The effect of topical dimethindene maleate on weal reactions

F. HUMPHREYS & S. SHUSTER

University Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

The topical effect of the histamine H_1 -receptor antagonist dimethindene maleate on the wealing response to intradermal histamine, compound 48/80 and house dust mite antigen was studied in 16 subjects using a double-blind procedure. The mean reduction in weal area $\pm$ s.e. mean was $44\% \pm 13\%$, $43\% \pm 13\%$ and $31\% \pm 13\%$ for histamine, 48/80 and antigen respectively. We conclude that dimethindene maleate is a moderately potent H_1 -receptor antagonist, and that the inhibition of the 48/80 and house dust mite induced weals is accounted for by the antihistaminic effect of dimethindene maleate.

Keywords dimethindene maleate antihistamine weal reactions

Introduction

Dimethindene maleate is available as a 0.1% gel for the treatment of pruritus due to urticaria, insect bites and other conditions. We have previously found the oral preparation of dimethindene maleate to have a dose-related H_1 -antihistaminic effect of moderate potency with dose-related sedative and anticholinergic effects (Humphreys & Shuster, in preparation). The present study was performed to assess the antihistaminic potency of the topical preparation and to determine if there was any differential reduction in weals induced by mast cell degranulation produced either chemically by compound 48/80 or by an antigen-antibody reaction than would be expected from H_1 -receptor antagonism alone.

Methods

Ten healthy volunteers and six patients took part in the experiment (9 male, 7 female, age range 23–72 years). Three of the patients had psoriasis, one had atopic eczema, one a leg ulcer and one was undergoing skin surgery. None of the volunteers or patients had any abnormality of the forearm skin. No subject had taken systemic antihistamines within the preceding 8 weeks nor the long-acting antihistamine astemizole within the preceding 6 months. Six of the volunteers

were known to have immediate weal reactions to house dust mite. One volunteer took part in both the histamine and the house dust mite experiments. A preliminary study in two subjects showed maximum reduction in histamine weal area after application of the dimethindene gel under occlusion for 1–3 h. Each subject, therefore, had 0.1% dimethindene gel applied to the flexor aspect of one forearm and identical inert gel-base applied to the other forearm for 3 h under occlusion. The gels were applied to a rectangular area of 30 cm^2 , the quantity of each gel used being approximately 0.4 g. The dressings were then removed, any remaining gel wiped from the arm and the intradermal test injections were made into the two treated areas. Ten minutes later the edge of each weal produced was marked with a fine ball point pen and the image transferred to paper using a transparent adhesive tape. Neither the subjects nor the experimenter knew which was the active and which the inert base. Five subjects received three intradermal injections of 0.5, 2 and $8\text{ }\mu\text{g}$ histamine acid phosphate in 0.1 ml 0.9% NaCl in each forearm; six subjects received a single injection of $100\text{ }\mu\text{g}$ compound 48/80 in 0.1 ml 0.9% NaCl in each forearm and six received 1 unit of house dust mite antigen (*Dermatophagoides pteromyssinus*, Pharmacia) in 0.1 ml albumin diluent in each forearm. The weal area was measured with

a computer linked digitising pad. Weal response was calculated after subtraction of values for weal area after an injection of 0.1 ml 0.9% saline. Flare was not measured but a direct visual comparison was made of size on both limbs.

Results

No subject developed any local or systemic adverse reaction following application of the gel.

Figure 1 shows the log dose-response curve to histamine with and without dimethindene. The reduction in mean weal area at the histamine doses of 8 and 2 μg were statistically significant (P values 0.02 and 0.03 respectively by the paired t -test) but the reduction in mean weal area with 0.5 μg histamine did not reach statistical significance. When change in weal area after treatment is expressed as a percentage of original weal size for each individual maximum mean reduction in weal area for any dose of histamine is $44\% \pm 13\%$ ($\pm$ s.e. mean) with 2 μg of histamine.

Figure 2 shows the effect of dimethindene on weals induced by 2 and 8 μg histamine, 100 μg 48/80 and 1 unit house dust mite. For 48/80 weals mean weal area was 0.93 ± 0.24 ($\pm$ 1 s.e. mean) on the active side compared with 1.58 ± 0.2 sq. cm on the placebo side, P value = 0.03. For the house dust mite weals mean weal area was 0.82 ± 0.14 compared with 1.25 ± 0.15 sq. cm for the active and placebo areas respectively. This inhibition just failed to reach statistical significance, $P = 0.057$. Mean percentage reduction in weal area was $43\% \pm 13\%$ ($\pm$ s.e. mean) with 100 μg 48/80 and $31 \pm 13\%$ ($\pm$ s.e. mean) with 1 unit house dust mite. There was no significant differ-

Figure 1 Dose-response curve to histamine with ($\square$) and without ($\bullet$) topical dimethindene maleate (mean $\pm$ s.e. mean).

Figure 2 Weal area with ($\blacksquare$) and without ($\hatched$) topical dimethindene for 2 and 8 μg histamine, 100 μg 48/80 and 1 unit house dust mite (mean $\pm$ s.e. mean).

ence in the degree of weal inhibition between the 2 or 8 μg histamine weals and the 48/80 and house dust mite induced weals (Figure 2).

Visual assessment showed a reduced area of flare on the dimethindene treated side in all five subjects with the 2 and 8 μg doses of histamine and four of the five subjects with the smaller dose of histamine, and in five of the six subjects in the 48/80 and house dust mite groups.

Discussion

The results indicate that topical dimethindene maleate inhibits weal and flare reactions from histamine, 48/80 and house dust mite antigen moderately and to a similar extent. Flare was only assessed by visual comparison and not by quantitative measurement but the inhibition of wealing was statistically significant despite the small number of subjects for the two larger doses of histamine and in the 48/80 group. The inhibitory effect on wealing produced by 2 μg of histamine was $44\% \pm 13\%$ which is not significantly different from the ($34\% \pm 10\%$) inhibition produced by a single 4 mg dose of dimethindene when taken orally (Humphreys & Shuster, in preparation) and is comparable with the systemic antihistamine effect of other conventional sedative H_1 -blockers (Reinberg *et al.*, 1978; Krause & Shuster, 1984a) and approximately half that achieved with the non-sedative H_1 -antihistamines astemizole (Krause & Shuster, 1984b) and terfenadine (Huther *et al.*, 1977; Shuster, 1986). The degree of inhibition of the 48/80 and house dust mite weals was not significantly different from that of the histamine weals and can

therefore be accounted for by the H₁-receptor antagonist effect of the dimethindene. Although topical dimethindene has a moderate H₁-antihistaminic effect unhampered by sedative and anticholinergic action we used the preparation under occlusion, and it is not known whether the magnitude of effect seen would also be found in clinical use. Furthermore therapeutic utility can-

not be defined from antihistamine potency alone, this would require therapeutic studies as well as studies of the capacity to induce contact sensitisation which is a well known problem associated with other topical antihistamines.

Our thanks to Zyma (UK) Limited.

References

- Huther, K. J., Renftle, G., Barraud, N., Burke, J. T. & Koch-Weser, J. (1977). Inhibitory activity of terfenadine on histamine-induced skin wheals in man. *Eur. J. clin. Pharmac.*, **12**, 195-199.
- Krause, L. B. & Shuster, S. (1984a). Evidence for a novel vasoactive mechanism in chronic idiopathic urticaria. *Br. J. Dermatol.*, **111**, 703.
- Krause, L. B. & Shuster, S. (1984b). H₁-receptor-active histamine not sole cause of chronic idiopathic urticaria (letter). *Lancet*, **ii**, 929-930.
- Reinberg, A., Levi, F., Guillet, P., Burke, J. T. & Nicolai, A. (1978). Chronopharmacological study of antihistamines in man with special references to terfenadine. *Eur. J. clin. Pharmac.*, **14**, 245-252.
- Shuster, S. (1986). Antihistamines in allergic skin conditions. In *Aspects of Allergy: A Symposium report*, pp. 32-35. Oxford Medical Education Services.

(Received 14 July 1986,
accepted 13 October 1986)