

## SHORT REPORTS

### Effect of Vasoactive Agents on Prostanoids in Suction Blister Fluid

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Iontophoresis of histamine in the skin has been shown to release prostaglandins and arachidonic acid in suction blister fluid. Application of DMSO had a similar effect. No effect was found after using the following erythema and oedema irritants: scraping, vibration and ketocaine. Treatment with vasoconstricting drugs such as noradrenaline, betamethasone and lidocaine-prilocaine mixture did not influence the prostaglandin or arachidonic acid levels. *Key words: Skin erythema; Prostaglandin level; Arachidonic acid; Histamine; Local anaesthetics; Vasoconstriction.* (Received July 21, 1983.)

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Inflammatory diseases are known to increase the synthesis of prostaglandins (1). Various experimental stimuli causing erythema of the skin, such as UV-irradiations (UV-A, UV-B, UV-C) heat (IR) nicotinic acid derivatives and anthralin have been found to have the same effect. We now wish to report the preliminary results of the action of vasodilating, vasoconstricting and anaesthetic agents on arachidonic acid and prostanoids.

#### METHODS

*Drugs used.* Histamine (HCl (1 mg/ml) and noradrenaline free base (1 mg/ml) in 5 ml distilled water were applied on a 4x4 cm gauze swab and introduced into the inner surface of human forearm skin by iontophoresis using 4 mA for 3 min. Control areas on the contra-lateral arm were subjected to iontophoresis of distilled water.

Bethamethasone, 100 µl 0.14% ointment (Glaxo) was applied under occlusive dressing on a 10 cm<sup>2</sup> area for 1 hour.

An anaesthetic cream (2) with an eutectic mixture of 5% lidocaine and 5% prilocaine (EMLA, Astra, Södertälje, Sweden) was applied under occlusion on a 10 cm<sup>2</sup> area for 1 hour. The cream base was applied as a control.

Ketocaine 5% in a formulation containing per 100 ml 43 g isopropanol, 12 g glycerol, 0.1 g acetic acid and 32 g water was applied under occlusion (500 µl in a 9 cm<sup>2</sup> cotton pad).

DMSO 80% in water (2 ml) on a 10 cm<sup>2</sup> paper towel was left on the skin for 30 min.

Gentle scraping with a scalpel blade to remove the stratum corneum was carried out to induce reddening and slight trauma.

Tangential vibration at 50 cycle/s with a vibrator described by Stüttgen et al. (3) was performed for 10 min to induce an urticarial-like reaction.

#### Subjects

The iontophoretic experiments were performed on male healthy volunteers, age 24-55 years. The tests with local anaesthetics were performed on volunteers and in the normal appearing skin of 3 patients with chronic urticaria, atopic dermatitis and pruritus.

#### Suction blister fluid

The blisters were raised under continuous suction at 200 mmHg atmospheric pressure as described previously (4).

#### Determination of prostanoids

Arachidonic acid, prostaglandin E<sub>2</sub>, D<sub>2</sub>, F<sub>2α</sub> and 6-oxo-PGF<sub>1α</sub> were determined after chromatography by combined gas-liquid chromatography-mass spectrometry as previously described in detail (5).

## RESULTS

Iontophoresis of histamine induced a pronounced wheal and flare response in the treated area that lasted for up to 2 hours. Noradrenaline induced a vasoconstriction which could be seen as blanching of the skin at the treated site which faded, after about 2 hours. The lidocaine-prilocaine mixture induced anaesthesia and a blanching of the skin lasting for 2–4 hours. Ketocaine produced anaesthesia and a reddening of the skin lasting for 3–4 hours. DMSO induced a reddening lasting for one hour. No reaction was noted during the time of the experiment after application of the bethamethasone. Scraping with knife and vibration induced erythema and some oedema lasting for 20–60 min. The time for developing blisters was not significantly changed by the treatments.

The levels of the various prostanoids are given in Table I. Iontophoresis of histamine produced a significant increase of all the prostanoids ( $p < 0.001$ ). Raised values were also seen after DMSO whereas no clear change was seen after the other treatments. Similarly the levels of free arachidonic acid were significantly elevated ( $p < 0.01$ ) by iontophoresis of histamine. The results with DMSO ( $n=2$ ) suggest that it also elevates both free arachidonic acid and its cyclooxygenase products.

## COMMENTS

Histamine has been shown to liberate various prostaglandins in superfused mini-pig skin, rabbit ear and cultured human endothelial cells (6–8). We have here demonstrated that in human skin histamine can also release prostaglandins. The increase of prostaglandins after DMSO could probable also be explained as an effect of histamine release. No increase of prostanoids was seen after ketocaine although it produces a longlasting erythema as well as anaesthesia. The hyperaemia is here of a passive type caused by a reduced flow on the venous side (9). No effect was seen after vasoconstriction induced by noradrenaline or the mixture of lidocaine and prilocaine, nor have we been able to block the increase of prostanoids induced by infra-red irradiation by immediately after inducing a vasoconstriction (unpublished).

Table 1. Levels of prostaglandins and arachidonic acid (AA) in suction blister fluid after various treatments

The figures show ng/ml and mean  $\pm$  SEM.  $N$  = number of subjects

Drug	$N$	Effect	AA	PG E <sub>2</sub>	PG D <sub>2</sub>	PG F <sub>2<math>\alpha</math></sub>	PG 6-oxo-F <sub>1<math>\alpha</math></sub>
Histamine	5	Vasodilat. + oedema	5 783 $\pm$ 600	40.1 $\pm$ 5.3	35.1 $\pm$ 4.6	42.3 $\pm$ 8.2	25.8 $\pm$ 6.3
Noradrenaline	4	Vasoconstriction	3 908 $\pm$ 350	19.2 $\pm$ 4.3	16.5 $\pm$ 3.2	16.5 $\pm$ 1.6	6.0 $\pm$ 4.2
Control iontoph.	3	0	3 357 $\pm$ 300	16.4 $\pm$ 5.1	16.9 $\pm$ 5.6	17.0 $\pm$ 3.2	5.1 $\pm$ 3.6
Scraping	3	Vasodilation	–	19.2 $\pm$ 6.1	15.0 $\pm$ 7.2	20.3 $\pm$ 8.3	14.0 $\pm$ 2.6
Vibration	2	Vasodilation	3 260	16.3–20.3	14.0–26.3	18.1–20.1	12.1–7.0
Lidocaine + Prilocaine	3	Vasoconstriction + anaesthesia	1 800	24.3 $\pm$ 8.6	19.8 $\pm$ 9.3	15.4 $\pm$ 8.2	6.1 $\pm$ 4.3
Ketocaine	3	Vasodilation + anaesthesia	3 581 $\pm$	23.3 $\pm$ 5.2	17.5 $\pm$ 4.6	19.0 $\pm$ 6.3	5.1 $\pm$ 3.9
Betamethasone	4	–	5 300 $\pm$	20.5 $\pm$ 4.6	22.0 $\pm$ 6.1	18.0 $\pm$ 4.2	8.1 $\pm$ 6.3
DMSO	2	Vasodilatation	8 875	72–83	38–46	22–45	32–39
Control	44	–	2 816 $\pm$ 288	15.7 $\pm$ 1.0	17.3 $\pm$ 1.0	13.9 $\pm$ 0.6	9.2 $\pm$ 0.5

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