2. Lloyd, T. C. and Wright, G. W.: Evaluation of methods used in detecting changes of airway resistance in man. Amer. Rev. resp. Dis. *87:* 529 (1963).
3. Dautrebande, L.; Lovelioy, F. W., Jr. and Constantine, H.: New studies on aerosols. XI. Comparative study of some methods used for determining constriction and dilation of the airways after administering pharmacological or dust aerosols; sensitivity of the plethysmograph method. Arch. int. Pharmacodyn. *129:* 469 (1960).
4. Cohen, A. A. and Hale, F. C.: Comparative effects of isoproterenol aerosols on airway resistance in obstructive pulmonary disease. Amer. J. med. Sci. *249:* 309 (1965).
5. Stein, M.; Tanabe, G.; Rege, V. and Khan, M.: Evaluation of spirometric methods used to assess abnormalities in airway resistance. Amer. Rev. resp. Dis. *93:* 257 (1966).
6. Payne, C. B., Jr.; Chester, E. H. and Hsi, B. P.: Airway responsiveness in chronic obstructive pulmonary disease. Amer. J. Med. *42:* 554 (1967).
7. Butler, J.: The work of breathing through the nose. Clin. Sci. *19:* 55 (1960).
8. Ferris, B. G., Jr.; Opie, L. and Mead, J.: Partitioning of respiratory resistance in man. Fed. Proc. *19:* 377 (1960).
9. Hyatt, R. and Wilcox, R. E.: Extrathoracic airway resistance in man. J. appl. Physiol. *16:* 326 (1961).
10. Ferris, B. G., Jr.; Mead, J. and Opie, L. H.: Partitioning of respiratory flow resistance in man. Ibid, *19:* 653 (1964).
11. Splitter, F. E. and Frank, N. R.: A technique for measuring nasal and pulmonary flow resistance simultaneously. Ibid *19:* 176 (1964).
12. Craig, A. B., Jr.; Dvorak, M. and McIlreath, F. J.: Resistance to airflow through the nose. Ann. Otol., *74:* 589 (1965).
13. Nolte, D. and Ulmer, W. T.: Measurement of nasal resistance with the whole body plethysmograph. Med. Thorac. *23:* 349 (1966).
14. Frederick, W. S.: The evaluation of drugs affecting airways resistance with a newly evolved apparatus. Proc. Research and Scientific Development Conference of the Proprietary Association. Dec. 9, 1965, pp. 33–44.

CONFIDENTIAL / TRADE SECRET AHP2-REG-004-0044909

AHP2-REG-004-0044909

15. CASS, J.: Scientific Exhibit. Measurement of total respiratory and nasal airflow resistance. J. amer. med. Ass. *199:* 146 (1967).
16. MCLAURIN, M. D.; SHIPMAN, W. F. and KIRKLEY, D. E., JR.: A modified technique of rhinometry with a preliminary note on the effect of nasal decongestants administered orally. Laryngoscope, *70:* 155 (19[illegible]).
17. COTTLE, N. H.: Concepts of nasal physiology as related to corrective surgery. Arch. Otol. *72:* 11 (1960).
18. OGURA, J. H.: Experimental observations of the relationships between upper airway obstruction and pulmonary function. Ann. Otol. *73:* 381 (1964).
19. OGURA, J. H.: Nasal obstruction and the mechanics of breathing. Arch. Otol. *83:* 135 (1966).
20. American Thoracic Society. Committee on diagnostic standards for nontuberculous respiratory diseases. Amer. Rev. resp. Dis. *85:* 762, 1962.
21. COHEN, B. M. and MCFARLAND, F. J.: Appraisal of bronchodilator microaerosols. I. Pitfalls in ventilatory estimation. J. new Drugs *4:* 237 (1964).
22. MEAD, J.: Volume displacement plethysmograph for respiratory measurements in human subjects. J. appl. Physiol., *15:* 736 (1960).
23. DUBOIS, A. B.; BOTELHO, S. Y. and COMROE, J. H., JR.: A new method for measuring airway resistance in man using a body plethysmograph. Values in normal subjects and in patients with respiratory disease. J. clin. Invest. *35:* 327 (1956).
24. OLDHAM, P. D.: A note on the analysis of repeated measurements of the same subjects. J. chron. Dis. *15:* 969 (1962).
25. COHEN, B. M.: The measurement of human nasal air[illegible] resistance. E. E. N. T. Dig. (in press).
26. SOLOMON, W. R.: Measurement of nasal airway resistance. J. Allergy *36:* 62 (1965).
27. SOLOMON, W. R. and STOHRER, A. W.: Considerations in the measurement of nasal patency. Ann. Otol. *74:* 978 (1965).
28. HAFF, R. F.; SCHRINTE, P. W. and STEWART, P. C.: Pathogenesis of influenza in ferrets – nasal manifestations of disease. Brit. J. exp. Path. *47:* 435 (1966).
29. WARDELL, J. R., JR.; FAMILIAR, R. G. and HAFF, R. F.: A technique for measuring nasal airway resistance in ferrets. J. Allergy *40:* 100 (1967).
30. (a) PROCTOR, D. F.: Physiology of the upper airway. Chapter 8.
(b) WIDDICOMBE, J. G.: Respiratory reflexes. Chapter 24, in: Hdb. of Physiol., Section 3. Respiration. Vol. I., Section Ed. W. O. FENN and H. RAHN. American Physiological Society. Washington, D. C. 1964.
31. STOESTED, P. and NIELSON, J. Z.: Rhinometric measurement of the nasal passage. Ann. Otol. *66:* 187 (1957).
32. Leading Article: Tonsils and pulmonary hypertension. Brit. med. J. *i:* 658 (1968).
33. BECKMAN, H.: Pharmacology: The Nature, Action and Uses of Drugs. Second Edition (Saunders Co., Philadelphia 1961).

Author's address: BURTON M. COHEN, M. D., Medical Arts Building, 230 West Jersey Street, *Elizabeth N. J. 07202* (USA).

CONFIDENTIAL / TRADE SECRET AHP2-REG-004-0044910
AHP2-REG-004-0044910

Findings

AHP2-REG-004-0044911

APPENDIX A6. SAFETY FINDINGS

A6.1 Listings of Clinical Safety Findings

AHP2-REG-004-0044912

Table A6.1-01

MEASUREMENTS OF PULSE RATES

1 7 TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	60	64	72	64	60	64	72	64	68	64
3	60	64	56	60	64	72	60	56	60	64
5	76	80	76	80	72	76	72	80	72	80
8	76	72	80	72	64	60	64	68	72	68
9	96	90	84	88	76	76	76	72	76	68
11	72	76	68	72	64	68	72	64	68	72
12	64	60	56	64	72	76	68	72	68	64
14	68	64	72	64	60	72	76	66	56	64
16	72	76	72	68	72	68	64	72	64	64
21	80	76	84	72	76	72	76	80	72	68
23	84	80	76	76	72	76	80	76	80	80
24	60	64	60	72	60	60	56	64	60	60
25	80	84	80	76	88	80	72	84	80	76
26	68	60	60	56	64	60	60	64	60	60
28	88	84	80	76	84	72	84	80	88	76
32	80	80	80	72	80	76	72	76	80	72
34	76	80	64	64	64		72	64	60	72
35	92	80	76	80	88	76	80	84	88	92
38	88	92	84	80	84	76	80	72	76	72
39	64	68	60	64	60	56	64	60	72	68
41	76	80	72	76	72	76	72	80	72	72
43	88	84	80	80	76	76	84	80	80	76
44	60	64	60	72	68	64	60	60	64	60
48	76	80	64	60	64	60	88	88	76	84
MEANS	75	75	72	71	71	70	72	72	71	71

* Pressure (cm H_2O) at 0.5 L/sec

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044913

AHP2-REG-004-0044913

Table A6.1-c (Cont'd.)

MEASUREMENTS OF PULSE RATES

2 7 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	76	92	88	84	72	72	80	72	76	80
15	60	64	56	64	60	60	68	60	72	68
18	56	52	60	64	56	56	52	56	60	56
19	80	84	72	76	72	68	72	68	68	68
37	60	64	88	88	92	96	80	74	72	72
40	60	64	72	64	68	68	72	64	64	72
42	60	68	72	64	60	72	68	64	68	72
46	68	72	68	68	64	76	72	64	76	72
MEANS	65	70	72	72	68	71	71	66	70	70

3 7 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	76	72	76	80	72	68	64	72	64	72
4	80	88	76	84	80	80	76	84	84	80
6	68	72	64	68	64	72	76	72	64	72
10	68	72	68	76	72	64	60	76	72	76
29	76	80	72	68	64	60	72	76	72	72
30	76	80	60	60	60	72	64	60	60	60
33	56	60	52	56	60	64	56	52	56	56
47	80	76	72	76	72	76	76	76	72	76
MEANS	73	75	68	71	68	70	68	71	68	71

4 7 TREATMENT GROUP Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	72	76	72	68	68	64	72	72	68	64
17	80	76	84	80	76	72	72	68	72	72
20	60	56	64	60	60	60	56	56	60	64
22	72	76	60	60	64	60	56	64	60	56
27	76	80	72	76	80	76	72	76	72	80
31	72	76	80	72	76	72	72	76	80	68
36	76	80	76	80	84	72	72	80	84	84
45	60	64	68	60	60	60	56	60	56	56
MEANS	71	73	73	70	71	67	66	69	69	71

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044914

AHP2-REG-004-0044914

Table AG.1-02

MEASUREMENTS OF BLOOD PRESSURES

1 A TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	125/70	120/70	125/65	120/70	130/70	125/70	130/70	125/70	120/65	120/65
3	120/70	125/75	120/70	115/70	125/70	130/70	125/80	130/70	125/60	125/70
5	125/70	130/70	125/70	130/70	125/70	130/80	120/70	125/70	130/70	130/75
8	130/80	125/70	130/70	125/70	130/70	140/75	135/70	125/70	130/70	125/80
9	120/75	130/60	120/70	125/70	120/70	125/80	130/70	125/70	130/70	125/70
11	130/80	125/70	125/70	120/80	115/75	125/75	120/70	125/70	130/70	125/80
12	125/70	130/70	125/75	120/70	125/70	130/70	125/70	125/75	130/70	125/80
14	120/65	125/70	115/70	120/70	115/65	120/70	125/70	130/65	120/70	125/70
16	130/70	125/70	130/70	125/70	130/75	140/70	125/70	130/70	125/80	130/85
21	120/65	125/70	130/70	115/75	120/80	125/65	115/70	120/70	115/70	120/75
23	135/70	140/70	130/75	125/75	130/75	130/75	140/80	135/65	130/70	130/70
24	140/70	145/70	135/70	130/70	130/70	125/70	135/70	140/70	130/70	125/85
25	135/70	125/70	130/75	125/80	130/70	125/70	130/80	125/70	130/75	125/70
26	115/80	120/80	110/65	120/70	130/70	125/80	130/75	125/80	130/70	115/75
28	125/70	125/70	130/75	130/70	125/70	130/70	125/70	120/70	125/70	130/70
32	120/80	125/70	130/70	115/70	110/70	120/70	115/70	120/70	125/70	125/70
34	140/80	135/80	140/80	125/70	140/70		140/75	135/70	140/70	140/70
35	120/70	125/70	130/70	125/70	130/70	125/75	130/70	125/70	130/70	125/70
38	140/70	130/70	125/70	130/70	125/70	140/70	135/70	140/70	135/70	140/80
39	125/70	130/70	125/80	130/70	120/65	115/65	120/70	125/70	115/70	115/70
41	130/70	125/70	135/70	125/70	130/70	135/70	135/70	125/80	130/70	125/70
43	150/70	135/75	140/70	135/75	140/70	140/70	145/70	140/80	140/70	140/70
44	120/65	130/70	115/70	120/70	130/70	125/70	120/70	125/70	130/70	125/70
48	135/65	140/70	130/70	125/70	125/70	130/70	135/70	140/70	130/65	140/75
MEANS	129/71	129/71	127/71	124/71	126/71	128/72	129/72	128/71	128/70	128/74

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

Continued

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044915

AHP2-REG-004-0044915

Table No. (Cont'd.)

MEASUREMENTS OF BLOOD PRESSURES

2 A TREATMENT GROUP: Nebsynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	125/70	130/65	125/65	120/70	130/65	125/80	120/80	120/80	125/80	120/80
15	130/65	135/70	140/70	125/70	130/70	135/60	125/65	130/70	125/70	130/75
18	130/70	115/70	120/75	115/75	120/70	130/70	115/70	120/70	120/70	120/70
19	130/70	125/70	130/70	125/80	130/75	125/70	130/65	125/70	130/70	125/70
37	115/70	120/70	135/80	140/80	135/70	125/70	130/75	115/70	120/70	115/75
40	130/75	125/75	130/70	125/80	120/70	125/80	130/70	120/70	125/80	130/70
42	120/70	115/70	125/80	120/80	130/70	120/70	115/65	120/75	115/80	120/70
46	125/80	130/70	135/70	140/70	135/70	120/70	125/80	130/70	125/70	130/70
MEANS	127/71	124/70	130/73	126/76	129/70	126/71	124/71	123/72	123/74	124/73

3 A TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	130/70	125/70	130/75	125/70	120/70	125/70	130/75	125/65	125/65	120/70
4	130/70	115/70	110/65	120/70	115/70	120/70	115/70	110/65	120/60	115/60
6	135/70	140/70	130/70	125/70	130/75	140/80	130/65	140/60	135/70	125/80
10	135/85	140/70	130/75	140/80	125/85	135/80	130/75	135/80	125/80	130/75
29	140/75	135/75	130/70	135/70	125/70	130/70	140/70	135/70	130/70	135/70
30	115/65	120/70	110/60	120/70	125/70	135/70	115/70	120/75	125/80	120/80
33	125/70	120/70	130/70	125/70	120/70	135/70	125/70	120/70	115/70	115/75
47	140/70	135/70	125/75	130/70	135/80	130/70	125/70	125/80	130/70	125/70
MEANS	129/72	129/71	124/70	128/71	124/74	129/74	126/71	126/71	126/72	123/73

4 A TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	130/70	125/70	130/75	135/80	140/75	130/70	125/70	130/70	125/70	130/70
17	130/70	140/80	125/75	130/70	125/70	130/70	125/80	130/80	125/80	120/70
20	130/70	125/70	130/70	125/70	125/75	130/70	125/75	120/75	120/70	125/70
22	125/70	120/75	130/70	125/70	120/70	125/65	130/60	140/60	135/70	140/70
27	120/70	115/70	120/70	125/70	130/75	135/70	115/65	120/70	115/70	120/70
31	130/80	125/80	130/75	130/75	135/70	125/70	130/75	130/70	140/70	130/70
36	135/65	130/70	125/70	125/75	130/70	125/70	130/70	125/70	130/70	125/70
45	115/60	110/65	120/60	110/60	115/60	120/65	115/65	110/70	110/65	110/65
MEANS	127/69	124/73	126/71	126/71	128/71	128/69	124/70	126/71	125/71	125/69

CONFIDENTIAL / TRADE SECRET

AHP2-REG-004-0044916

AHP2-REG-004-0044916

4. STUDY PROTOCOL

4.1 PROTOCOL DESCRIPTION

4.1.1 Objective

To compare the effects of single doses of Dimetapp Elixir with each of its components on nasal airway resistance in patients with upper respiratory infections.

4.1.2 Study Design

This is a single investigator well controlled special study in which each of the patients with upper respiratory infections received a single dose of Dimetapp Elixir (24 patients) or one of its three components (8 patients/component) on a single test day; measurements of nasal airway resistance, and subjective evaluations of nasal mucosa were made every 30 minutes after drug administration for 4.5 hours.

4.1.3 Patient Description

A. Selection Criteria

1. Treated Condition(s) and Diagnostic Criteria

   Nasal congestion due to upper respiratory infections whose duration was not less than 24 hours and not more than 72 hours at time of test day.

2. Prior Treatment Criteria

   48 hours off all drugs having the same general pharmacological actions as the study medication.

3. Safety Exclusion Criteria

   a. Chronic pulmonary disease

   ~~b. Allergic rhinitis~~

   c. Pregnancy

4. Miscellaneous Criteria

   a. Adults

   b. Males and females

   c. Outpatients (office)

   d. Willingness to participate in a one day study.

AHP4-REG-310-0104264

B. The patients were numbered serially as they entered the study and were assigned to one of the study medications on the basis of a randomization schedule (see Appendix A4.3) prepared by the Biometry Unit, A. H. Robins Company.

4.1.4 Treatment Groups

A. Test Groups

1. Dimetapp Elixir containing 4 mg of brompheniramine maleate, 5 mg of phenylephrine hydrochloride, and 5 mg of phenylpropanolamine hydrochloride per 5 cc.

B. Control Groups

1. Dimetane Elixir containing 2 mg of brompheniramine maleate per 5 cc.

2. Neosynephrine Elixir containing 1 mg of phenylephrine hydrochloride per 1 cc.

3. Propadrine Elixir containing 4 mg of phenylpropanolamine hydrochloride per 1 cc.

C. Dosage Schedules

Using the Randomization Schedule in Appendix A4.3 each patient received single doses of test medication on the morning of the test day according to the following schedules:

Treatment Group 1: 10 cc of Dimetapp Elixir (8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride).

Treatment Group 2: 20 cc of Dimetane Elixir (8 mg brompheniramine maleate).

~~Treatment Group 3: 10 cc of Neosynephrine Elixir (10 mg~~ phenylephrine hydrochloride).

Treatment Group 4: 2.5 cc of Propadrine Elixir (10 mg phenylpropanolamine hydrochloride).

Since the test medications were not identical in appearance they were administered by a disinterested third party; hence, the investigator and the technician making the measurements and assessments were "blind" to the test medication received by each subject.

At four hours (240 minutes) after dosing, each patient received Afrin (oxymetazoline hydrochloride) nasal solution.

AHP4-REG-310-0104265

C. Concomitant Treatments

1. Excluded

Nasal decongestants (oral and topical)

2. Included

Any medications and/or treatments needed for concurrent conditions were permitted but were to be recorded on data sheets.

4.1.5 Assessment of Special Findings

At "0 hour" and at 30, 60, 90, 120, 180, 240 and 270 minutes after test medication was administered, the following assessments were made:

A. Nasal Airway Resistance

Using the Respiron both nasal inspiratory and expiratory resistances were measured. The results were reported as pressure (cm H_2O) at 0.5 L/sec.

See Appendix A5.3 for the following reference on Respiron methodology.

Cohen, Burton M., "Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders." *Respiration* 26:35-46, 1969.

B. Characteristics of Nasal Mucosa

Subjective evaluations were made of the following:

1. Nasal mucosal congestion

2. Nasal mucosal hyperemia

3. Nasal secretion

4. Ease of nasal breathing

Items 1-3 above were rated on a 5-point scale as follows:

0 = absent
1 = mild
2 = moderate
3 = severe
4 = very severe

AHP4-REG-310-0104266

Item 4 above was rated on a 5-point scale as follows:

0 = normal
1 = only mildly impaired
2 = moderately impaired
3 = severely impaired
4 = total obstruction

[It should again be noted that Afrin (oxymetazoline hydrochloride) nasal solution was administered immediately after the above measurements were made at 240 minutes.]

4.1.6 Effectiveness Assessment: None

4.1.7 Safety Assessment

The investigator observed particularly for the following adverse effects: nervousness, headache, nausea, dizziness or light-headed, drowsiness, dry mouth, urticaria, palpitation, and blurred vision.

Blood pressures (right arm, sitting three minutes) and pulse rates (sitting three minutes) were measured pre-drug and post drug according to the following schedule:

"0 hour"	120 minutes
30 minutes	180 minutes
60 minutes	240 minutes
90 minutes	270 minutes

4.1.8 Data Management and Analysis

After initial medical screening by the Data Monitor (M.D.), primarily from a safety viewpoint, the data sheets were carefully monitored by a research physician in order to ascertain if they met the selection and treatment criteria of the protocol (see 4.1.3 and 4.1.4). Standard statistical methods were used to analyze the special ~~findings (see Section 5).~~

4.1.9 Summary of "Bias Minimization" Aspects

1. Assignment of patients to treatment groups by a pre-determined randomization schedules.

2. Drug administration of the differing test medications by a disinterested third party (i.e. the investigator and technician were "blind" to the medication each patient received).

3. Careful and independent medical auditing of the data sheets for "acceptability" (e.g. with respect to patient selection criteria, etc.) prior to biometric evaluation of the special findings.

AHP4-REG-310-0104267

4.2 PROTOCOL DEVIATIONS: None

4.3 INVESTIGATOR INFORMATION

One clinician supplied the data on the 48 patients participating in this study. The name and address of the investigator is shown in A4.4. Also included are the *curriculum vitae* of the investigator and pertinent information about the investigation.

AHP4-REG-310-0104268

INVESTIGATOR

Investigator:	Cohen, Burton Marcus, M.D.
Address:	230 W. Jersey Street Elizabeth, New Jersey 07202
Academic Affiliation:	Associate Clinical Professor of Medicine The New Jersey College of Medicine
Type of Practice:	Internal Medicine
Study Number:	0101
Date Initiated:	05/69
Study Status:	Complete
Status Date:	02/71
Patients Reported:	48

AHP4-REG-310-0104269

NASAL AIRWAY RESISTANCE-INSPIRATION: MEANS (a), RANKS AND DIFFERENCES
(Protocol C1-A-01)

TIMES (Min)	TREATMENT GROUP MEAN AND RANKS: 10 mg Phenylephrine (8)+	10 mg Phenylpropanolamine (8)+	8 mg Brompheniramine (8)+	Combination (24)+	DIFFERENCES BETWEEN COMBINATION AND INDICATED COMPONENTS (+ = lower resistance for combination): Phenylephrine	Phenylpropanolamine	Brompheniramine
0	3.93	3.92	4.01	4.07	---	---	---
30	3.80 (3)	3.82 (4)	3.71 (1)	3.78 (2)	+0.019	+0.038	-0.069
60	3.36 (2.5)	3.42 (4)	3.35 (2.5)	3.15 (1)	+0.202	+0.264	+0.208
90	3.07 (3.5)	3.07 (3.5)	2.98 (2)	2.65 (1)	+0.421*	+0.421*	+0.327
120	3.09 (4)	2.73 (2)	2.92 (3)	2.51 (1)	+0.588**	+0.225	+0.412*
150	3.31 (4)	2.92 (3)	2.87 (2)	2.42 (1)	+0.862***	+0.475**	+0.425*
180	3.69 (4)	3.14 (3)	3.05 (2)	2.70 (1)	+0.983***	+0.433*	+0.345
210	3.66 (4)	3.41 (3)	3.21 (2)	3.10 (1)	+0.558**	+0.308	+0.102
240	3.79 (4)	3.50 (3)	3.38 (1.5)	3.38 (1.5)	+0.412*	+0.119	0.000
Overall Means (b)							
Resistance	3.471	3.25	3.186	2.967			
Ranks	(3.6)	(3.2)	(2.0)	(1.2)			

( )+ = Number of subjects

(a) cm H_2O at 0.5 L/min flow rate

(b) Means of 30 to 240 minutes, inclusive

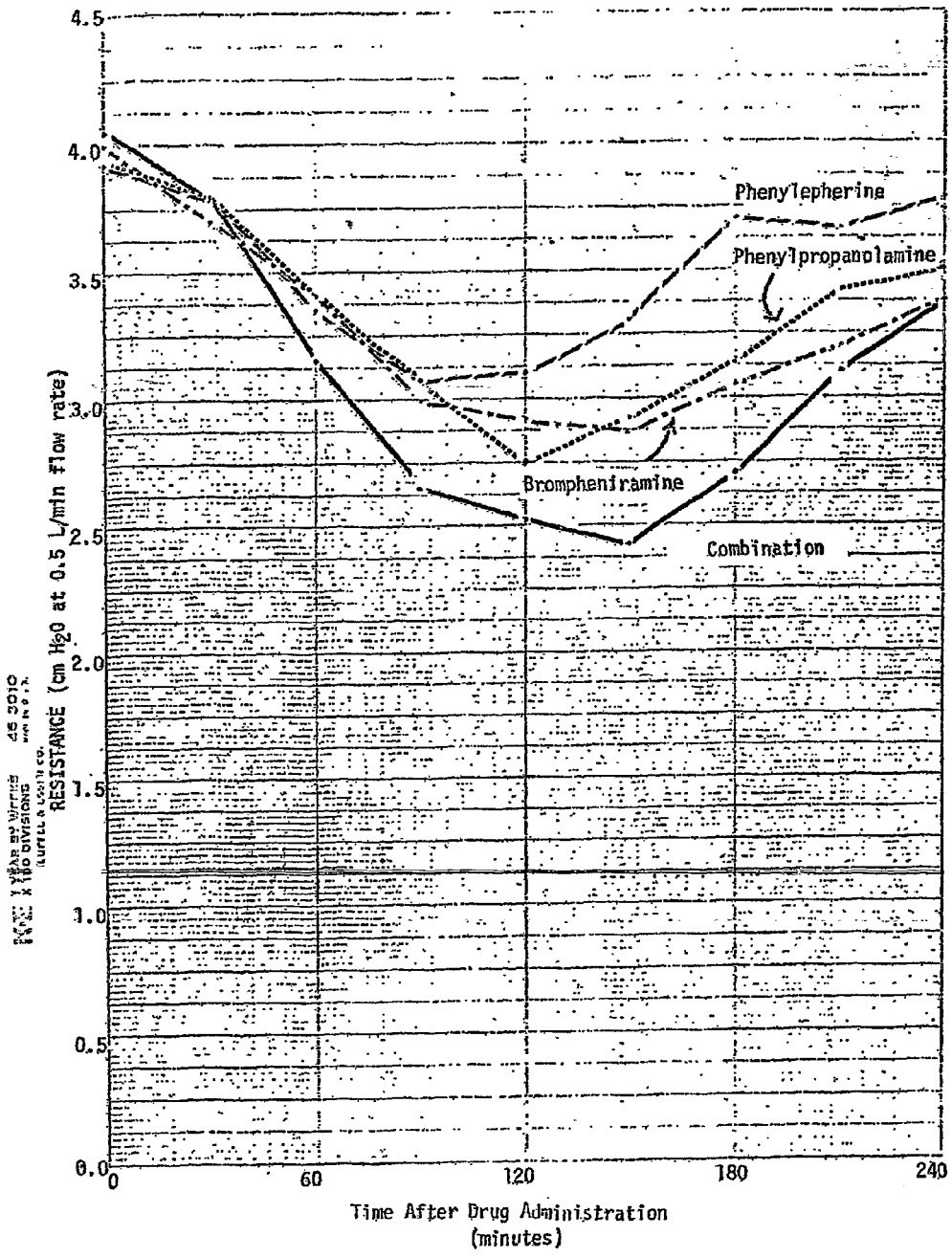
* = Statistical Significant Difference at 10% level (t-test/two-tail)
** = Statistical Significant Difference at 5% level (t-test/two-tail)
*** = Statistical Significant Difference at 1% level (t-test/two-tail)

CONFIDENTIAL

AHP4-REG-310-0104270

AHP4-REG-310-0104270

NASAL AIRWAY RESISTANCE-INSPIRATION
(Protocol G1-A-01)



AHP4-REG-310-0104271

NASAL AIRWAY RESISTANCE - EXPIRATION: MEANS (a), RANKS AND DIFFERENCES
(Protocol G1-A-01)

TIMES (Min)	TREATMENT GROUP MEAN AND RANKS			
	10 mg Phenylephrine (8)+	10 mg Phenylpropanolamin (8)+	8 mg Brompheniramine (8)+	Combination (24)+
0	3.52	3.12	3.21	3.13
30	3.29 [4]	3.02 [2]	3.19 [3]	2.86 [1]
60	2.87 [3]	2.94 [4]	2.76 [2]	2.37 [1]
90	2.74 [4]	2.52 [3]	2.36 [2]	2.20 [1]
120	2.60 [4]	2.27 [3]	2.22 [2]	2.07 [1]
150	2.56 [4]	2.21 [2]	2.31 [3]	1.97 [1]
180	3.21 [4]	2.39 [2]	2.56 [3]	2.20 [1]
210	3.06 [4]	2.97 [3]	2.61 [2]	2.54 [1]
240	3.34 [4]	3.00 [3]	2.97 [2]	2.76 [1]
OVERALL MEANS (b)				
Resistance	2.959	2.665	2.622	2.371
Ranks	[3.9]	[2.8]	[2.4]	[1.0]

DIFFERENCES BETWEEN COMBINATION AND INDICATED COMPONENTS
(+ = lower resistance for combination)

Phenylephrine	Phenylpropanolamine	Brompheniramine
---	---	---
+0.435**	+0.160	+0.335*
+0.496**	+0.565***	+0.390**
+0.535***	+0.323*	+0.154
+0.531***	+0.200	+0.156
+0.599**	+0.242	+0.342*
+0.998***	+0.183	+0.352*
+0.512***	+0.425	+0.069
+0.581***	+0.238	+0.212

( )+ = No. of subjects

(a) - cm H_2O at 0.5 L/min flow rate

(b) - Means of 30 to 240 minutes, inclusive

* = Statistical significant difference at 10% level (t-test/two-tail)

** = Statistical significant difference at 5% level (t-test/two-tail)

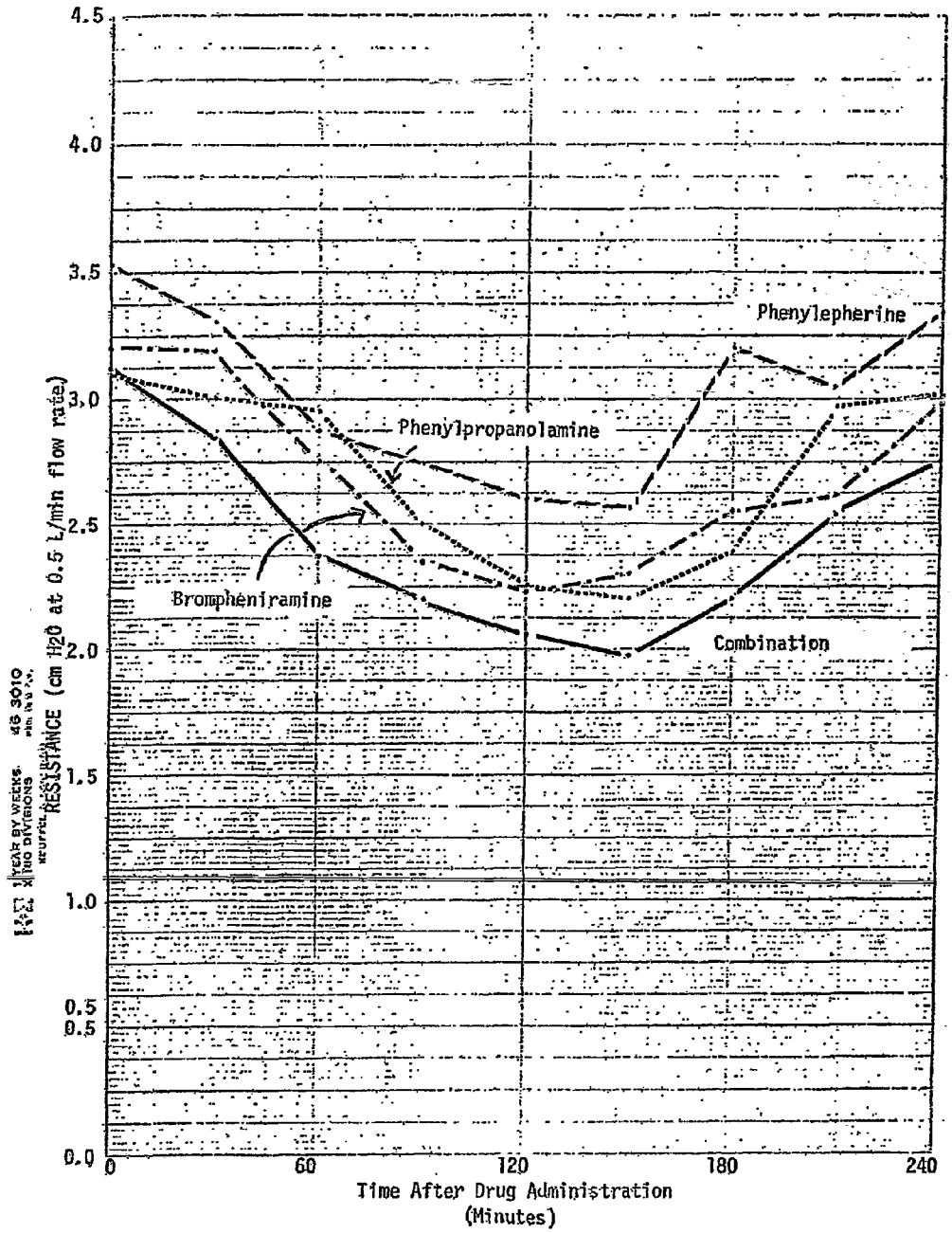
*** = Statistical significant difference at 1% level (t-test/two-tail)

CONFIDENTIAL

AHP4-REG-310-0104272

AHP4-REG-310-0104272

NASAL AIRWAY RESISTANCE-EXPIRATION
(Protocol 61-A-01)



AHP4-REG-310-0104273