The Sensitivity of Uremic and Normal Human Skin to Histamine

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Cutaneous reactions induced by intradermal histamine injection were studied in uremic patients with and without pruritus who were undergoing maintenance hemodialysis and also in healthy subjects. Flare reactions were significantly smaller in both groups of patients than in controls. However, the itch responses following histamine injection were greater in patients with pruritus than in non-pruritic patients and healthy subjects, indicating an augmented sensitivity to pruritogens in these patients. The development of histamine tachyphylaxis was demonstrated in healthy human skin. After repeated histamine injections at intervals of 90 min, both itch and flare responses decreased rapidly. A similar decline in histamine reactivity occurred when the interval between injections was extended to 24 h. The phenomenon of histamine tolerance was confirmed in 2 uremic patients. *Key word: Pruritus.* (Received December 2, 1987.)

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Pruritus is one distressing symptom of chronic renal failure, affecting 60–80% of patients undergoing maintenance hemodialysis (1, 2). The pathogenesis of uremic pruritus remains to be clarified, although various possible explanations such as xerosis of the skin, derangement of sweating, secondary hyperparathyroidism and cutaneous mast-cell proliferation have been suggested (3–6).

Histamine injected into the skin evokes a pruritic sensation and is generally regarded as a mediator in urticaria, where antihistamine drugs usually have an antipruritic effect provided they are given in sufficient dosage. However, the role of histamine in pruritic conditions other than urticaria has not been established and the use of antihistamines in these disorders—although almost routinely prescribed—is questionable.

We considered it of interest to study the sensitivity to histamine in uremic patients with pruritus. If histamine is involved as a pruritogen in uremic skin the sensitivity to exogenous histamine might be decreased due to tolerance phenomena. Increased sensitivity on the other hand, could indicate a generally itchy skin with decreased itch threshold in uremic pruritus. The cutaneous reactions to intradermally injected histamine were therefore examined in uremic patients with and without pruritus and in a control group of healthy subjects. Further, the development of histamine tolerance was studied in healthy subjects and in uremic patients.

SUBJECTS, MATERIALS AND METHODS

I. *Uremic patients vs. controls—recordings of itch and flare*

The study material comprised 29 patients undergoing maintenance hemodialysis at the Division of Nephrology, Department of Medicine, Karolinska Hospital, and 11 healthy volunteers. Three patients (one with and 2 without pruritus) and one healthy volunteer did not respond to histamine and were excluded from the study. The age range of the remaining 26 patients, 13 men and 13 women, was 27–76 (mean 57.9) years, and of the volunteers, 3 men and 7 women, 37–78 (mean 57.1) years. At the time of the investigation, 18 patients (69%) complained of pruritus, while 8 patients (31%) were free from itch.

Patients with pruritus had significantly higher serum concentrations of parathyroid hormone than patients without pruritus. In other respects, e.g. duration of dialysis, renal function expressed as predialytic creatinine level, and medication (no one was taking antihistamines), there was no difference between the two groups of patients (2). The volunteers were free of drugs and had no history of skin disease.

Solutions of histamine (1.0, 3.3, and 10 μg/ml) in a volume of 0.01 ml were injected intradermally on the lateral aspect of the upper arms. Each subject received three injections. The intensity of the histamine-induced itch was recorded continuously for a maximum of 5 min by the subjects, who were asked to move an indicator sliding along a 20 cm scale on a metal ruler (i.e. a visual analogue scale). One end of the scale represented 'no itch', the other 'maximal itch'. The indicator was attached to a potentiometer connected to an ink-writer out of sight of the subjects. By determining the area under the curve (AUC) we obtained a measure of the itch as a resultant of both duration and intensity. The flare reaction was outlined 5 min after injection with a marking pen on the skin, traced onto a plastic film and then measured with a planimeter as described earlier (7). In the present study some subjects still perceived itching at 5 min, which in our experience is rare at the histamine doses given. However, the itch recording was terminated at 5 min, since the pressure of the pen delineating the flare reaction was liable to interfere with the itch sensation.

II. *Uremic patients vs. controls—registration of itch only*

This study comprised 28 patients undergoing chronic hemodialysis at the same Department (see I) and 9 healthy volunteers. Five patients were excluded, of whom three were taking antihistamine drugs and two (both without pruritus) did not respond to histamine. The age range of the remaining 23 patients, 14 men and 9 women, was 33–73 (mean 59) years and of the volunteers, 4 men and 5 women, 35–75 (mean 57) years. At the time of the investigation 13 patients (57%) suffered from pruritus, while 10 patients (23%) were free from itch. There was no difference between the two grups of patients regarding serum levels of parathyroid hormone, duration of dialysis, renal function expressed as predialytic creatinine concentration and medication (no one was taking antihistamines). The volunteers were free of drugs and had no history of skin disease.

The investigation was thus performed in two separate sessions, I and II. The experimental procedure was identical except that in II we did not study the flare, only the itch response induced by histamine. In Study II, recordings were not terminated at 5 min, as in study I, but continued until the itch spontaneously disappeared.

Tachyphylaxis to histamine in healthy subjects

In a parallel investigation we studied the effects of repeated intradermal injections of histamine in 16 healthy volunteers (age 21–57, mean 37.3 years). In 8 subjects, 0.01 ml of a histamine solution (10 μg/ml) and 0.01 ml of saline were injected intradermally on the lateral aspect of each upper arm, i.e. the injections were given in duplicate. At exactly the same sites the injections were repeated four times at intervals of 90 min. The fifth time, another 90 min later, histamine was injected at all four injection sites. The itch and the flare responses were recorded after each injection . The mean value of the duplicate determinations is presented.

In another 8 subjects the procedure was repeated identically, but the interval between injections was extended to 24 h.

Tachyphylaxis to histamine in uremic patients

The development of histamine tolerance over one day was studied in 2 uremic patients as described above. The interval between injections was 90 min.

Statistical methods

The Kruskal-Wallis test and the Mann-Whitney U-test were used for statistical evaluation of data in the study of uremic patients vs. controls. Wilcoxon's rank-sum test was performed for data analysis in the investigation of tachyphylaxis in healthy controls.

RESULTS

Uremic patients vs. controls

I. Flare reactions induced by all concentrations of histamine were significantly smaller in uremic patients than in controls, as shown in Fig. 1. There was no difference between uremic patients with vis-à-vis without pruritus. There was a tendency towards higher itch scoring in

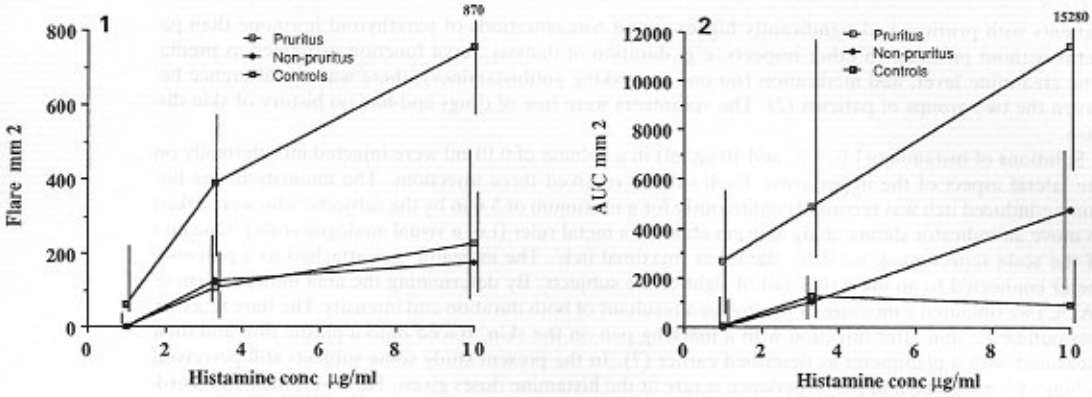

Fig. 1. Histamine-induced flare reactions in uremic patients with pruritus (n=18), without pruritus (n=13) and controls (n=9). Median values with indication of the 75th and 25th percentile are presented. Flare reactions were significantly smaller in uremic patients than in controls at each histamine concentration ($p<0.01$, $p<0.02$ and $p<0.01$ respectively).

Fig. 2. Histamine-induced itch responses (AUC) in uremic patients with pruritus (n=13), without pruritus (n=10) and controls (n=9). Median values with indication of the 75th and 25th percentile are presented. Itch responses in patients with pruritus were significantly greater than in non-pruritic patients and controls at each histamine concentration ($p<0.02$, $p<0.01$ and $p<0.05$ respectively).

uremic patients with pruritus than in patients without pruritus and in controls, but the difference was not statistically significant.

II. Patients with pruritus had significantly stronger itch responses for all histamine concentrations than did patients without pruritus or healthy controls as shown in Fig. 2. There was no difference between non-pruritic patients and controls, except at the strongest histamine concentration ($p<0.05$).

Tachyphylaxis to histamine in healthy subjects and in uremic patients

Figs. 3, 4 and 5 show the results after repeated injections of histamine and saline at intervals of 90 min. In healthy subjects, flare (Fig. 3) and itch (Fig. 4) induced by the fifth histamine

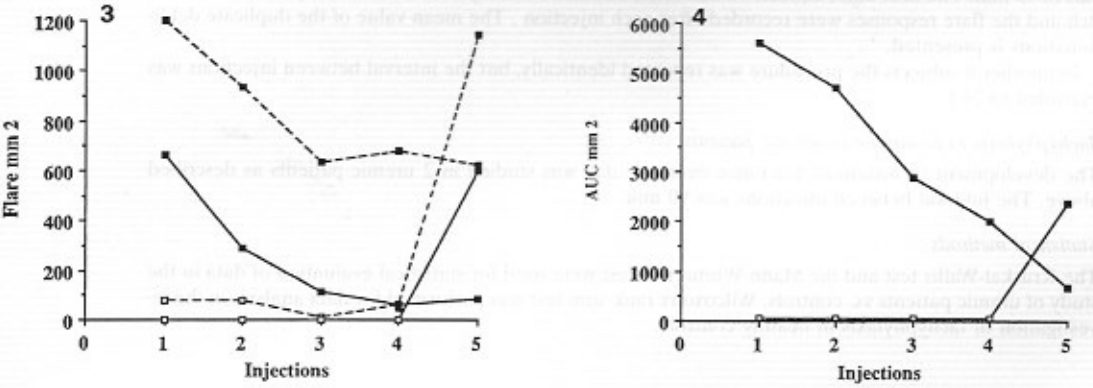

Fig. 3. Flare reactions induced by histamine, 10 µg/ml, (■) and saline (□) in uremic patients (——, n=2) and healthy subjects (----, n=8). Median values are presented. Flare reactions induced by the fifth histamine injection were significantly smaller in the site pretreated with histamine than in that pretreated with saline ($p<0.01$) in both groups.

Fig. 4. Itch responses induced by histamine, 10 µg/ml, (■) and saline (□) in 8 healthy subjects. Median values are presented. Itch responses induced by the fifth histamine injection were significantly smaller in the site pretreated with histamine than in that pretreated with saline ($p<0.01$).

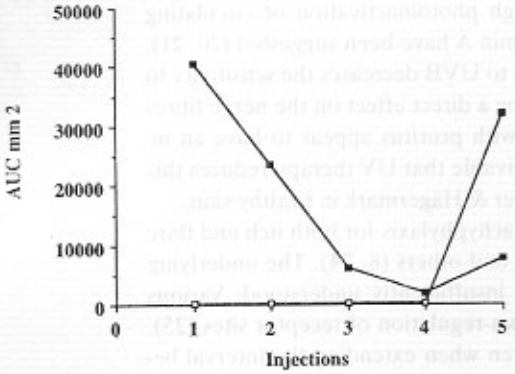

Fig. 5. Mean itch responses induced by histamine in 2 uremic patients. Symbols and differences as in Fig. 4.

injection were significantly smaller at the site pretreated with histamine than at that pretreated with saline ($p<0.01$). The same pattern was seen in the 2 uremic patients (Figs. 3 and 5). A similar decrease in histamine reactivity occurred when the interval between injections was extended to 24 h. The difference calculated as above was statistically significant ($p<0.01$).

DISCUSSION

Intradermal injection of histamine evokes cutaneous reactions: an erythema at the injection site, a wheal, a spreading flare and an itching sensation (8). The flare and the itch responses are usually closely correlated and both are dose-dependent, i.e. they increase with increasing doses of histamine.

In this study the uremic patients and the healthy volunteers responded in different ways to intradermal injections of histamine. Despite significantly smaller flare reactions in uremic patients, the experience of itching persisted—and in patients with pruritus even augmented—indicating an increased sensitivity to pruritogenic stimuli in these patients.

The flare reaction is due to cutaneous vasodilatation mediated by antidromic transmission in sensory nerves and hence dependent on both innervation and on microcirculation (9, 10). It is well known that chronic renal failure is associated with peripheral neuropathy and with microangiopathy affecting cutaneous vessels (11–15). Thus, the decreased flare reactions found in uremic patients might result from either neuropathy in small sensory neurons, or disturbed microcirculation—or a combination of the two.

It might be argued that if the pruritic mediator of uremia were histamine, it would by acting on the nerve endings, induce a state of tolerance and consequently a decreased itch response to the injected histamine. However, the uremic patients with pruritus perceived more intense itching after histamine injection than those without pruritus, or the healthy subjects. This could indicate that mediators other than histamine were enhancing the histamine response in the same way as has been shown for prostaglandins and opioids (16, 17). Another explanation could be increased sensitivity of the itch receptors. Polyneuropathy in patients with diabetes mellitus is known to evoke hyperpathic sensations such as hyperalgesia transmitted by small non-myelinated nerve fibres (18). One could therefore speculate that neuropathy affecting sensory neurons in chronic renal failure might induce hypersensitivity augmenting the reactivity to pruritogenic stimuli in these patients. Still, any explanation can only be hypothetical and the pathophysiological basis for our observations remains to be established.

In recent years several reports have appeared on the beneficial effect of ultraviolet phototherapy, especially UVB, on pruritus in chronic renal failure (19, 20). The mechanism by

which this is achieved remains to be clarified, although photoinactivation of circulating pruritogenic substances and reduction of epidermal vitamin A have been suggested (20, 21). Fjellner & Hägermark have demonstrated that exposure to UVB decreases the sensitivity to histamine-induced itch in healthy human skin, possibly by a direct effect on the nerve fibres (22, 23). In the present investigation, uremic patients with pruritus appear to have an increased reactivity to pruritogenic stimuli, and it is conceivable that UV therapy reduces this hypersensitivity in a mode similar to that shown by Fjellner & Hägermark in healthy skin.

In this study we have confirmed the phenomenon of tachyphylaxis for both itch and flare after repeated histamine injections, as studied by Lewis and others (8, 24). The underlying mechanisms for the development of tachyphylaxis are insufficiently understood. Various theories are discussed, mainly interference with and down-regulation of receptor sites (25). The fact that we were able to provoke tachyphylaxis even when extending the interval between injections to 24 h is theoretically interesting. Histamine has been suggested as a mediator in most itching disorders, including uremic pruritus (26). Our findings of increased reactivity to histamine, in combination with rapidly developing tachyphylaxis, seem to discredit endogenous histamine as the cause of pruritus in uremic patients.

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