Lack of Effect of Cimetidine in Chronic-Idiopathic Urticaria

L. J. Cook and Sam Shuster

University Department of Dermatology, Royal Victoria Infirmary, Newcastle-upon-Tyne, England

Received November 20, 1982

Abstract. The effect of an H_1 and an H_2 receptor blocker singly and in combination was studied in 20 patients with chronic idiopathic urticaria. Both H_1 receptor blockade alone and in combination with H_2 receptor blockade produced a significant reduction in wealing and itch; there was no significant difference between these treatments. H_2 blockade alone produced no significant reduction in wealing; there was a slight increase in itch, though not statistically significant.

H_1 receptor blockers are only partly effective in chronic idiopathic urticaria (13). H_2 blockers reduce both the flare and weal response to histamine (7, 10), yet their effect in chronic idiopathic urticaria is still uncertain (2).

We have carried out a controlled double-blind clinical study of an H_2 receptor blocker, alone and in combination with an H_1 receptor blocker in this condition. A preliminary report of these findings has already been published (3).

MATERIALS AND METHODS

20 otherwise healthy male and female patients with chronic idiopathic urticaria between the ages of 18 and 62 years were studied.

At the first interview all therapy was stopped and the patients were given diary cards on which weal was to be recorded, as none, few, or many; itch was recorded as none, some, or severe and itch duration as <1 hour, 1-6 hours, or >6 hours. For statistical analysis these were recorded on a 3-point scale. Severity of itch was recorded weekly by the patient as the distance along a 10 cm line.

At each subsequent interview the patients and the same clinician assessed overall change relative to the previous visit on a 5-point scale, from marked deterioration to marked improvement. The number of lesions present at the time of assessment were scored on a 3-point scale.

At the second interview each patient was allocated a double-blind treatment schedule consisting of all three treatment blocks comprising cimetidine with placebo, chlorpheniramine with placebo, or cimetidine plus chlorpheniramine, taken in a predetermined random order. The chlorpheniramine was administered as a single white tablet. The cimetidine was administered in its prescribable form. The active preparations and their respective placebo tablets were of identical appearance. Each treatment block lasted 2 weeks and at the end of each fortnight the patients attended for assessment. Five patients were withdrawn from the study: 3 due to erratic attendance, in one the rash had resolved and one had become pregnant.

Analysis. The results were analysed using the non-parametric Freedman two-way analysis and the Wilcoxon matched pairs sign test.

RESULTS

Weals

The results are given in Fig. 1.

Patients' assessment: with the data from the diary card the Freedman two-way analysis of variance showed a statistically significant difference between the groups ($p<0.001$). Further analysis using the Wilcoxon matched pairs sign test showed that cimetidine alone did not reduce wealing significantly. Cimetidine with chlorpheniramine reduced wealing ($p<0.02$) but not as much as did chlorpheniramine alone, although this difference was not statistically significant.

Clinician's assessment: the Freedman two-way analysis of variance showed that the difference between groups was significant ($p<0.01$). During cimetidine administration, wealing was less—though not significantly so. Chlorpheniramine both alone and in combination with cimetidine gave a significant reduction of wealing ($p<0.01$) and a significantly greater reduction in wealing than cimetidine alone ($p<0.01$).

Itch

The results are given in Fig. 2.

Patients' assessment. The results for degree, duration, and severity of itch were all similar. On cimetidine alone there was no change—or a slight increase in itch, although this did not reach statistical significance and there was a decrease in all indices with chlorpheniramine alone and cimetidine plus chlorpheniramine. This was significant only with chlorpheniramine alone for degree and duration ($p<0.05$) and with both chlorpheniramine alone and the combination of chlorpheniramine and cimetidine for severity ($p<0.05$).

Assessment of overall change relative to previous visit. The physician's assessment and the patients' own assessment of progress showed no significant difference between the treatment groups.

Side effects. 4 subjects on chlorpheniramine

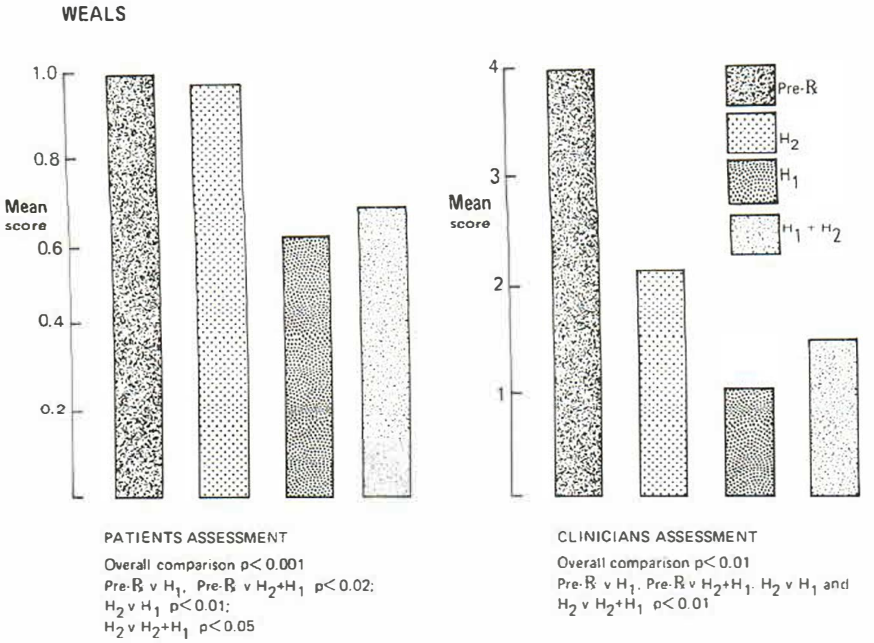

Fig. 1. The patients' weal assessment is shown on the left. Scores after H_1, and H_1 with H_2 blockade were significantly less than pre-treatment ($p<0.02$) and after H_2 blockade ($p<0.01$ and 0.05). The clinician's assessment is shown on the right. Scores after H_1 and H_2 blockades were significantly less than pre-treatment and after H_2 blockade ($p<0.01$) but the change after H_2 blockade alone was not significantly different from pre-treatment.

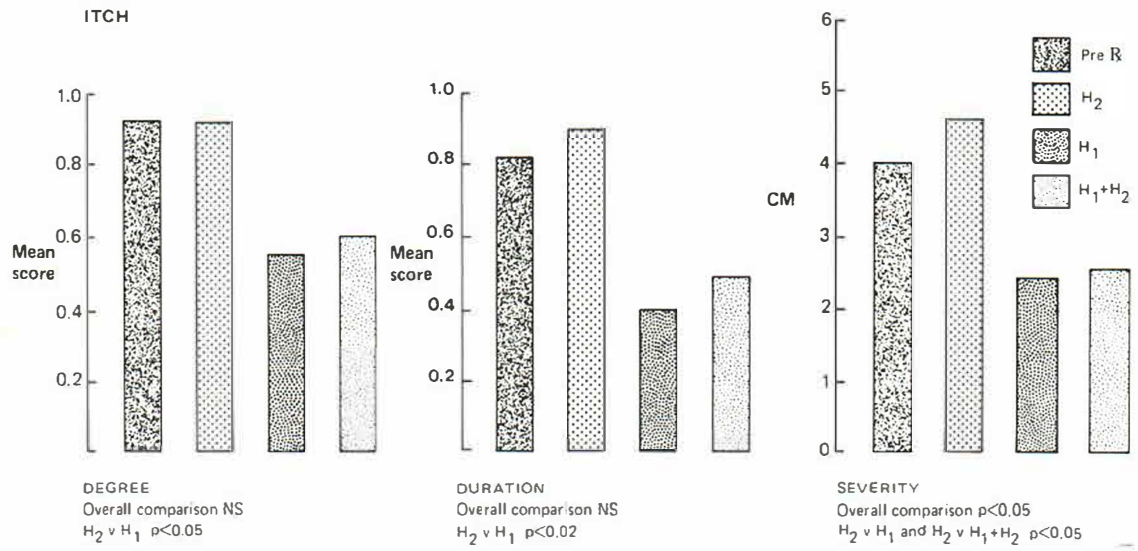

Fig. 2. The patients' subjective assessment of severity of itch is shown on the left, duration of itch in the centre and severity of itch on a 10 cm line on the right. After H_1 blockade, scores were significantly less for all indices than after H_2 blockade ($p<0.05$); the slight increase after H_2 blockade was not statistically significant.

alone and one on the combination noted drowsiness.

DISCUSSION

Although only 15 of the 20 patients completed the study, since all had daily attacks of moderate or severe urticaria, it would be anticipated that a therapeutically useful change in weal and itch would have been detected. Indeed our results show that chlorpheniramine is effective, which is further evidence for the role of histamine in chronic idiopathic urticaria (8). More importantly, cimetidine alone was ineffective and the combination of cimetidine and chlorpheniramine was slightly but consistently less effective than chlorpheniramine alone. Thus we cannot confirm the slight improvement with the combination found by Commens & Greaves (2), but our findings are consistent with those of Michell et al. (12) regarding solar urticaria. One explanation for the slight worsening is that H_2 receptor blockers may increase the amount of local histamine either by increased production (9) or reduced metabolism (14) or even by histamine release, since we have found evidence of wealing suggestive of this after intradermal injections of cimetidine. This may explain the exacerbation of the itch which has also been noted after H_2 blockade for dermographism (11).

The present findings are surprising, since the combination of chlorpheniramine with cimetidine has been found to be slightly more effective than either alone in reducing the response to intradermal histamine (4, 10). It could therefore be that urticaria is concerned with a pathological or additional histamine receptor (1, 6) or that the wealing is due to some other vasoactive materials. In this respect we have shown that the time course of response to intradermal histamine in normal human skin indicates that the histamine itself leads to the release or formation of a secondary mediator of inflammation (5) which is unaffected by chlorpheniramine and cimetidine (4). If the more potent H_2 blockers now becoming available have a similarly poor effect on chronic idiopathic urticaria and other urticarias, more fundamental studies on the pharmagological basis of urticarial wealing will be required.

REFERENCES

1. Ash, A. S. F., Schild, H. O.: Receptors mediating some actions of histamine. Br J Pharmacol *27:* 427, 1966.
2. Commens, C. A., Greaves, M. W.: Cimetidine in chronic idiopathic urticaria: a randomised double blind study. Br J Dermatol *99:* 657, 1978.
3. Cook, L. J., Shuster, S.: Lack of effect of H_2 blockade in chronic urticaria. Br J Dermatol *101* (Suppl. 17): 21, 1979.
4. Cook, L. J., Shuster, S.: Persistence of histamine weals and production of secondary vasoactive agents. J Invest Dermatol *74:* 6, 460, 1980.
5. — Histamine weal formation and absorption in man. Br J Pharmacol *69:* 579, 1980.
6. Eyre, P., Shand, N.: Preliminary evidence for two sub-classes of histamine H_2 receptors. Agents Actions *9:* 1, 1979.
7. Harvey, R. P., Schockett, A. L.: The effect of H_1 and H_2 blockade on the cutaneous histamine response in man. J Allergy Clin Immunol *65* (2): 136, 1980.
8. Kaplan, A. P., Horakova, S., Katz, S. I.: Assessment of tissue fluid histamine levels in patients with urticaria. J Allergy Clin Immunol *61* (6): 350, 1978.
9. Lichtenstein, L. M., Gillespie, E.: Inhibition of histamine release by histamine controlled H_2 receptor. Nature *244:* 287, 1973.
10. Marks, R., Greaves, M. W.: Vascular reactions to histamine and compound 48/80 in human skin. Suppression by a histamine H_2 blocking agent. Br J Clin Pharmacol *4:* 367, 1977.
11. Matthews, C. N. A., Boss, J. M., Warin, R. P., Storari, F.: Effect of H_1 and H_2 antagonists on symptomatic dermographism. Br J Dermatol *101:* 57, 1979.
12. Michell, P., Hawk, J. L. M., Shofrir, A., Corbett, M. F., Magnus, I. A.: Assessing the treatment of solar urticaria. The dose response as a quantifying approach. Dermatologica *160:* 198, 1980.
13. Warin, R. P., Champion, R. H.: Acute and chronic urticaria. *In* Treatment in Urticaria, p. 100, W. B. Saunders Co. Ltd., London.
14. Yamomoto, S., Francis, D., Greaves, M. W.: In vitro anaphylaxis in guinea pig skin: amplification by burimomide. J Invest Dermatol *67:* 696, 1976.