

Degree and duration of skin test suppression and side effects with antihistamines

A double blind controlled study with five antihistamines

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The ability of antihistamines to suppress the wheal response of an intradermal skin test is well recognized, but the degree and duration of this suppression have not previously been adequately studied. This double blind study employed five commonly used antihistamines in recommended therapeutic doses. Wheal suppression was recorded immediately after completing a 3 day course of the respective drug and was followed for up to 7 days or until the wheal regained control levels. Mean suppression ranged from 30.7 per cent to 62.7 per cent and required from 1.39 to 4.31 days to re-establish control levels. Incidence and degree of side effects from each antihistamine are also discussed.

The 1972 edition of the *Physician's Desk Reference* lists 103 antihistaminic drugs, either as single medications or in combination with other pharmacologic agents. The claims for their effectiveness and paucity of side effects are legion and mostly unconfirmed.

Since suppression of symptoms is greatly influenced by a number of unpredictable variables, the qualitative assessment of wheal and flare suppression following allergy skin testing appears to offer a practical and reproducible parameter for the measurement of effectiveness in this group of drugs. However, there is a great variance of opinions regarding the significance and magnitude of skin test suppression from antihistamines.

Several objective studies have pointed toward the inhibitory action of antihistamines on skin testing.¹⁻⁵ Two papers presented at the 1971 and 1972 annual meetings of the American Academy of Allergy^{6,7} have demonstrated statistically significant inhibition of the skin reaction with these drugs for 24 hour periods. However, a search of the literature failed to reveal any evidence of suppression beyond a period of 24 hours, nor have correlations between wheal

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and flare inhibition and side effects from antihistamines been documented. Clarification of these issues has been the purpose of this study.

METHODS

Patients

Eighteen young adults who had recently been evaluated by intradermal testing and found to have significant wheal and flare reactions from testing with inhalant allergens volunteered for a double blind study. None of these patients were started on hyposensitization therapy until completion of the study. Since only some of these patients were symptomatic at the time of the study, symptom relief from antihistamines was not considered in the evaluation of the medications used.

Testing materials

Aqueous pollen and mold extracts from Purex Laboratory, Hanover, New Jersey, Center Laboratories, Port Washington, New York, Greer Laboratories, Lenoir, North Carolina, and Endo Dust from Endo Labs., Inc., Garden City, L. I., N. Y., were used for this study. Antigen dilutions were freshly prepared once a month and kept separately for this study. In all instances, a 4+ reaction (wheals greater than 10 mm. in diameter with two or more pseudopods) had previously been demonstrated in these patients with test doses of 100 or 1,000 protein nitrogen units per milliliter by the intradermal injection of 0.01 ml. in the deltoid area. On repeat testing, alternate arms were used for each subsequent test and the testing site changed in a downward progression. All skin tests were read at 10 minutes after application. All tests were applied one hour after the last dose of the 3 day course of antihistamine therapy had been taken (usually at 9 A.M.) and, subsequently, at 24 hour intervals after initial testing.

Antihistamines

One representative drug was used from each of the five major antihistamine groups (Fig. 1):

Ethanolamines	Diphenhydramine (Benadryl, Parke, Davis & Co.)
Ethylenediamines	Tripeleminamine (Pyribenzamine, Ciba Pharm. Co.)
Alkylamines	Chlorpheniramine (Chlor-Trimeton, Schering Corp.)
Cyclizines	Hydroxyzine (Atarax, Vistaril, J. B. Roerig & Co.)
Phenothiazines	Promethazine (Phenergan, Wyeth Labs.)

The dosages used were those recommended by the manufacturers as the usual and customary dosages (50 mg. q.i.d. for diphenhydramine and tripeleminamine, 25 mg. q.i.d. for hydroxyzine and promethazine, and 4 mg. q.i.d. for chlorpheniramine). All drugs were administered over a 3 day period (from Friday afternoon to Monday morning), in an effort to simulate a course of treatment that would, in practice, precede skin testing in many patients. Since the rate of metabolism of antihistamines is suspected to vary from drug to drug and from patient to patient, it was hoped that a 3 day course would allow for equilibration between cumulation and metabolism during each treatment course. All drugs had been converted into powder form by the hospital pharmacy and individual doses pressed into red gelatin capsules that were then completely filled with lactose. Three-day supplies of the respective drugs were packaged in containers marked with the patient's name and a code number. The code was maintained in the hospital pharmacy until completion of the study.

Randomization

A member of the hospital pharmacy staff prepared a list with random distribution of the five drugs for each patient, so that the sequence in which drugs were given could not be predicted. Patients were issued a prescription in the Allergy Clinic and were issued their 3 day supplies of the respective antihistamine by the pharmacist in accordance with a randomization schedule. Randomization numbers had been generated on a computer (PDP-10), by Program RNDAP in block letters, to assure equal representation on an optimal basis (number of patients being a multiple of the number of drugs). All 18 volunteers were issued all five drugs

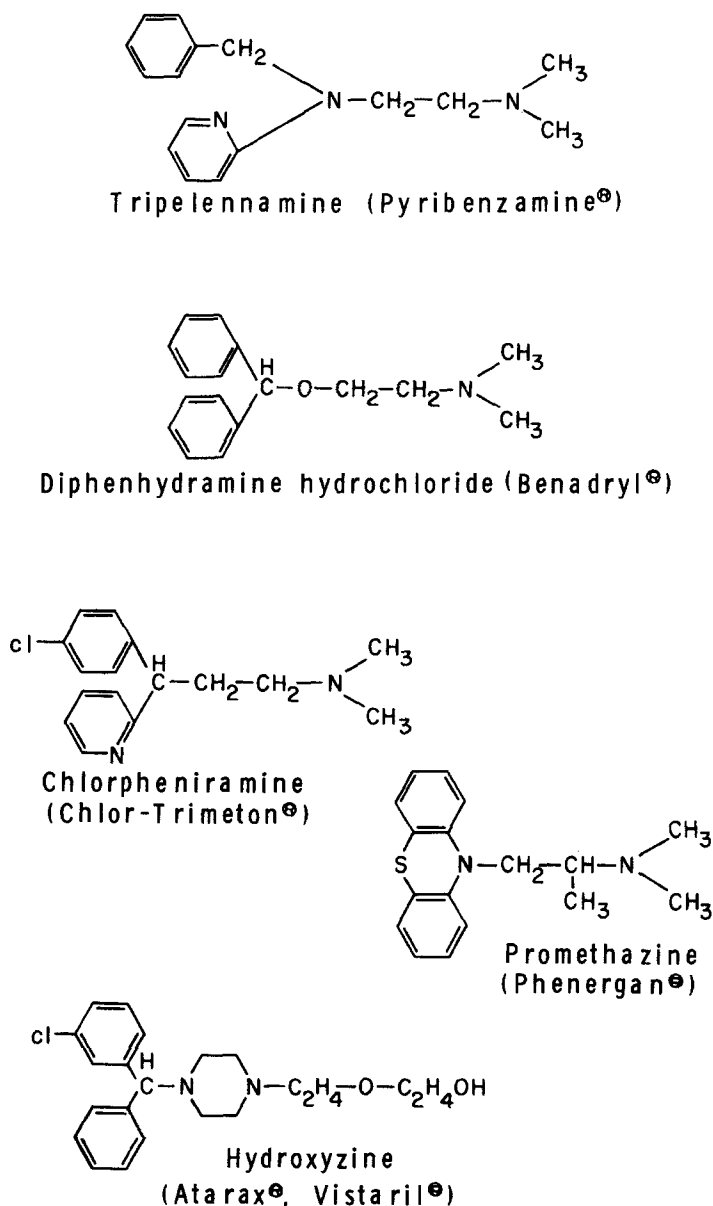


FIG. 1. Structural formulas of representative antihistamines used in this study.

according to this schedule. However, not all volunteers were able to complete all five courses of treatment in a manner satisfactory to the investigators. In instances of inadequate treatment courses, the respective course was excluded from statistical evaluation.

Side effect scores

When patients returned for re-testing on Monday morning, they were requested to fill out a questionnaire reporting the presence or absence and degree of the following symptoms: vertigo, drowsiness, dry mouth, irritability, nervousness, insomnia, and disorientation.

TABLE I. Per cent suppression of wheal size

Drug	Sample size	Mean	Range	Standard deviation
Chlorpheniramine	10	34.4	0 -68.7	23.0
Tripeleennamine	14	43.9	6.4-88.7	23.7
Promethazine	18	51.2	24.6-75.2	16.6
Hydroxyzine	18	62.7	34.1-80.9	15.7
Diphenhydramine	15	30.7	0 -66.3	23.4

Skin test quantitation

A pre-treatment reaction to the respective antigen was documented in each patient by outlining the wheal size and shape with a ballpoint pen and imprinting the image of this outline on moist paper. The same procedure was followed when patients returned to the Clinic on Monday morning, one hour after having taken the last dose of their 3 day course of antihistamine treatment. Tests were then repeated each morning during the week until a pre-test wheal size was again reached.

Tabulation of results

The images of the skin test wheals were measured by planimetry and the depression of the wheal size expressed for each day in percentage of surface area of the control wheal size. These data were then stored together with the side effect questionnaire until completion of the study.

Evaluation of results

After completion of testing in 18 patients, the code was partially broken by the pharmacist by indicating the time sequence in which identical drugs had been taken by each patient. The drugs were then designated by Roman numerals I, II, III, IV, and V.

Statistical comparisons were made among the five drugs with respect to wheal size suppression, duration of suppression, and side effects. For each parameter an overall comparison among means of the five drugs was made by analysis of variance, taking due account of differences among patients.

After establishing that significant differences existed among the drugs tested in their ability to suppress skin tests, comparisons of the means were made between the drugs, two at a time. No attempt was made to compare clinical effectiveness at that time. All statistical analyses were performed utilizing computer program BMDX63.⁸ The Student's *t* test for small samples was utilized for statistical evaluation.

RESULTS

Wheal size suppression

Table I indicates sample number, mean wheal size suppression, range of suppression, and standard deviation for each of the five drugs. The most significant suppression (mean of 62.7 per cent) and the least variability (standard deviation of 15.7) was observed with drug No. IV, while drug No. V appeared to give the least suppression and the greatest variability (mean suppression 30.7 per cent and standard deviation of 23.4). The other three drugs ranged in between in effectiveness and variability.

Duration of suppression

Table II describes the number of days before the control wheal size was reached again. Duration of suppression appears to coincide roughly with the degree of initial suppression, the longest suppression being seen with drug

TABLE II. Days duration of skin test suppression

Drug	Sample size	Mean	Range	Standard deviation
Chlorpheniramine	11	2.45	0-6	1.81
Tripeleennamine	14	2.75	1-7	1.63
Promethazine	18	2.75	1-4.5	1.00
Hydroxyzine	16	4.31	2-8	1.86
Diphenhydramine	14	1.89	0-4.5	1.52

TABLE III. Side effects from antihistamines

Drug	Sample size	Mean	Range	Standard deviation
Chlorpheniramine	13	2.31	0- 6	2.14
Tripeleennamine	15	3.40	0- 7	2.29
Promethazine	17	5.41	0-18	4.68
Hydroxyzine	18	5.94	0-13	4.57
Diphenhydramine	17	5.41	0-15	4.60

No. IV (mean of 4.31 days), and the shortest with drug No. V (mean of 1.89 days). It is of interest that, with the exception of drug No. V, all drugs suppressed the mean skin test in excess of 48 hours.

Side effects

As indicated in Table III, the cumulative side effect score (0 for no side effect, 1 for mild, 2 for moderate, and 3 for marked discomfort) ranged from 0 to 18. The most effective drug in wheal suppression (No. IV) also had the highest mean side effect score, which, however, only slightly exceeded the score of the least effective drug (No. V). The lowest side effect score was recorded for drug No. I, which, however, ranked fourth in effectiveness and duration of wheal size suppression.

Comparison of five drugs with each other

Tables IV, V, and VI depict a comparison of each drug with every other drug in regard to its effectiveness in suppressing the wheal size, the duration of this effect, and the side effect scores. Significant differences in effectiveness were seen (P less than 0.05) between drugs I and III, I and IV, III and V, and IV and V. The effectiveness of drug No. IV could be approached only by drug No. III. However, drug No. III exceeded only drug No. V in effectiveness. All other comparisons were below the level of significance.

The duration of suppression differed significantly between drugs Nos. I and II, I and IV, II and III, II and IV, III and IV, and IV and V. Drug No. IV exhibited significantly longer duration than any other drug.

The differences between side effect scores were less significant than those of wheal suppression and duration of suppression. Drug No. I had a significantly lower score than drugs Nos. III, IV, and V, while drug No. II had a significantly lower score than drug No. IV. There was no significant difference between the side effect scores of the most effective and the least effective drugs (Nos. IV and V).

TABLE IV. Comparisons of five drugs in wheal suppression

Drugs	Differences in per cent suppression	Student t value	Significance
Chlorpheniramine vs. tripeleannamine	9.5	1.28	$p > 0.05$
Chlorpheniramine vs. promethazine	16.8	2.69	$p < 0.01$
Chlorpheniramine vs. hydroxyzine	28.3	4.22	$p < 0.001$
Chlorpheniramine vs. diphenhydramine	3.7	0.05	$p > 0.05$
Tripeleannamine vs. promethazine	7.3	1.55	$p > 0.05$
Tripeleannamine vs. hydroxyzine	18.8	3.27	$p < 0.01$
Tripeleannamine vs. diphenhydramine	13.2	1.36	$p > 0.05$
Promethazine vs. hydroxyzine	11.5	1.88	$p > 0.05$
Promethazine vs. diphenhydramine	20.5	3.05	$p < 0.01$
Hydroxyzine vs. diphenhydramine	32.0	4.82	$p < 0.001$

TABLE V. Comparisons of five drugs in days duration of suppression

Drugs	Differences in days duration	Student t value	Significance
Chlorpheniramine vs. tripeleannamine	0.30	2.62	$p < 0.01$
Chlorpheniramine vs. promethazine	0.30	0.77	$p > 0.05$
Chlorpheniramine vs. hydroxyzine	1.86	3.90	$p < 0.001$
Chlorpheniramine vs. diphenhydramine	0.56	0.56	$p > 0.05$
Tripeleannamine vs. promethazine	0.00	0.36	$p > 0.05$
Tripeleannamine vs. hydroxyzine	1.56	3.39	$p < 0.01$
Tripeleannamine vs. diphenhydramine	0.86	1.40	$p > 0.05$
Promethazine vs. hydroxyzine	0.86	3.20	$p < 0.01$
Promethazine vs. diphenhydramine	0.86	1.83	$p > 0.05$
Hydroxyzine vs. diphenhydramine	2.42	4.78	$p < 0.001$

Final drug identification

After complete tabulation of effectiveness, duration of effectiveness, and side effect scores and their respective statistical evaluations, the pharmacist was asked to reveal identification of the five antihistamines. They are as follows:

- Drug No. I Chlorpheniramine
- Drug No. II Tripeleannamine
- Drug No. III Promethazine
- Drug No. IV Hydroxyzine
- Drug No. V Diphenhydramine

DISCUSSION

The purpose of this study was twofold: one, to compare a number of antihistamines in humans by only one criterion—the suppression of the allergy skin test; the other, to provide guidelines for the allergist as to how long drugs with antihistaminic action need to be withheld prior to skin testing. Clinical evaluation of the different antihistamines was not intended in this study and would require a different protocol. From the results the following conclusions could be drawn:

1. All antihistamines of the five major groups can be expected to suppress allergy skin tests. The mean of this suppression ranges from 30 to 60 per cent, if the drug is given over a 3 day course and testing is performed one hour after the last dose is given.
2. Wheal size suppression has a variable duration for the five drugs tested,

TABLE VI. Side effects from antihistamines

Drugs	Differences in side effects	Student t value	Significance
Chlorpheniramine vs. tripeleannamine	1.09	0.93	p > 0.05
Chlorpheniramine vs. promethazine	3.10	2.64	p < 0.05
Chlorpheniramine vs. hydroxyzine	3.63	3.07	p < 0.01
Chlorpheniramine vs. diphenhydramine	3.10	2.64	p < 0.05
Tripeleannamine vs. promethazine	2.01	1.77	p > 0.05
Tripeleannamine vs. hydroxyzine	2.54	2.23	p < 0.05
Tripeleannamine vs. diphenhydramine	2.01	1.77	p > 0.05
Promethazine vs. hydroxyzine	0.53	0.48	p > 0.05
Promethazine vs. diphenhydramine	0.00	0.00	p > 0.05
Hydroxyzine vs. diphenhydramine	0.53	0.48	p > 0.05

being longest with hydroxyzine (four days) and shortest with diphenhydramine (two days).

3. Side effects, such as drowsiness, vertigo, irritability, disorientation, etc., were most pronounced with the most suppressive drug but do not necessarily parallel effectiveness quantitatively.

4. If skin test wheal size suppression can be accepted as a measurement for potency of antihistamines, hydroxyzine appears to be the most active drug of the five antihistamines tested with the longest duration of activity. Its side effect score is only slightly higher than that of the least effective antihistamine by these criteria.

5. Low side effect scores and low wheal suppression activity for chlorpheniramine and tripeleannamine suggest that the dosages recommended by the manufacturers may not be equivalent to those recommended for promethazine and hydroxyzine.

6. There appear to be individual differences in some patients' ability to metabolize antihistamines, which affect both wheal suppression and side effect scores. Whether an extrapolation of this observation from skin test suppression to clinical usage is permissible will have to depend on the outcome of double blind therapeutic trials.

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