Br. J. clin. Pharmac. (1977), **4**, 367–369

VASCULAR REACTIONS TO HISTAMINE AND COMPOUND 48/80 IN HUMAN SKIN: SUPPRESSION BY A HISTAMINE H_2-RECEPTOR BLOCKING AGENT

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1 The ability of a specific competitive histamine H_2-receptor antagonist, cimetidine, to inhibit vascular responses to histamine in human skin provides new evidence that skin blood vessels possess histamine H_2 receptors.

2 Simultaneous systemic administration of cimetidine and chlorpheniramine (an H_1-receptor antagonist) was more effective than either drug alone in inhibition of the erythematous reaction both to exogenous histamine, and endogenous histamine secreted by skin mast cells in response to compound 48/80.

3 These results suggest that combined therapy of histamine-mediated skin diseases including urticaria and dermatitis using a combination of H_1- and H_2-histamine receptor antagonists may be more effective than either class of drug alone.

Introduction

The existence of two distinct classes of histamine receptors was first proposed by Ash & Schild (1966). Subsequently Black, Duncan, Durant, Ganellin & Parsons (1972) established the distribution of H_2-receptors in several different tissues and described the blockade of these receptors by a specific histamine H_2-receptor antagonist burimamide. The presence of H_2-receptors in human skin blood vessels is supported by our finding that 4-methyl histamine, a highly specific H_2-receptor agonist (0.1–10.0 μg), causes dose-related erythema and wealing (Marks & Greaves, unpublished data). The availability of a specific non-thiourea H_2-receptor antagonist, cimetidine (Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons, 1975) which has been shown to inhibit flushing caused by intravenous histamine infusion (Burland, Duncan, Hesselbo, Mills, Sharpe Haggie & Wyllie, 1975) enabled investigation of the possibility that cimetidine either alone or in combination with H_1-receptor antihistamines might be more effective than H_1-receptor antihistamines by themselves in supression of inflammation due to histamine in human skin.

Methods

Subjects

The study was made in four male and eight female healthy volunteer subjects aged 22–43 years, all of whom were fully aware of the nature and objectives of the study. Subjects with evidence of atopy were excluded. None of the subjects had taken any systemic drug within 24 h preceding the study. Each provided blood for red and white cell indices, biochemistry and liver function tests and urine for analysis before and after administration of cimetidine.

Materials

The following oral medications were studied: cimetidine (200 mg), green film coated tablets and inactive tablets of identical taste and appearance: chlorpheniramine (4 mg), yellow tablets and inactive tablets of identical taste and appearance. Study medications contained four tablets in each dose as follows: cimetidine (200 mg) × 2 and chlorpheniramine placebo tables × 2; cimetidine placebo tablets × 2 and chlorpheniramine (4 mg) × 2; cimetidine (200 mg) × 2 and chlorpheniramine (4 mg) × 2; cimetidine placebo tablets × 2 and chlorpheniramine placebo tablets × 2.

Each was given in a double-blind randomized crossover comparison of the effect of single doses on the dose response curve for intradermal histamine and compound 48/80. The order of medications was randomized using a Latin square design.

Histamine reactions

Reactions to intradermal injection of exogenous histamine and to endogenous histamine in response to intradermal injection of the chemical histamine liberator compound 48/80 (Burroughs Wellcome Ltd) were studied. All injections were given in the flexor surface of the forearms. Responses at each injection

site were measured 10 min after injection, in the same order as the injections were given, as follows:

1 Area of weal. A tracing was taken of the outline of the raised central area of the weal, disregarding pseudopod-like projections or satellite weals. The area of the weal was measured in mm^2 on the tracing by planimetry.
2 The area of the erythematous reaction was measured as for the weal.

Care was taken to avoid giving more than one injection at the same site.

Intradermal histamine and 48/80 dose response curves

The following doses of histamine and compound 48/80 were given in timed intradermal injections in 0.05 ml of 0.15 M saline diluent: 0.1, 1.0 and 10 μg of base. The histamine was given into the right arm and the compound 48/80 into the left arm.

There were five study days for each subject separated by not less than 48 hours. One the first day the dose response curves were produced with no pre-study medication. On the following four study days, the appropriate trial medication was given according to a coded prescribing list and the time recorded. After 90 min, intradermal injections were made. On these occasions a 10 ml venous blood sample was withdrawn for measurement of cimetidine blood concentration immediately after the 10 min reading of results. Cimetidine blood concentrations were determined by high pressure liquid chromatography.

Statistical analysis

The experimental design was a 2 x 2 x 2 factorial one, with two measurements (weal area, flare area) from each subject. The appropriate method of evaluation was, therefore, to conduct analysis of dispersion of the data, and to examine the significance of the factorial contrasts among treatment combinations by means of a Hotelling's T^2 test (Cherrington & Smart, 1972). This is the multi-variate equivalent of Student's *t*-test. The findings from this section of the analysis obviated the need to examine differences at individual doses, so that the results obtained are averaged out over the three concentrations of histamine or 48/80.

Results

Histamine

The results were summarized in Table 1 and Figure 1. The erythematous response to histamine was significantly reduced by cimetidine thus providing additional indirect evidence that human skin blood vessels possess H_2-receptors. Chlorpheniramine by itself also inhibited the erythematous reaction. Combined pre-treatment with cimetidine and the histamine H_1-receptor antagonist, chlorpheniramine, resulted in inhibition of histamine erythema which was significantly greater than erythema inhibition by either cimetidine or chlorpheniramine alone. Both cimetidine and chlorpheniramine given alone caused significant inhibition of the histamine weal. When cimetidine and

Table 1 Effect of cimetidine and chlorpheniramine both together and separately on weal and flare reactions due to histamine and 48/80

	Histamine		*48/80*	
Medication	*Weal*	*Erythema*	*Weal*	*Erythema*
Nil	130.8	1614.3	80.2	966.8
Cimetidine	106.1*	1264.8***	78.8	901.7
Chlorpheniramine	91.2**	1129.2†	63.8†††	721.3‡
Cimetidine + chlorpheniramine	84.2	973.0††	55.8	622.0‡‡
s.e. mean	5.8	56.4	5.8	56.4

Each value represents mean area (mm^2) averaged within each subject over the three doses and then averaged again over the twelve subjects.
* Nil v cimetidine : $t = 4.2$, $P < 0.001$.
** Chlorpheniramine v cimetidine: $t = 2.6$; $0.01 > P < 0.01$.
*** Nil v cimetidine: $t = 6.2$; $P < 0.001$.
† Chlorpheniramine v cimetidine: $t = 2.4$; $0.02 > P > 0.01$.
†† Cimetidine + chlorpheniramine v chlorpheniramine: $t = 2.8$; $0.01 > P > 0.001$.
††† Chlorpheniramine v cimetidine: $t = 2.6$; $0.02 > P > 0.01$.
‡ Chlorpheniramine v cimetidine: $t = 3.2$; $0.01 > P > 0.001$.
‡‡ Cimetidine + chlorpheniramine v chlorphenitramine: $t = 1.8$; $0.1 > P > 0.05$.

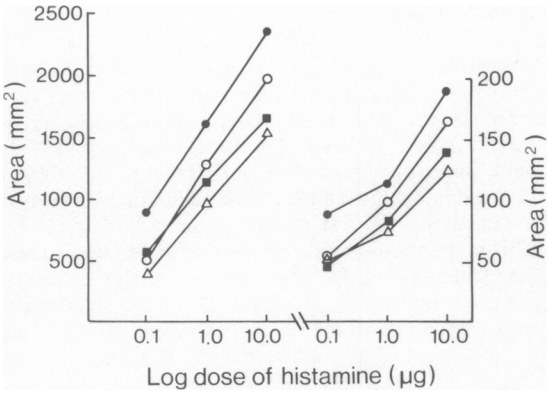

Figure 1 Effect of cimetidine (○) and chlorpheniramine (■) alone and given simultaneously (△) and placebo (●) on the weal and flare reactions to three doses of histamine in human skin. Each value represents mean area (mm²) in twelve subjects.

chlorpheniramine were given together, the mean weal size was smaller than when either drug was given alone, but this difference did not reach statistical significance.

Compound 48/80

The results are summarized in Table 1.

Cimetidine had no significant effect on the weal response to compound 48/80, and the combination of cimetidine and chlorpheniramine was not significantly more effective in weal suppression than chlorpheniramine alone. Although the inhibitory actions of cimetidine on the erythematous reaction to compound 48/80 did not achieve statistical significance, administration of cimetidine and chlorpheniramine together caused slightly greater inhibition of the erythema reaction than chlorpheniramine alone ($P < 0.1$).

Cimetidine plasma concentrations were measured in all subjects, 90 min after administration and in those who had taken cimetidine the values were 1.46–3.2 μg/ml (mean 2.08) (cimetidine and placebo) and 0.97–3.56 μg/ml (mean 1.97) (cimetidine and chlorpheniramine). No symptoms were noted by any subjects receiving cimetidine and all blood and urine laboratory examinations were normal or negative.

Discussion

A single dose of cimetidine caused a highly significant reduction of both the weal and the erythema response to intradermal histamine without significantly affecting the slope of the histamine dose response curve (Figure 1). Since cimetidine is devoid of significant H_1 antagonist activity (Brimblecombe *et al.*, 1975) these findings provide further strong indirect evidence for the presence of histamine H_2-receptors in human skin blood vessels.

Blockade of both classes of receptor together was more effective in suppressing vascular reactions to histamine than blockade of either receptor separately. as demonstrated by significantly greater inhibition of histamine erythema by a combination of cimetidine and chlorpheniramine (an H_1-receptor antagonist) than by either drug given alone. Cimetidine had little or no effect on wealing due to compound 48/80 but, as with histamine, combined treatment with chlorpheniramine and cimetidine caused a greater suppression of the erythema reaction to 48/80 than either alone although this did not reach statistical significance. The reason for the lower sensitivity of the 48/80 response is uncertain, but the effects of a wide range of doses of cimetidine on the reactions to 48/80 would clearly be of great interest.

Our results suggest that combined treatment with both H_1 and H_2 histamine receptor antagonists is more effective than either alone in the suppression of histamine reactions in skin and should prompt clinical evaluation of combined therapy in skin diseases, including the several clinical types of urticaria and dermatitis, which are known to be associated with histamine liberation in skin.

The work was supported by the Medical Research Council and the Wellcome Trust. We thank the Clinical Research Group, Research Institute, Smith, Kline and French Laboratories Ltd, Welwyn Garden City, Herts, and Allen and Hanbury Ltd, Ware, Herts, for letting us have cimetidine, chlorpheniramine and the placebo preparations.

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(Received September 6, 1976)