

EFFECTS OF HISTAMINE RECEPTOR ANTAGONISTS ON HISTAMINE-INDUCED RESPONSES IN HUMAN SKIN

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Abstract. The effects of intradermally administered histamine H₁- and H₂-receptor antagonists on the cutaneous responses—redness, weal, flare and itch—induced by intradermal injection of histamine were studied in man. Weal and redness were studied after blockade of the axon reflex by local infiltration with lidocaine. All responses were significantly inhibited by the H₁-receptor antagonist mepyramine. The H₂-antagonists cimetidine and metiamide reduced flare and itch significantly but not to the same extent as mepyramine and not in a clearly dose-related manner. The size of weal and redness was not significantly reduced by cimetidine. No further reduction of flare, itch or weal was obtained by adding metiamide or cimetidine to mepyramine. After blockade of the axon reflex with lidocaine the histamine-induced weals turned white at the centre. This blanching was more prominent when histamine was injected in combination with cimetidine. Substituting mepyramine for cimetidine resulted in small weals with an intense red colour. It is concluded that, apart from being engaged in the direct vasodilatory response to histamine, H₂-receptors do not seem to be involved in the other cutaneous responses to histamine studied.

Key words: Histamine H₁- and H₂-receptors; Cimetidine; Metiamide; Mepyramine; Triple response; Itching

Two classes of histamine receptors have been described and termed H₁- and H₂-receptors respectively (1, 2). Responses following stimulation of H₁-receptors can be inhibited by such classical antihistamines as mepyramine, while H₂-receptor-mediated effects, e.g. gastric secretion, are antagonized by H₂-receptor antagonists such as burimamide, metiamide and cimetidine (2, 3, 4, 5, 12).

In human skin, histamine elicits the familiar triple response characterized by vasodilatation (redness), increased permeability (weal) and an axon reflex mediated vasodilatation (flare). In addition itching is often experienced. A significant reduction by pretreatment with either oral chlorpheniramine (H₁-receptor antagonist) or oral cimetidine of the ery-

thematous response and the weal induced by intradermal (i.d.) injection of histamine has been reported (10). Administration of the two drugs together was found to be more effective than the use of either drug alone in suppressing the erythematous reaction.

The present investigation was undertaken in an attempt to further characterize the receptors involved in the human cutaneous responses to histamine. By using i.d. injections the quantitative effects of the H₁-(mepyramine) and H₂-(metiamide, cimetidine) receptor antagonists on the redness, weal, flare and itch elicited by histamine were studied.

MATERIALS AND METHODS

The study was conducted in 31 healthy volunteers aged 19-44 years. The histamine-induced itch and flare reactions were elicited and measured as described previously (8, 9). About 0.01 ml of histamine dihydrochloride, 10 µg/ml, i.e. 100 ng, was injected i.d. into the lateral aspect of the upper arm. The duration of the itch response was recorded. The antihistamines were given i.d. together with histamine or in 0.01 ml prior to histamine. The size of the flare was measured by planimetry 5 min after injection of histamine.

As an H₁-receptor antagonist, mepyramine (Pharma Rhodia A/S, Copenhagen, Denmark) was used and as H₂-receptor antagonists, metiamide and cimetidine (Smith, Kline & French Laboratories Ltd., Welwyn Garden City, England). Histamine and antihistamines were dissolved in physiological saline containing 10% (v/v) Sörensen phosphate buffer (Na₂HPO₄+KH₂PO₄, 67 mM), pH 7.4. The solutions were passed through a Millipore filter (Millex TM 0.22 µm) before use.

When studying the weal and redness, the axon-mediated flare reaction was eliminated by injecting about 0.7 ml of a local anaesthetic, lidocaine, 20 mg/ml (Xylokain, Astra, Södertälje, Sweden). The anaesthesia of the area was tested by gently striking the skin with a small tip of cotton-wool. As a rule, complete anaesthesia was produced in 15 to 20 min. An erythematous reaction induced by the local anaesthetic disappeared within 20 min and

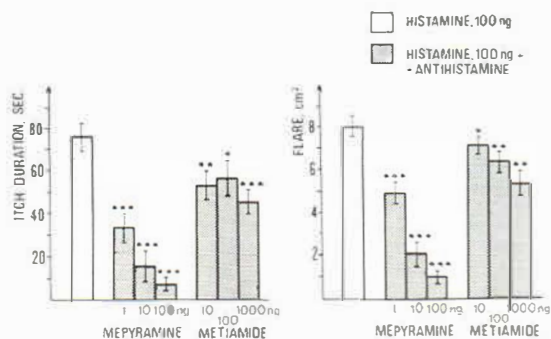


Fig. 1. Effect of mepyramine and metiamide on histamine-induced itch and flare responses (mean $\pm$ S.E.; $n=12$). *** $p<0.001$, ** $p<0.01$, * $p<0.05$, significant inhibition compared with histamine.

antihistamines and histamine could be injected. The erythematous reactions and weals induced by histamine under these conditions were much smaller (<100 mm²) than the flare reactions obtained without local anaesthesia. Planimetry was not found suitable for measuring these small responses. The injections and measurements were therefore done in a double-blind fashion and the diameter and colour of the responses were followed for a period of 1 hour. Maximal responses to histamine occurred 10 min after injection and the 10 min observation data are presented. The area of a response was calculated by using the mean of two perpendicular diameters (assuming the response to be circular).

Statistical analysis was performed using the Student's *t*-test for paired observations. As a non-parametric statistical method, the sign test was used (6).

RESULTS

Unanaesthetized skin

When added to the histamine solution, mepyramine caused a dose-dependent reduction of the histamine-induced flare and itch responses. Thus, 1 ng mepyramine caused a ca. 50% reduction and 100 ng almost abolished the effect of 100 ng histamine. Metiamide and cimetidine in a dose range from 10 ng to 1 μ g also significantly reduced the responses, though not to the same extent as mepyramine and not in a clearly dose-related manner (Figs. 1 and 2).

To study the possible synergistic effect of combining an H₁- and an H₂-receptor antagonist, 1 ng of mepyramine was given together with 10 or 100 ng of metiamide plus histamine, 100 ng. As shown in Fig. 3 the inhibition by mepyramine of the flare and itch was not augmented by metiamide. On the contrary the itching even seemed to be less inhibited than by mepyramine alone.

In the experiments described above, histamine and antihistamines were injected together. To study whether the introduction of a pretreatment period would further enhance the inhibitory effect of an antihistamine, mepyramine, 1 ng, and metiamide, 100 ng, were injected alone or as a mixture 2 or 5 min prior to histamine. However, in 8 subjects the inhibition produced by giving the inhibitors prior to histamine was of a similar order of magnitude to that obtained by giving them together with histamine.

Anaesthetized skin

The vasodilating effect of i.d. injected histamine leading to redness is difficult to observe, since it is obscured by the axon-mediated flare reaction. Therefore, the flare reactions were eliminated by infiltrating the injection site with the local anaesthetic lidocaine prior to injection of the histamine. When histamine, 100 ng, was injected i.d. in an anaesthetized site, there appeared a weal with an average diameter of 7 mm surrounded by a red zone, 1–3 mm wide. The effects of mepyramine and cimetidine on these responses were studied. To ensure maximum inhibition the antihistamines were given i.d. both 2 min prior to as well as together with 100 ng histamine, thus at each injection 100 ng mepyramine, 1 μ g cimetidine or a mixture of both with or without histamine was administered. The size of the reactions was measured 10 min after histamine injection. Both the total area involved

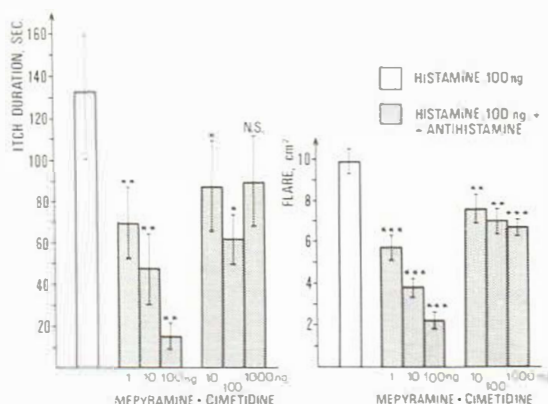


Fig. 2. Effect of mepyramine and cimetidine on histamine-induced itch and flare responses (mean $\pm$ S.E.; $n=8$). *** $p<0.001$, ** $p<0.01$, * $p<0.05$, significant inhibition compared with histamine. N.S.=not significantly inhibited.

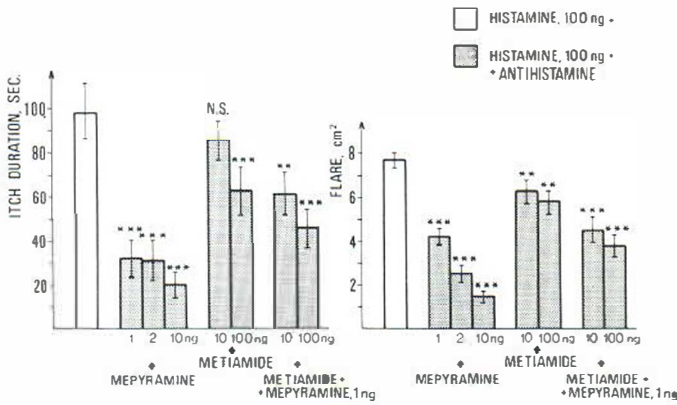


Fig. 3. Effect of mepyramine and metiamide alone and in combination, on histamine-induced itch and flare responses (mean $\pm$ S.E.; $n=12$). *** $p<0.001$, ** $p<0.01$, significant inhibition compared with histamine. NS=not significantly inhibited.

(weal plus redness) and the weal alone were measured. The reactions were markedly inhibited by mepyramine ($p<0.001$) while the slight reduction obtained with cimetidine was not statistically significant (Fig. 4). Combining mepyramine with cimetidine did not yield further inhibition of the reactions.

In anaesthetized areas the histamine-induced weals turned white at the centre a few minutes after injection. This white appearance was more prominent when histamine was injected in combination with cimetidine. Substituting mepyramine for cimetidine resulted in small weals of an intense red colour. When mepyramine was given in combination with cimetidine this red colour did not appear. The colour differences appeared in all 10 subjects ($p<0.01$, sign test). Thus, the antihistamines and the mixture of them each influenced the histamine response in a characteristic manner. Administration of mepyramine resulted in small, red-coloured weals, cimetidine in well delineated, white weals and the combination in a reduction of the size but in virtually no colour change.

DISCUSSION

In our study the histamine-induced cutaneous responses—redness, weal, flare and itching—were markedly inhibited by the H_1 -receptor antagonist mepyramine in a dose-dependent manner. In contrast to Marks & Greaves (10) who found that simultaneous oral administration of H_1 - and H_2 -antagonists caused a greater suppression of histamine "erythema" than either drug alone, we obtained no further effect by adding an H_2 -receptor antagonist to the H_1 -antagonist. At present the dis-

crepancy may be ascribed to the differences in administration routes of the antihistamines, i.e. local vs. systemic administration.

In a study on histamine analogues with H_1 and H_2 activities respectively Robertson & Greaves (11) found pain and itch to be elicited by both types of compounds. In the present investigation the H_1 antagonist mepyramine markedly reduced the itching whereas the H_2 antagonists metiamide and cimetidine caused weak but significant inhibition of the itching as well as of the flare reaction. Since the inhibiting effects of the H_2 antagonists were not dose related, the possibility of a non-specific action remains. Accordingly it seems doubtful whether these effects are mediated via H_2 -receptors.

The redness and the weal, i.e. the direct vascular effects of histamine, were studied after blocking the axon-mediated flare reaction by local anaesthesia.

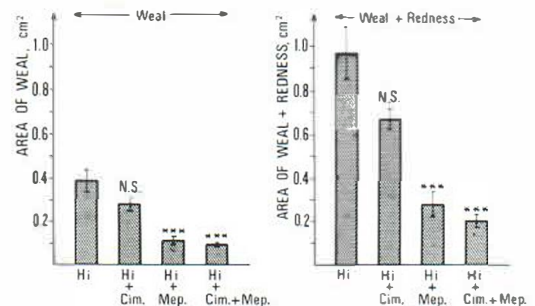


Fig. 4. Effect of mepyramine and cimetidine on histamine-induced weal and redness in anaesthetized skin (mean $\pm$ S.E.; $n=10$). *** $p<0.001$, significant inhibition compared with histamine. NS=not significantly inhibited. Hi=histamine, 100 ng. Cim=cimetidine, 1 μ g. Mep=mepyramine, 100 ng.

Under these conditions mepyramine was found to significantly reduce the responses, whereas no significant inhibition of the area of weal and redness was produced by cimetidine. However, cimetidine did inhibit the red colour of the weal. Simultaneous injection of H_1 - and H_2 -antagonists did not cause any additional suppression of the weal. Provided that mepyramine is a selective H_1 -antagonist, our results imply that weal, flare and itch are mediated by H_1 -receptors, whereas the redness to some extent seems to be due to a stimulation of H_2 -receptors.

It has been discussed (7) whether treatment of urticaria would be more effective by combining H_1 - and H_2 -antagonists. In the present experiments weal, flare and itch reactions were effectively inhibited by an H_1 -antagonist without additional effects of any of the H_2 -antagonists studied. Therefore, it seems doubtful that any further effects of therapeutic significance could be obtained in urticaria by adding H_2 -antagonists to the usual treatment with the classical H_1 -inhibitors.

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ADDENDUM

After this paper had been submitted for publication Commens and Greaves reported that in a double-blind study of cimetidine in chronic urticaria they failed to reveal any significant advantage in administration of cimetidine together with the H_1 -receptor antagonist chlorpheniramine (Br J Dermatol 99: 675, 1978). Thus, the clinical findings are consistent with our experimental data.

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