

A CONTROLLED EVALUATION OF TWO ANTIHISTAMINE COMPOUNDS USING NASAL ENGORGEMENT AS AN INDEX OF RESPONSE

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THE evaluation of antihistamine compounds intended for the treatment of various allergic states in man is generally based, first, on the protection offered by the compound in animal studies (e.g., antagonism toward histamine-induced spasm in segments of guinea pig intestine, or inhibition of increased capillary permeability induced by injection of dextran), and, second, on the subjective experiences of patients having chronic or seasonal allergies who have received the drug.

While the first method is pharmacologically valuable and the data so derived are capable of fairly precise measurements, it is none the less somewhat distant to the situation encountered by the physician who undertakes the treatment of a patient with allergic rhinitis.

The second approach, utilizing patients who have a seasonal pollinosis during the period of their difficulty, is unquestionably more germane to this particular aspect of antihistamine therapy, but, as usually performed, has many variables which cloud the true pharmacodynamics of the compound under study. Some of the problems encountered in such an investigation are described in an excellent report by Wahner and Peters.¹

The method of study reported here represents an effort to create a controlled treatment situation which is similar to that which occurs in medical practice, but which will yield data subject to fewer unwanted variables.

MATERIALS AND METHODS

The technique of study was adapted from the earlier work of Holmes and co-workers² in which the changes in appearance of the nasal mucosa were correlated with pollen dispersal and other factors in an air-conditioned room. The subject sat in the same spot in the room each time, but several greased slides were placed about the room in order to provide evidence that dispersal of pollen was approximately uniform. By trial-and-error, the amount of pollen necessary to produce a 15-minute "fallout" of 30 grains per square centimeter was determined. Dissemination was accomplished by the currents of air from an oscillating

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fan playing over a siliconized watch glass in which the proper amount of pollen had been placed. This required approximately 10 minutes. The room was damp-mopped after each trial to reduce contamination of the atmosphere with "house dust" and accumulated pollen. A recording thermometer indicated a 24-hour temperature variation of less than 10° F. Humidity was not determined. A diagram of the room arrangement is shown in Fig. 1.

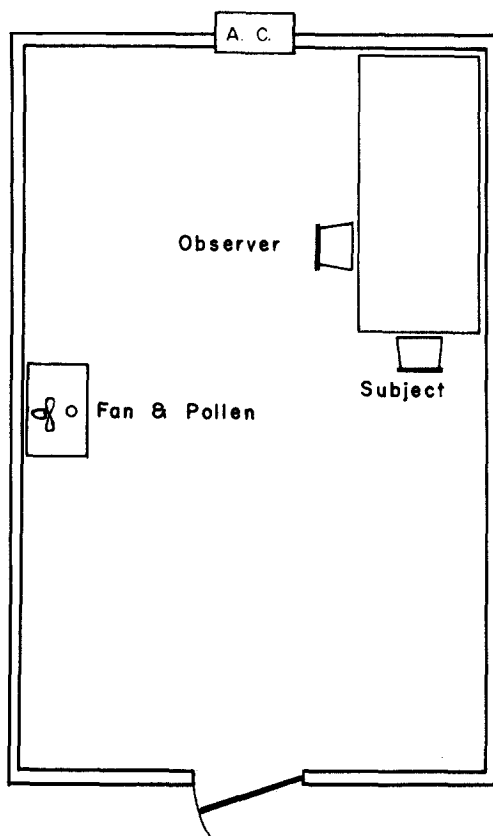


Fig. 1.—The pollen room (not to scale).

The subjects were chosen from a group of volunteers who suffered from seasonal pollinosis. Selection was made during the winter season when they were asymptomatic and hence had mucous membranes in a "resting" or "basal" state. The candidates were exposed to a mixture of fresh ragweed pollens (giant, western, and short) under the test conditions and the nasal mucosa was observed before the pollens were dispersed and again 15 minutes later. Those who developed engorgement of the mucosa were accepted as subjects for the study. The structures of the nose were examined under standard lighting conditions with the use of a warm speculum. Color was compared to a standard color scale.

and swelling and moisture were roughly quantitated on a 0-4+ scale in a manner similar to that described by Holmes and associates.³ In order to provide a permanent record for comparison, color photographs of the interior of the nose were made by means of a Coreco Model 300 camera with an attached nasal speculum.

Two antihistamine compounds (chlorphenpyridamine, 4 mg.; and methdilazine, 8 mg.) and a placebo were used. These agents were dispensed in capsules of identical appearance and were simply coded as R, S, and T. These were administered in a double-blind cross-over study so that each subject received all three agents during the investigation in a balanced random order. For each trial, the subject ingested the agent on an empty stomach, with only a cup of milk or coffee to swallow the capsule. One hour later he reported to the pollen room where his nasal mucosa was examined and photographed. The pollen dispersion was then begun, and the observations and photographs were repeated at 15-minute intervals for the ensuing 45 minutes. As we also wished to determine the duration of drug activity, subjects whose nasal mucosa showed but little reaction during the 45-minute pollen inhalation were asked to return 5 hours later for a 15-minute re-exposure. An interval of at least 24 hours elapsed between each trial and the subjects were allowed no other medication of any type during this study.

Because a wide variety of "side effects" are often reported by patients taking antihistamines, we also attempted to evaluate this aspect of the drugs. A printed questionnaire covering such items as drowsiness, headache, and euphoria was answered by the subject at each visit and the affirmative answers were tabulated. Because some patients are engaged in hazardous occupations in which any interference with motor coordination would entail considerable risk, the Purdue Pegboard was employed to measure manual dexterity. We also assessed mental alertness by use of a timed digit-symbol association test after the method of Wechsler.⁴

RESULTS

Illustrative photographs of the variations observed in nasal reaction are shown in Figs. 2, 3, and 4. Fig. 2 is typical of the "no protection" classification. There is progressive swelling of the inferior turbinate and increasing mucus secretion. Fig. 3 shows the nasal mucosa of a subject with slight protection; here the changes are less pronounced than those seen in Fig. 2. Fig. 4 shows a subject enjoying very good protection; very little change is noted between the initial pre-pollen photograph and the last one made after 45 minutes of exposure to the pollen stimulus.

The degree of protection was graded according to a rating scale which assigned a 0 value to the type of response seen in Fig. 2, and a value of 4 to that seen in Fig. 4. Intermediate changes were graded 1, 2, or 3. The photographs were scored independently of the written observations, but a high degree of correlation was found to exist. Only after the ratings were completed was the code broken and the three agents identified. Table I lists the scores for the

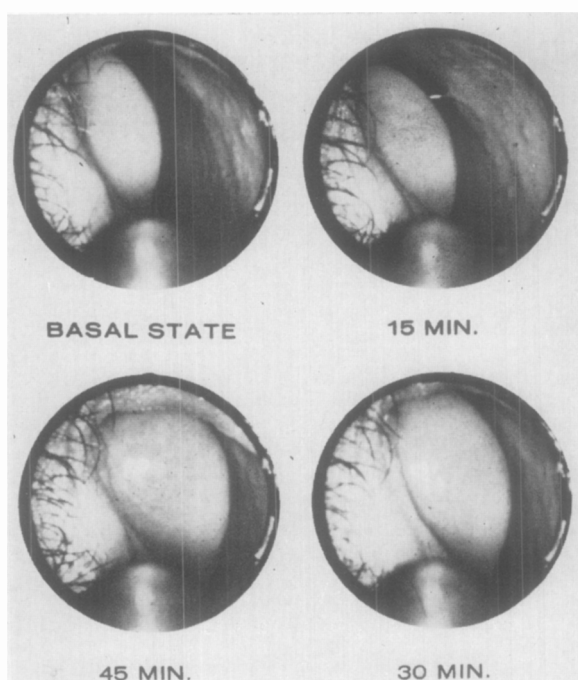


Fig. 2.—The inferior turbinate shows marked engorgement and mucus secretion. This was scored as 0 protection on the rating scale.

three agents in the 12 subjects. Chlorprophenpyridamine and the placebo produced like total scores on the one-hour test. After 6 hours, 2 subjects who had been given the placebo still had good protection and 2 subjects who had received chlorprophenpyridamine showed slight to poor protection. Subjects receiving

TABLE I. NASAL PROTECTION SCORES

SUBJECT	1 HOUR			6 HOURS		
	R	S	T	R	S	T
1	3	2	4	1	0	4
2	3	0	0	0	0	0
3	0	3	2	0	0	0
4	0	1	1	0	0	0
5	3	0	3	0	0	3
6	3	0	0	2	0	0
7	2	1	3	0	0	1
8	4	0	1	0	0	1
9	0	2	1	0	0	0
10	0	1	1	0	0	0
11	1	0	3	0	0	0
12	1	0	1	0	0	0
Totals	20	10	20	3	0	9

Drug Key

R = Chlorprophenpyridamine (4 mg.)

S = Methdilazine (8 mg.)

T = Placebo

Scoring

0 = No protection

1 = Slight protection

2 = Poor protection

3 = Moderate protection

4 = Good protection

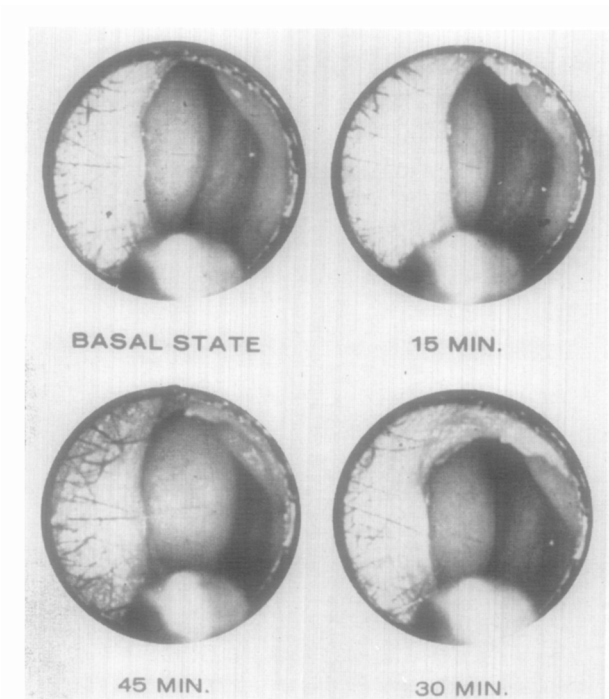


Fig. 3.—Engorgement of the mucosa is less pronounced than that seen in Fig. 2. Scored as 1 on the rating scale.

methdilazine fared less well; none of the subjects showed any protection after 6 hours. The one-hour total score was half that of the other two agents.

The Purdue Pegboard scores are shown in Table II. Apart from slight increments resulting from practice, they are remarkably similar. The digit-symbol tests also show no apparent changes attributable to the drugs (Table III). Table IV lists the number of positive responses obtained on the questionnaire.

TABLE II. PURDUE PEGBOARD

SUBJECT	BY DRUG			BY TRIAL		
	R	S	T	1ST	2ND	3RD
1	91	96	96	91	96	96
2	77	82	82	77	82	82
3	92	88	93	88	93	92
4	99	93	105	93	99	105
5	106	104	108	108	106	104
6	91	92	82	82	92	91
7	93	90	100	93	90	100
8	84	80	82	84	82	80
9	99	89	89	89	89	99
10	85	90	85	90	85	85
11	89	89	97	97	89	89
12	85	89	82	82	89	85
Mean	90.92	90.17	91.75	89.08	91.00	92.33

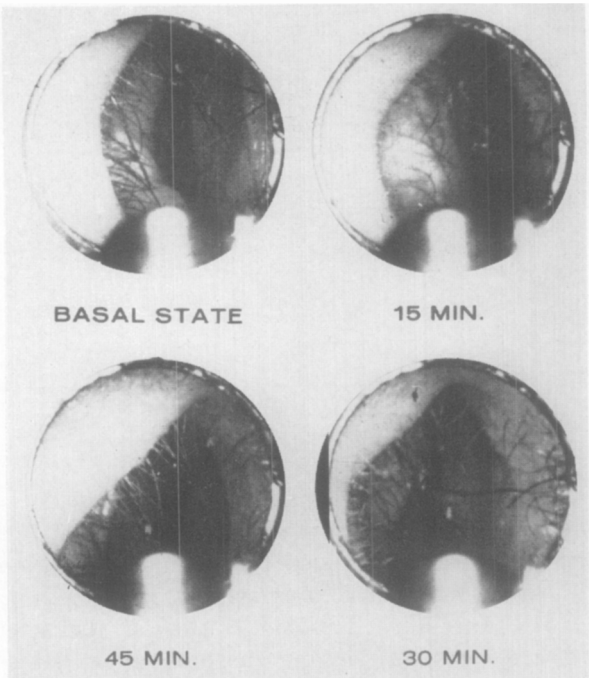


Fig. 4.—Rating score of 4. Very little change has occurred between the first and last observations. The very narrow nares of this subject made insertion of the camera speculum difficult and some variation in perspective has resulted.

It is clear that “side effects” occurred almost as frequently with the placebo as with either of the drugs being tested.

TABLE III. DIGIT-SYMBOL TEST SCORES*

SUBJECT	CORRECT			ERRORS		
	R	S	T	R	S	T
1	60	49	48			
2	43	45	47			
3	39	42	40	1		
4	47	47	44			
5	39	38	35	1		1
6	40	33	41	4	4	1
7	40	38	37		0.5	
8	51	47	51		0.5	1
9	43	47	39			1
10	42	39	39		1	4
11	44	42	41			
12	31	29	25			
Totals	519	496	487	6	6	8

*The Wechsler Digit Symbol Subtest measures the speed and accuracy with which the subject can record the proper symbols associated with a series of digits printed on a special form. Sixty seconds were allotted for the test, and the numbers of correct and erroneous answers tabulated. To minimize the “learning effect,” the test was modified to use three different sets of symbols, since each subject was tested on three occasions. “Half-wrong” answers are those in which the proper symbol is written but in which it is turned: e.g., > instead of <.

TABLE IV. INCIDENCE OF "SIDE EFFECTS" ONE HOUR AFTER INGESTION OF DRUG AND BEFORE POLLEN EXPOSURE

	R	S	T
Drowsiness	1	2	1
Dryness of mouth	1	1	1
Dryness of nose	1	1	1
Headache	0	1	1
Grogginess or drunkenness	1	1	1
Irritability	0	0	0
Tinnitus	0	1	1
Dizziness	1	1	0
Weakness	1	1	0
Cough	0	0	0
Clumsiness	0	0	0
Euphoria	0	0	0
"Nervousness"	0	0	1

DISCUSSION AND CONCLUSIONS

Under the conditions imposed by this study, it is evident that neither of the antihistamines tested provided better protection than did the placebo to the pollen challenge. It may be argued that the test situation is at variance with that encountered in therapeutic usage where the drug is ordinarily administered regularly over an extended period of time so that a cumulative effect might occur. It is also possible that the one hour allowed for absorption was inadequate, even though the agents were administered under circumstances which should facilitate prompt entrance into the circulation. For these reasons, a modified study eliminating these factors has been undertaken for comparative purposes.

This study brings into sharp relief the disparity which often exists between clinical observation and the controlled therapeutic experiment and, although no general conclusion can be made secure at this time, the data presented raise the question as to whether or not the effectiveness of these two antihistamines in the treatment of ragweed-induced rhinitis has its basis in any specific pharmacodynamic effect.

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