Clinical Report and Investigation of a Patient with Localized Heat Urticaria

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Localized heat urticaria is a rare disorder, in which the nature of the mediator is not fully established. We report the case of a 41-year-old woman with the condition, dependent upon mast cell integrity, in which histamine was demonstrated as the dominant, if not sole mediator. Non-sedative antihistamines conferred some therapeutic benefit, but subsequent sequential desensitization has enabled her to lead a full and active life again.

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Localized heat urticaria is a rare condition distinct from the other types of physical urticaria. There are relatively few documented cases in the world literature and the pathogenesis of the condition remains obscure. The following case is only the fifth to be reported from the UK (1–4) and the detailed investigation aims to shed light on the nature of the mediator involved.

CASE REPORT

A 41-year-old woman presented with a history that for 12 months she had developed urticarial weals in areas of skin exposed to heat. The condition had developed quite suddenly following a hot bath and subsequently lesions developed whenever she was exposed to heat. The onset of lesions was heralded by pruritus within seconds of contact with heat, the subsequent weal and flare response was confined to the site of heat exposure. The duration of lesions was related to the intensity of heat, but generally lasted 2–3 h. On 2 occasions following immersion in a hotbath, she experienced flush, dizziness and syncope. Ingestion of hot food and drinks produced intraoral itching, numbness and swelling.

The severity of symptoms necessitated major alterations in the patient's lifestyle, causing her to give up work, and even to contemplate suicide. Her past medical history was unremarkable and there was no personal or family history of atopy. Physical examination was normal and there was no dermographism.

Contact with a glass beaker containing water at *45°C* for 30 sec produced localized urticaria 5 min after the beaker was removed.

Investigations

General. The following investigations were within normal limits or negative: – haematological indices and biochemical profiles, IgM, IgG, IgA and IgE, complement levels, Treponema Pallidum haemagglutination assay, HBs Ag, viral titres, autoantibodies, serum electrophoresis, standard prick tests.

Specific clinical investigations

The urticaria could not be provoked by a 1°C rise in systemic temperature (15 min vigorous exercise on an exercise bicycle). Cold challenge with an ice cube for 5 min produced no reaction.

1. Characteristic of the urticaria

a) *Threshold.* Using a 2.5 cm diameter glass probe, through which water at a constant temperature was circulated, the threshold temperature for elicitation of weals was established at 42°C. There was a dose-response relationship in that exposures for longer periods of time were accompanied by more severe reactions, but prolonged exposure to sub-threshold temperatures were without effect. For all subsequent investigations the heat stimulus of 45°C for 1 min was used.

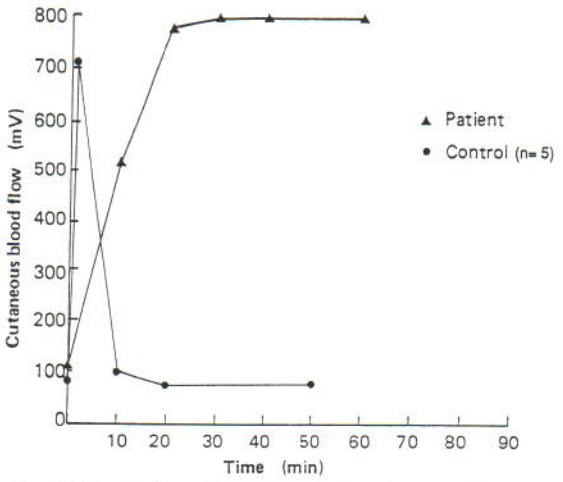

Fig. 1. Comparison of cutaneous blood flow through heat exposed skin in patient and control female subjects.

b) Time course of lesion

After removal of the heat source there was immediate erythema confined to the area of application of heat, followed by blanching. Erythema returned over 2 min with subsequent development of a flare, extending beyond the area of heat application. Weal formation was delayed until 5 min after removal of the heat source, and was confined to the area of heat application. Using the standard stimulus of 45°C for 1 min the lesion lasted 1½ hours.

The change in cutaneous blood flow through heat-exposed skin was measured with a Laser Doppler Flowmeter (pf 2 Perimed; Sweden) and compared to a similarly exposed site in five control female subjects (Fig. 1). Cutaneous blood flow was increased in response to heat exposure, but the response was considerably prolonged in the patient compared to controls.

c) Refractory period

Re-exposure of a site, up to 2 h after initial application of heat produced no reaction, but at 3 h the full sequence of reaction was observed. Exposure to sub-threshold temperatures was not associated with development of tolerance.

2. Pharmacological investigations

a) *Local inhibitors.* Subcutaneous injection of *2% lignocaine* or 0.6 mg *atropine* intradermally failed to inhibit the heat-induced urticaria, excluding neurological and cholinergic mechanisms, respectively. Heparin is known to inhibit several inflammatory mediators (5), but intradermal injection of 100 μ *heparin* had no effect on the weal and flare response to heat. Topical application of *2% indomethacin* in gel base under occlusion for 2 h prior to heat exposure had no effect on the cutaneous response.

b) Dependence on intact mast cells

An area of forearm skin was subjected to repeated intradermal injection of the mast-cell degranulating agent compound 48/80 (10 μg in 0.1 ml normal saline 2 hourly), until no further reaction occurred. Exposure of this area of skin to heat then produced no reaction. However, the response to intradermal histamine was unchanged.

c) Measurement of histamine C_3 and C_4 and IgE levels

The right hand was immersed in water at 45°C for one min and serial blood samples withdrawn sequentially via a venous canula sited in the right forearm for estimation of histamine, complement and IgE. Plasma histamine was analysed by radio-immunoassay (3). There was a rise in plasma histamine maximal at 5 min (12.3 ng/ml; N = 0.2 – 0.3 ng/ml) but no significant changes in C_3, C_4 or IgE levels.

d) Antihistamines

i) *Local*

Tropical application of 2% mepyramine maleate cream (Antihistan®) (an H1 antihistamine cream) inhibited the development of weal and flare, but not erythema at the site of heating.

ii) Systemic

Terfenadine. Although oral Terfenadine 60 mg b.d. for one week was without effect, 120 mg b.d. (sufficient to abolish the weal and flare response following injection of 8 μg histamine intradermally), absolished pruritus, and the development of weal and flare reaction up to temperatures of 50°C. However, persistent erythema was noted confined to the site of local application. Exposure to 45°C for longer intervals (up to 5 min) produced no weal or flare. Although terfenadine prevented the development of heat urticaria under these experimental conditions, temperatures above 50°C (e.g. a hot bath) still provoked weal and flare, and were a considerable inconvenience in patient's daily living.

H_1 and H_2 Block. The addition of the H_2-blocker Cimetidine (400 mg b.d.) had no effect.

e) Heat desensitisation

As the patients daily life was still considerably disrupted by heat urticaria despite systemic antihistamines alone, she underwent controlled temperature desensitization. Desensitization was closely supervised and performed under oral antihistamine cover (Terfenadine 120 mg b.d.). The right leg was exposed to water at 45°C for 1 min at hourly intervals, until no further reaction occurred. The area exposed and duration of exposure were gradually increased, until the whole limb could be immersed for 5 min without reaction. The interval between exposures was then increased until twice daily exposure to 45°C for 5 min elicited no reaction. Desensitization was then repeated to all limbs individually and then the trunk, until immersion of the whole body for 5 min twice daily, and then once daily elicited no symptoms. After induction of tolerance heat challenge was not associated with persistent erythema noted with antihistamines alone.

Course and progress

Abolition of symptoms could not be maintained by desensitization alone and the patient continues to take Terfenadine 120 mg b.d. Omission of either daily immersion or systemic antihistamines results in recurrence of urticaria. On the combined regimen of oral Terfenadine and daily immersion in water at 45°C the patient remains well 12 months follow-

ing discharge from hospital. She has been able to return to work and lead a full life again.

DISCUSSION

Localized heat urticaria is a rare condition, there being only 40 reported cases in the world literature. An increased incidence of atopy (3) (70%) and other physical urticarias (40%) (4) have been reported in patients with localized heat urticaria, but were not demonstrable in our patient.

Although clinical experience is limited, the response of localized heat urticaria to treatment is variable and avoidance of the trigger impractical. Supervised desensitization (2, 3) has been demonstrated to be beneficial, probably by maintaining a state of mediator depletion, but alone was inadequate to achieve complete abolition of symptoms in our patient.

The nature of the mediator in localized heat urticaria has been the source of controversy. Various mechanisms have been implicated including complement activation by the alternative pathway (6–8), histamine (1, 4, 9) and prostoglandin D_2 release (4).

We have shown that the development of lesions is dependent on intact mast cells. Our observation that the time course for the formation and resolution of the weal produced by heat closely parallels that induced by intradermal injection of histamine provides compelling evidence that histamine is the sole mediator of the process. In support of this is the fact that the weal and flare is abolished by potent H1 antihistamines. It could be argued that following antihistamine blockade of the weal and flare, the persistent erythema seen confined to the site of heat application reflects the effect of other mediators such as PGD_2. However, prostaglandins would be expected to induce changes with a very different time course (5). It seems more likely that since maximal H1 blockade can only inhibit the response to histamine by up to 90% (10), this erythema is an effect of very high dose histamine. This would also explain why the combination of desensitization and H1 blockade are necessary for complete systemic relief – the densensitisation once every 24 h keeps mast cell histamine stores depleted to a level that caused no detectable effect in the presence of 90% inhibition by antihistamines. The ultimate question remains of what is the fundamental alteration that causes a susceptible population of mast cells to release histamine upon heat stimulation.

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