To our knowledge, there are several unsolved skin problems among employees in the fish industry. We are therefore making a further examination.

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The Effect of H_1 and H_2 Receptor Antagonists on the Dermographic Response

John Cook and Sam Shuster

University Department of Dermatology, Royal Victoria Infirmary, Newcastle-upon-Tyne, Ne1 4LP, England

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Abstract. The effect on dermographic wealing of an H_1 and H_2 receptor antagonist was studied separately and in combination. A double-blind protocol was used and dermographism was measured as the diameter of weal response to a measured force. Both H_1 and H_2 antagonists had a small but non-significant effect, but the combination of H_1 plus H_2 antagonist had an approximately additive effect which was significant. Although this indicates a role for H_2 receptors in dermographism it does not establish the degree of involvement, nor whether H_2 antagonists necessarily have any advantage over a potent H_1 blocker alone in the treatment of dermographism.

Key words: H_1, H_2, receptor antagonist; Dermographic response

Histamine is thought to be a mediator of dermographism (5) and H_1 antagonists are generally used for its treatment. H_2 receptors are also involved in weal and flare reactions (2, 4, 8) but it is still not clear what part they play in dermographism. We therefore studied the effect of H_1 and H_2 receptor antagonists singly and in combination on the production of dermographic weals.

PATIENTS AND METHODS

Patients and procedures. 14 female and 6 male otherwise healthy patients with dermographism, aged 19–45 years, were studied. They were assessed at their first vivit and all medication was stopped. They were seen 7 days later and their dermographic response was measured, after which they were given various treatment: either 4 mg chlorpheniramine plus an inert tablet, 400 mg cimetidine plus an inert tablet, or a combination of 4 mg chlorpheniramine plus 400 mg cimetidine. All the tablets loked alike and their order had been randomized according to a latin square design and they were given double-blind. The patients took the tablets with water 2 hours before each visit and the time between vivits was at least 2 days. At each visit the dermographic response was measured and a new medication given until each patient had taken all three treatments. The code was broken when the study had been completed.

Measurement of dermographism. Dermographic weals were produced with a spring-loaded stylus which travelled down a slit in a flat guide plate as described by Kerby et al. (6). The instrument was calibrated and the responses to forces of 24.5 and 36.1, 48.6, 60.9 and 74.6 g/mm^2 were measured in each subject. The weals were raised on the left side of the back below the spine of the scapula with a gap of approximately 3 cm between each weal, by passing the stylus backwards and forwards three times along the same track. The diameter of each weal was measured at 3 points 2 cm apart 10 minutes after initiation and the mean weal diameter was calculated.

RESULTS

The dose–response curves of stylus pressure and weal diameter were linear, both before and after each treatment, and the results are expressed as means of standard errors (in Fig. 1) and as the cor-

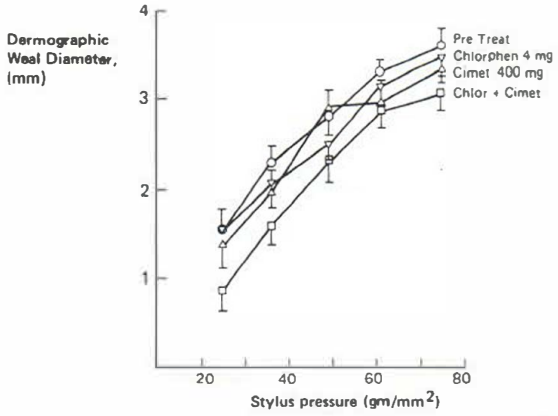

Fig. 1. Dermographic stimulus–response curves (mean ± SE) before and after various treatments in 20 patients with dermographism.

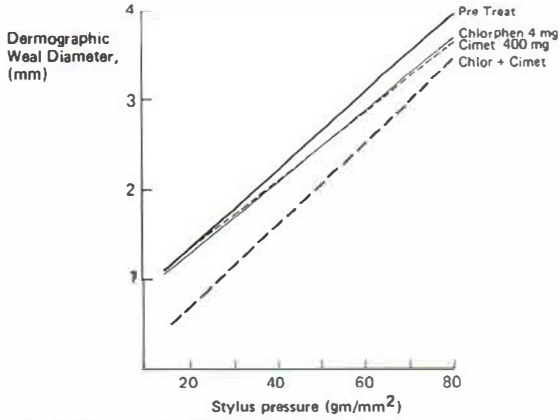

Fig. 2. Regression lines calculated from data in Fig. 1.

responding calculated regression lines (in Fig. 2). Both chlorpheniramine (4 mg) and cimetidine (400 mg) reduced the dermographic response slightly but the reduction was not significant. By contrast, the combination of the H_1 and H_2 antagonists reduced the weal response and this decrease was significant both by comparison with the untreated patients ($p<0.01$) and by comparison with patients taking either the H_1 or H_2 antagonist alone ($p<0.05$). Further analysis of the curves showed that corresponding λ values were 0.3 pretreatment, 0.55 after chlorpheniramine, 0.54 after cimetidine, and 0.47 after the combined dose of chlorpheniramine and cimetidine. The shift in the dose–response curves is shown as potency ratios in Fig. 3 and the decrease in potency with the combination of H_1 and H_2 blocker is of the order which would be predicted from the additive effect of each antagonist alone.

DISCUSSION

The dose–response curve of stylus pressure and weal diameter over the range studied was sufficiently linear and discriminant to permit measurement of the effect of drugs which alter the dermographic response. There was a slight response to both 4 mg chlorpheniramine and 400 mg cimetidine but neither was significant, whereas the combination of both drugs was more effective than eigher drug alone, the response being approximately additive. These results are very similar to the effects of the same drugs on histamine-induced weals (3), suggesting that the dermographic response has features in common with histamine wealing. Although the study of Matthews et al. (9) was done concurrently with ours and was similarly sponsored by the makers of cimetidine, it used a different protocol which did not include measurements of wealing before treatment, so that only the comparative effects of the treatment could be assessed. Nor were dose–response curves done, and as the only significant difference occurred at one of the two stroke forces used it is difficult to reach any firm conclusion as

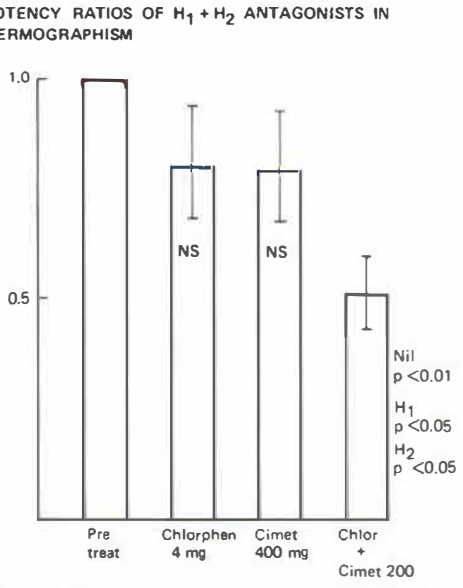

Fig. 3. Relative potency (potency ratio) of various treatments as compared with untreated state, calculated from the shift in the dose–response curves.

to the effect of chlorpheniramine and cimetidine on dermographic wealing. A further problem with both the study of Matthews et al. (9) and our own is that although the dose of cimetidine used was probably adequate for H_2 receptor antagonism, the dose of chlorpheniramine used for a therapeutic effect was too low.

The clinical relevance of our findings is not clear because despite the very similar effects on histamine wealing of the same H_1 and H_2 antagonists (1) the combination of cimetidine and chlorpheniramine appears not to add to the response of chronic idiopathic urticaria to the H_1 antagonist alone (1); indeed the itch was slightly worse (1). Although there was no increased itching in our patients with dermographism, they were only given a single dose of the antagonists, whereas in the study of Matthews et al. (9), where the drugs were given over a period of weeks, there was some increase in itch similar to that which we had found in chronic idiopathic urticaria. This cannot be due to a general effect of H_2 antagonists on histamine metabolism (10) nor to an inhibition of the negative feed-back of histamine on the mast cell (7), as the dermographic weal size would have been increased which it was not (3). However, there is evidence that histamine wealing leads to release of secondary mediators (2); one possibility is that of a change in production of a nonwealing pruritic agent in the dermis or a wealing or non-wealing pruritogen in small quantities but high concentrations locally at the itch receptors during prolonged administration of H_2 receptor blockers.

Finally, whilst our evidence that the dermographic weal response can be reduced by a combination of an H_1 and H_2 antagonist suggests the involvement of both receptors, in the absence of full dose–response studies to establish the effect of amximum H_1 and H_2 receptor baockade, it is impossible to assess the degree of involvement of these two receptor classes in dermographism. Thus we cannot conclude from the present observation that the combination of H_1 and H_2 antagonists will necessarily be of any advantage in the treatment of dermographism over an effective H_1 antagonist by itself.

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Successful Treatment of Cold Angio-Oedema by H^2-Antihistamine Therapy

P. Klemp, B. Staberg,[1] N. Agdal and I. M. Munkvad

Departments of Dermatology and Clinical Physiology, The Finsen Institute, DK-2100 Copenhagen, Denmark

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Abstract. Two patients with severe cold angio-oedema were practically relieved from their symptoms during H_2-blocker therapy (cimetidine 1 000 mg daily). Classic H_1-blocker therapy had no effect on their symptoms and combined H_1- and H_2-blocker treatment was just as effective in ameliorating the symptoms of cold angio-oedema as H_2-blocker treatment alone. A low dose of the H_2-blocker (400 mg cimetidine daily) was almost able to control the angio-oedema formation after cold exposure, but provoked typically urticarial lesions. This observation strongly indicates that H_2-receptors may play an important role in the pathogenesis of cold angio-