

Prostaglandins in Contact Urticaria Induced by Benzoic Acid

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TO STUDY the role played by prostaglandins (PGs) in contact urticaria, concentrations of 13,14-dihydro-15-keto-PGF_{2α}, 6-keto-PGF_{1α}, and thromboxane B₂, the stable metabolites of PGF_{2α}, prostacycline and thromboxane A₂ were measured by radio-immunoassay of the fluid taken from suction blisters in 11 patients. The blisters were raised on contact urticarial reactions induced by benzoic acid. The effect of peroral indomethacin on contact urticaria from benzoic acid was studied in a further 14 dermatological patients.

The levels of these prostanoids in the blister fluid of urticarial skin did not differ from those derived from control blisters raised on apparently normal skin.

Premedication with indomethacin, 50 mg t.i.d., completely prevented contact urticarial reactions to benzoic acid in all patients. *Key words: Thromboxane A₂; Prostacycline; Prostaglandin F_{2α}; Indomethacin; Suction blisters.* (Received December 29, 1982.)

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Contact urticaria is divided into two main types: immunological (immediate-type hypersensitivity) and non-immunological. The principal mediator in immunological contact urticaria is histamine released from mast cells (12). It has been suggested that histamine is the mediator involved in non-immunological contact urticaria as well (6, 7, 15), but the data available do not consistently support this hypothesis (8, 11). Different mechanisms may be involved in contact urticarias from different substances (8). Other mediators of non-immunological contact urticaria besides histamine might be prostaglandins (PGs), kinins, complement factors and slow-reacting substance of anaphylaxis (SRS-A) (12). SRS-A has been shown to be a mixture of leukotrienes (14), and leukotrienes C3 and D4 in particular increase the vascular permeability of the skin appreciably (2).

PGs are involved in several pathological conditions in human skin. Elevated levels of PGs are found in a number of conditions, e.g. ultraviolet light-induced erythema, dermatitis herpetiformis and primary irritant dermatitis (1, 3, 4), but their involvement in non-immunological contact urticaria has not been studied. The presence of two new prostanoids, PGI₂ and TxA₂, was recently demonstrated in human skin blister fluid (13). These prostanoids ought to be of key importance in contact urticaria, because PGI₂ is vasodilatory and TxA₂ is vasoconstrictory (10), and the main clinical findings of contact urticaria are oedema and erythema.

To clarify the role of PGs in non-immunological contact urticaria to benzoic acid not mediated by histamine, prostacycline (PGI₂), thromboxane A₂ (TxA₂) and PGF_{2α} were assayed from the fluid of blisters induced on urticarial lesions produced by benzoic acid. The effect of indomethacin, a well-known cyclo-oxygenase inhibitor was also studied.

PATIENTS AND METHODS

Eleven voluntary dermatological patients (6 women, 5 men, aged 16-53 years) with an oedema and redness reaction to 10% benzoic acid in petrolatum were chosen for this study. None received antiprostaglandin medication for at least 2 weeks before the experiment.

Four patients had infectious eczema and 2 had exanthema of unknown origin. Acne, photodermatitis, impetigo contagiosa, allergic rhinitis and chronic urticaria of unknown aetiology were each diagnosed in one of the other patients.

About 0.1 ml of 10% benzoic acid in petrolatum was applied to an area measuring 5×5 cm on the volar side of the forearm. Petrolatum alone was used as a control substance on the other forearm.

One hour later, when the wheal and flare reaction was at its maximum, the test substances were wiped off gently with a piece of blotting paper, and suction blisters were induced on both sites simultaneously as described in an earlier work (5). Blister fluid was collected with a Mantoux syringe immediately after blister formation (after 65 ± 8 min). Pooled samples were put into cooled tubes containing indomethacin (final concentration 10^{-5} mole/l) and kept at -20°C until assayed.

PGI_2 , TxA_2 and $\text{PGF}_{2\alpha}$ were assayed by measuring their stable metabolites, 6-keto- $\text{PGF}_{1\alpha}$, thromboxane B_2 (TxB_2) and 13,14-dihydro-15-keto- $\text{PGF}_{2\alpha}$ (M- $\text{PGF}_{2\alpha}$), respectively, by radio-immunoassay (13).

Further 14 hospitalized dermatological patients with wheal and flare reaction to 5% benzoic acid in petrolatum were studied on 2 consecutive days.

On the first day 0.1 ml of 5%, 2.5%, 1%, 0.5%, 0.25%, 0.1%, 0.05% and 0.025% benzoic acid in petrolatum was spread over 5×5 cm areas of apparently normal skin on the upper back. Wheal and flare reactions were recorded 60 min after the application. After the initial reactivities had been recorded, the patients ingested 50 mg of indomethacin at 2.00 p.m. and 8.00 p.m., and at 8.00 a.m. on the following day, when the contact urticarial tests were repeated between 10.00 and 12.00 a.m. on the other side of the back.

The results were analysed using a *t*-test on paired observations.

RESULTS

The concentrations of PGI_2 , TxA_2 and $\text{PGF}_{2\alpha}$ in blister fluid from the urticarial lesion caused by benzoic acid did not differ from those found in control suction blister fluids (Table I).

Indomethacin 50 mg t.i.d. completely prevented contact urticaria from benzoic acid in all 14 patients tested.

DISCUSSION

The interesting result of the present study was the complete inhibition of the contact urticarial reaction to benzoic acid by pretreatment with indomethacin, a known cyclooxygenase inhibitor. This finding suggested that PGs might be involved in the production of the reaction. It was therefore surprising that no changes in PGI_2 , TxA_2 and $\text{PGF}_{2\alpha}$ production were discovered in blisters raised on contact urticarial lesions.

One reason for this discrepancy could be that it took about one hour to induce the blisters after the reaction had reached its maximum. This may have been too long to pinpoint immediate changes, and the released PGs might have been already washed off or

Table I. Concentrations (pg/ml) of 6-keto- $\text{PGF}_{1\alpha}$, thromboxane B_2 (TxB_2) and, 13,14-dihydro-15-keto- $\text{PGF}_{2\alpha}$ (M- $\text{PGF}_{2\alpha}$) in the fluid of suction blisters induced on the forearm skin of 11 patients at the site of contact urticaria produced by benzoic acid and at the control site

Substance in blister fluid	Contact urticaria (10% benzoic acid in petrolatum)	Control site (petrolatum only)
6-keto- $\text{PGF}_{1\alpha}$	241 (130–340) ^a	248 (194–341)
TxB_2	899 (196–1 809)	946 (217–2 205)
M- $\text{PGF}_{2\alpha}$	1 171 (539–2 277)	1 467 (726–2 066)

^a Mean (range in parentheses).

overdiluted. It is also possible that the induction of blisters could have brought about small changes in the amount of prostanooids in the skin.

The mechanism of the effect of indomethacin on the contact urticarial reaction could not be established from the present results, but the following possibilities exist:

1. The wheal and flare reaction is mediated through metabolites of the arachidonate metabolism that have not yet been studied in this connection.
2. Although the lipo-oxygenase pathway is usually resistant to indomethacin (9, 14), there is some evidence that in certain experimental models indomethacin can also inhibit the formation of leukotrienes (16).
3. The inhibition of the wheal and flare reaction is a completely new effect of indomethacin, and has nothing to do with its effects on arachidonate metabolism.
4. The mediators are PGs, but the suction blister method was inadequate for detecting the changes.

At the moment we do not have enough data to deduce which of the explanations mentioned is the most likely. Thus, further studies should be initiated on the mechanism and mediators of non-immunological contact urticaria.

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