Enhanced weal and flare response to histamine in chronic idiopathic urticaria

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Weal and flare histamine dose-responses were measured in 30 normal subjects and 15 patients with chronic idiopathic urticaria. The log dose-response curves were shifted to the left corresponding to an increase in histamine potency of 2.5 for weal and 3.1 for flare. An enhanced response to histamine may be important in chronic idiopathic urticaria and comparison of potency of antihistamines in different subjects may be unreliable where initial weal response is abnormal.

Keywords histamine urticaria dose-response

Introduction

We have recently carried out several unrelated studies comparing the effect of two new non-sedating histamine H₁-receptor antagonists with some previously available agents (chlorpheniramine, azatadine and trimeprazine) both in normal subjects and patients with chronic idiopathic urticaria (Krause & Shuster, in preparation). When the data from these studies were analysed a difference became apparent in the weal and flare response to intradermal histamine. This paper presents a quantitative analysis of the findings since they are relevant to future studies of histamine receptor antagonists as well as to the mechanisms of urticaria disease.

Methods

All the subjects were part of separate studies into the response of chronic idiopathic urticaria and histamine weal and flare to different H₁-receptor antagonists. All of the studies in chronic idiopathic urticaria had used a double-blind format but some of the studies in normal subjects were open. There were 30 normal male and female subjects aged 19 to 23 years (mean 21 years) and 15 patients with chronic idiopathic urticaria aged 21 to 68 years (mean 41.3 years). All had had the disease for longer than 3 months and the interval between attacks was no longer than 1 day. None had previously taken the long-

acting H₁-receptor antagonist astemizole and none had taken other H₁-receptor antagonists or aspirin-like drugs for at least 3 days before the study. The intradermal response to histamine was carried out on the clinically normal skin of the flexor aspect of the forearm as previously described (Cook & Shuster, 1980; Krause & Shuster, 1984) using 0.5 – 32 µg histamine in 0.1 ml 0.9% NaCl and measuring weal area by planimetry of a cellophane tape tracing taken 10 min after the injection (Huther *et al.*, 1977) and axon reflex flare as a mean diameter measured at 5 min. Three doses of histamine had been used in the studies in normal subjects and five doses in chronic idiopathic urticaria. The measurements were treated statistically by analysis of variance and potency calculated from the shift in computed dose-response curves which were also compared for parallelism (Bliss, 1952).

Results

The histamine weal and flare area dose-responses were log-linear (Figure 1) and were greater in the patients with chronic idiopathic urticaria than in the normal subjects. The slopes of the computed curves for weal and flare did not differ significantly ($P > 0.05$) despite the steeper appearance of the curve for flare in patients with urticaria and the difference between chronic

Figure 1 Weal and flare histamine dose-response curves in 15 patients with chronic idiopathic urticaria (●) and 30 normal subjects (○).

idiopathic urticaria and normal subjects was highly significant both for weal and flare ($P < 0.001$). Taking the potency of histamine in normal subjects as unity the relative potency for histamine in chronic idiopathic urticaria was increased to 2.5 for wealing and 3.1 for flare.

Discussion

The findings are that in chronic idiopathic urticaria the weal and flare response to intra-dermal histamine is displaced from the normal in parallel and to the left. This observation did not arise from a planned study looking for differences, but became apparent from unrelated investigations of H_1 -receptor antagonists. Since, therefore, there was no bias from observer expectation and the studies were mostly double-blind and carried out by the same observer using the same experimental procedure, the comparisons are likely to be valid. From our previous studies of histamine wealing (e.g. Cook & Shuster, 1980) the age difference between the groups is unlikely to be important. There have been surprisingly few studies of the response to histamine in the urticarias and those which have been done have either failed to define the clinical disorder or to use adequate measurement of weal and flare with a range of histamine doses. Thus Juhlin & Michaelson (1969) found no difference in weal response to a single dose of histamine at 20 min in what appears to have been a variety of urticarial disorders. In contrast Prasad

et al. (1967) found an increased response to histamine in chronic idiopathic urticaria using iontophoresis and a subjective scoring (+, ++, +++) of response as did Bateman *et al.* (1983) in six patients with unspecified urticarial disorders. In their review of the urticarias Warin & Champion (1974) conclude that the response to histamine and 48/80 is normal and recent reviews (e.g. Monroe & Jones, 1977) do not discuss the problem. Our own findings are both unequivocal and quantitative, showing an increased response of 2.5–3-fold for histamine weal and flare in chronic idiopathic urticaria.

The mechanism of the increased responsiveness to histamine is uncertain. Previous administration of H_1 -receptor antagonists in the patients with chronic idiopathic urticaria (but not the normal subjects) appears not to be the explanation since we have found no evidence of altered response to histamine after previous administration of H_1 -receptor antihistamines (Krause & Shuster, preliminary observations). Although the wealing response to injected histamine shows tachyphylaxis (Greaves & Shuster, 1967) this does not exclude the possibility that an enhanced response to histamine is provoked by continuous release of small amounts of agonist. In this respect it would be important to know whether histamine release in urticarias other than chronic idiopathic urticaria might similarly enhance the response to histamine. Likewise measurement of weal and flare response to histamine in other dermatoses in which histamine is not involved would indicate whether the phenomenon is disease and mediator specific. Histamine itself induces release of secondary vasoactive agents (Cook & Shuster, 1980) and it is possible that the magnitude of this secondary release may be greater in chronic idiopathic urticaria. Since, however, the shift in histamine weal and flare dose-response curves is parallel it can be concluded that the primary mechanism is likely to involve an enhanced response to histamine acting on the H_1 -receptor. It follows that the incremental increase in response to histamine at the H_1 -receptor should be precisely matched by the inhibitory effect of a competitive antagonist. Thus it is unlikely that the increased weal response to histamine in chronic idiopathic urticaria will diminish the response of the disease to H_1 -receptor antagonists and we have preliminary evidence to support this view using terfenadine, astemizole and chlorpheniramine (Krause & Shuster, in preparation). It follows, furthermore, that the potency of H_1 -receptor antagonists as measured by shift in histamine weal and flare dose-response curves will appear greater in patients with chronic idiopathic

urticaria than in normal subjects. Comparison of the therapeutic and H₁-receptor antagonistic potency of different H₁-receptor antihistamines may therefore be invalid when the initial weal response is different. In conclusion, there is a

two to three fold increase of weal and flare potency of histamine in chronic idiopathic urticaria which may be relevant to the assay of the effect of treatment as well as to the disease mechanism,

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