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 H1 and H2 Receptor Antagonists on the Dermographic Response

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Abstract: The effect on dermographic wealing of an H1 and H2 receptor antagonist was studied separately and in combination. A double-blind protocol was used and dermography was measured as the diameter of weal response to a measured force. Both H1 and H2 antagonists had a small but non-significant effect, but the combination of H1 plus H2 antagonist had an approximately additive effect which was significant. Although this indicates a role for H2 receptors in dermographic it does not establish the degree of involvement, nor whether H2 antagonists necessarily have any advantage over a potent H1 blocker alone in the treatment of dermographic.

Key words: H1, H2, receptor antagonist; Dermographic response

Histamine is thought to be a mediator of dermography (5) and H1 antagonists are generally used for its treatment. H2 receptors are also involved in weal and flare reactions (2, 4, 8) but it is still not clear what part they play in dermography. We therefore studied the effect of H1 and H2 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 dermographicism, aged 19-43 years, were studied. They were assessed at their first visit 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 looked 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 visits 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 dermography. 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/mm² 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-
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 H1 and H2 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 H1 or H2 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 H1 and H2 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 either 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. 1. Dermographic stimulus–response curves (mean ± SE) before and after various treatments in 20 patients with dermographism.](image1)

![Fig. 2. Regression lines calculated from data in Fig. 1.](image2)

![Fig. 3. Relative potency (potency ratio) of various treatments as compared with untreated state, calculated from the shift in the dose–response curves.](image3)
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 proba­
bly adequate for H2 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 H1 and H2 antagonists (1) the
combination of cimetidine and chlorpheniramine
appears not to add to the response of chronic idiop­
athic urticaria to the H1 antagonist alone (1); in­
deed the itch was slightly worse (1). Although there
was no increase in itching in our patients with dermog­
raphism, 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 itching similar to
that which we had found in chronic idiopathic
urticaria. This cannot be due to a general effect of
H2 antagonists on histamine metabolism (10) nor to
an inhibition of the negative feed-back of histamine
on the mast cell (9), 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 pruritogen in small quantities but high
concentrations locally at the itch receptors
during prolonged administration of H2 receptor
blockers.

Finally, whilst our evidence that the dermog­
raphic weal response can be reduced by a combi­
nation of an H1 and H2 antagonist suggests the
involvement of both receptors, in the absence of
full dose–response studies to establish the effect of
aximum H1 and H2 receptor blockade, it is im­
possible to assess the degree of involvement of
these two receptor classes in dermography. Thus
we cannot conclude from the present observation
that the combination of H1 and H2 antagonists will
necessarily be of any advantage in the treatment of
dermographism over an effective H1 antagonist by
itself.

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Successful Treatment of Cold Angio­
Oedema by H2-Antihistamine Therapy

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Abstract. Two patients with severe cold angio-oedema
were practically relieved from their symptoms during
H2-blocker therapy (cimetidine 1 000 mg daily). Classic
H1-blocker therapy had no effect on their symptoms
and combined H1- and H2-blocker treatment was just
as effective in ameliorating the symptoms of cold angio­
oedema as H2-blocker treatment alone. A low dose of
the H2-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 H2-receptors may play
an important role in the pathogenesis of cold angio­