INDIAN J DERMATOL VENEREOL LEPROL 1987; 53 : 158-161

RELATIVE EFFICACY OF SEVEN COMMON H1 RECEPTOR ANTAGONIST ANTIHISTAMINES IN CHRONIC IDIOPATHIC URTICARIA

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The order of clinical potency of seven H_1 receptor antagonist antihistamines in usual therapeutic doses was evaluated in 30 patients of chronic idiopathic urticaria by a double blind, placebo controlled trial utilizing a self assessment method. The analysis of mean whealing and itching scores established a potency sequence in the decreasing order of cyproheptidine, hydroxyzine, chlorpheniramine, embramine, promethazine, dimethindene and dexchlorpheniramine. The differences between the first five antihistamines were not statistically significant, though these were superior to dexchlorpheniramine and placebo. Dexchlorpheniramine was statistically better than placebo.

Key words : Antihistamines, Urticaria, H_1 receptors.

The antihistamines have been advertised widely to the laity as preventive and suppressive agents of urticaria and other histamine mediated inflammatory skin lesions. The dermatologists are confronted with scores of drugs to choose from, the ultimate selection depending upon the prescribing habit, advertising compaigns and anecdotal evidence.[1] Antihistamine administration usually leads to reduction of whealing and relief from pruritus. Some antihistamines fail to sufficiently suppress whealing in therapeutic doses, requiring an increase in the dosage at the expense of side effects of drowsiness and antimuscarinic (atropine like) activity, making this approach impracticable.[2] Alternatively, an antihistamine of another therapeutic class, a combination of two different groups of H_1 receptor antagonists or combined H_2 and H_1 antagonists should be tried.[2-5] However, there is little statistically valid evidence to support the claims of supremacy of one drug over another. Hence, a rational basis of relative potency of antihistamines is needed. We evaluated the relative clinical potency of 7 commonly used antihistamines in therapeutic doses, using a randomised self assessment method in patients with chronic idiopathic urticaria.

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Materials and Methods

Thirty patients having chronic idiopathic urticaria were studied. These patients had been having daily extensive whealing for more than 12 weeks. All patients underwent extensive medical evaluation that failed to disclose an underlying cause, therefore considered to have chronic idiopathic urticaria. Pregnant women and children were excluded from the study. Routine urinalysis, haemogram, three consecutive stool examinations, blood chemistry, liver functions, HbSag and skiagrams were performed in all patients. All medications including antihistamines were stopped 5 days prior to the start of the study. The patients were given 7 packets numbered in a random order, each containing 5 days supply of the following antihistamines with written instructions, promethazine hydrochloride 25 mg once a day, chlorpheniramine maleate 4 mg 4 times a day, hydroxyzine hydrochloride 10 mg 4 times a day, cyproheptidine hydrochloride 4 mg 4 times a day, embramine hydrochloride 25 mg twice a day, dimethindene maleate 1 mg 4 times a day and dexchlorpheniramine maleate 2 mg 4 times a day. The last drug was lactose powder-

filled gelatin capsules, serving as a placebo. The patients were also supplied with a cyclostyled form with instructions and a questionnaire. Each drug was to be taken for 5 days followed by a rest period of 2 days required for washout. At 9 p.m., the patient was asked to record the approximate number of hives experienced that day, severity of itch (4 grades : none, mild, moderate and severe), suitability of the tablets (yes or no) and unwanted side effects. After completion of the form, patients visited for follow up and evaluation of the questionnaire. The self assessment questionnaire was analysed by applying arbitrary scoring system for whealing (1 wheal=1 point) and itching (none=0, mild =0.5, moderate=1.0 and severe=1.5). Mean whealing and itching scores, standard deviation and standard error were calculated for each antihistamine used, and 't' test of significance applied to the overall mean whealing and itching indices of all patients for each group of antihistamines.

Results

Of the 30 patients entered in the trial, 25 completed the study. Of the remaining five, 3 failed to continue treatment and 2 did not fill up the proforma provided. The 25 patients consisted of 18 females and 7 males with a mean age of 27.5 years and mean urticaria duration of 3.3 years. Relative effectiveness of the seven antihistamines is shown in table I. Cyproheptidine was the most effective drug. Mean wheal and itch scores showed statistically significant superiority of the first five antihistamines to dexchlorpheniramine and placebo. Dexchlorpheniramine was statistically better than the placebo. The sequence of potency in decreasing order was established as cyproheptidine, hydroxyzine, chlorpheniramine, embramine, promethazine, dimethindene and dexchlorpheniramine. Since each drug was used for 5 days, the side effects were minimal. Drowsiness was commonest and experienced by 8 patients with all the drugs. It was more common with chlorpheniramine, hydroxyzine and cyproheptidine.

Comments

A relative potency list of the commonly available antihistamines should guide physicians to choose the next most potent drug rather than giving these in a haphazard manner. The

Table I. Analysis of patients' self assessment record for mean wheal and itch scores. Lesser score means more effectiveness.

Group	Antihistamine	Dose	Mean wheal score ±S. E. (mean)	Mean itch score ±S. E. (mean)	Significant 't' values between groups for whealing scores
1.	Promethazine hydrochloride	25 mg OD	8.50±1.72	0.74±0.08	t 1,7=2.17*
2.	Chlorpheniramine maleate	4 mg QID	5.90±1.58	0.48±0.08	t 1,8=7.25***
3.	Hydroxyzine hydrochloride	10 mg QID	5.00±1.46	0.39±0.07	t 2,7=2.94** t 2,8=8.10***
4.	Cyproheptidine hydrochloride	4 mg QID	4.24±1.76	0.41±0.08	t 3,7=3.20** t 3,8=8.39***
5.	Embramine hydrochloride	25 mg BD	5.92±1.85	0.56±0.75	t 4,7=3.42*** t 4,8=8.64***
6.	Dimethindene malcate	4 mg QID	8.66±1.90	0.75±0.11	t 5,7=2.93** t 5,8=8.09***
7.	Dexchlorpheniramine maleate	2 mg QID	15.90±3.44	1.02±0.14	t 6,7=2.12* t 6,8=7.20***
8.	Placebo	50 mg OD	30.70±3.35	1.31±0.06	t 7,8=4.35***

*p<0.05, **p<0.01 and ***p<0.001

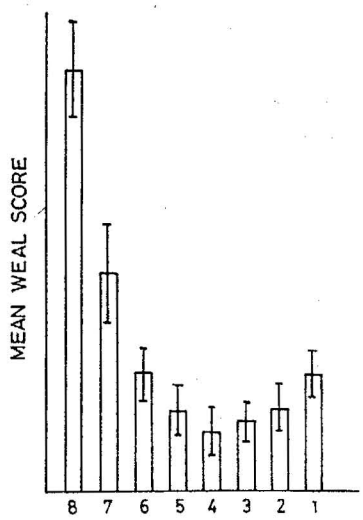

FIG. 1 COMBINED PATIENT MEAN WEALING SCORES WITH 7 ANTIHISTAMINES. NO. 8 IS PLACEBO.

clinician's objective analysis of the effect of antihistamines on urticaria is impracticable because of the variable intensity, severity and frequency of whealing and pruritus. A subjective analysis using a self assessment proforma as used by us can be a valuable method of assessing the potency of the administered drug. This method has been used by others also.[1,6] It may also be argued that the chosen drug regimens may not be comparable. Since a comparison of equimolar concentration of antihistamines in the skin is difficult due to variable pharmacokinetics, the most commonly used drug regimens were applied to secure a comparable system of evaluation.[1]

Of the different patterns of urticaria, chronic urticaria gets maximum relief from antihistamines but all patients may not respond equally well.[2] Bain et al[7] found 18% non-responders out of 500 patients. Of the 91 patients of chronic urticaria on therapy with antihistamines, the wheals could be suppressed in 25, reduced to little discomfort in 35 and reduced with some discomfort in 25, whilst in 6 the doses of antihistamines required to produce effect were not tolerated.[5] In another study, the response to antihistamines was good in 31%, moderate in 46%, slight in 17% and none in 6%.[8] The response to treatment was also found to be related to the average duration of disease.[8] The comparative evaluation of antihistamines has been attempted by a few. Coutts and Greaves[1] used a similar method in patients having chronic urticaria to evaluate six antihistamines and established a potency order of cyproheptidine, chlorpheniramine, hydroxyzine, promethazine, mepyramine and trimeprazine. These antihistamines were also judged for histamine antagonism by an in vitro method on the myentric plexus longitudinal muscle preparation of guinea pig ileum and were found to have a potency order of trimeprazine, mepyramine, promethazine, chlorpheniramine, cyproheptidine and hydroxyzine, in that order. It was concluded that an in vitro evaluation may produce misleading results in terms of clinical usefulness of a given antihistamine. Employing a single dose, 150 mg of mepyramine was found to be equipotent with 25 mg of promethazine.[9] Bailey[10] reported excellent results from cyproheptidine, though drowsiness was common. Similar studies in physical urticaria, in which histamine release in the skin is known, have shown the value of hydroxyzine and cyproheptidine.[2,11] Hydroxyzine was found to be superior to chlorpheniramine in the treatment of dermographism and chronic urticaria.[12,13] It was also more effective than brompheniramine in 8/14 patients of cholinergic urticaria.[14] Cyproheptidine has been reported to be effective in cold urticaria.[11,15] A combination of H_1 and H_2 receptor antagonists has been found to be beneficial by some but not by others.[6,16]

Actions other than those on H_1 and acetylcholine receptors could be responsible for the potency and clinical utility of an antihistamine[1-3] Cyproheptidine, promethazine and chlorpheniramine have been shown to interact with 5-HT receptors in the rat uterus.[1] Promethazine acts as a non-competitive antagonist on H_2 receptors

in the heart and its anti-pruritic effect may be due to its local anaesthetic property.[18] Sucrose gap technique applied to rabbit cervical vagus nerve showed cyproheptidine to be more potent than procaine or diphenhydramine.[19]

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