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SKIN REACTIONS TO IONTOPHORETICALLY ADMINISTERED EPINEPHRINE AND NOREPINEPHRINE IN ATOPIC DERMATITIS*

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Patients with atopic dermatitis react to various stimuli with vasoconstriction of the cutaneous vessels (1–3). The cause of their increased vascular contractility is unknown. One explanation could be an increased sensitivity to epinephrine or norepinephrine. Lobitz and Campbell (2) found normal reactions to intracutaneously injected epinephrine in ten patients with atopic dermatitis; however, they did not ascertain whether the minimum dose needed to cause blanching was different in normal subjects and patients with atopic dermatitis.

The following investigation was therefore performed to study the blanching reaction to epinephrine and *l*-norepinephrine administered by a quantitative iontophoretic method into the non-diseased skin areas of normals and patients with atopic dermatitis, eczema and psoriasis.

METHODS

Iontophoretic Apparatus: The anodes of platinum (0.64 cm². each) from which positively charged substances are introduced into the skin are arranged in twelve equal-sized and separate cylindrical chambers, mounted in a plexi-glass block. They thus make a multi-electrode unit (Fig. 1a and b). The discs of platinum are mounted 1 cm above the skin surface. Each chamber receives its own amperage. In chamber No. 1, this is 40 μA; this increases in equal percentual steps (see fig. 3) towards chamber No. 11, where the value is 1280 μA. Chamber No. 0 received no current at all and is a control. The different electrodes are arranged (Fig. 1) in order to avoid interference between the electrodes. The control electrode (No. 0) is near those with the highest currents (No. 11 and 10).

To avoid the influence of variations in skin resistance, resistances from 0.22 to 7.2 MΩ (megaohms) were connected to the anodes (r_1–r_{11}, fig. 2). A constant voltage of 315 V was used. The resistance of the body under the electrode (r_b in MΩ) was calculated: $r_b = (312/i) - r$, where i is the current through the chamber in μA and r, the series-resistance (in MΩ) connected to this anode (fig. 2). The resistances r_1–r_{11} were checked by measuring the currents i_1–i_{11} without patient (short connection 1–11 with C in fig. 2). The following values in MΩ were found for r_1–r_{11}:

$r_1 = 7.20$	$r_5 = 2.66$	$r_9 = 0.45$
$r_2 = 6.37$	$r_6 = 1.83$	$r_{10} = 0.33$
$r_3 = 5.28$	$r_7 = 1.28$	$r_{11} = 0.22$
$r_4 = 3.71$	$r_8 = 0.92$	r_0

The resistance of the body under the electrode for each amperage is shown in fig. 3. Here it becomes evident that the resistance of the body under the electrode is between 5.5 and 10.9% of the series resistance connected with the anode. Changes in body resistance are therefore negligible. The stripping experiment described below also illustrates this fact.

Experimental Procedure: The flexor aspect of the forearm was washed with water, dried, and the multielectrode fastened with rubber bands about 7–17 cm below the antecubital fossa. The cathode, a 6.3 x 6.3 cm brass plate, was fastened on the opposite arm. An electrode ointment containing 10 per cent NaCl was applied between the skin and brass plate. The multielectrode chambers were then filled with the solution to be tested. Electrode current was used for 30 seconds and the anode removed. Under those anodes, where the current had been great enough, the reaction to epinephrine and norepinephrine consisted of round, sharply limited, blanched spots (0.78 cm²) with or without piloerection. The minimal dose causing reaction could thus be determined. The control anode without current never showed any reaction. The reactions were maximal after about four minutes and usually declined after ten to twenty minutes, beginning in areas having received the lower currents. The skin reaction noted five minutes after cessation of the current has been utilized in the following portion of these experiments. All experiments were made at room temperature (20–22° C.)

CONTROL EXPERIMENTS

Drug Concentration: The influence of concentration of the epinephrine and norepinephrine has been tested in 10 normal subjects and 5 patients with atopic dermatitis. Each patient was tested

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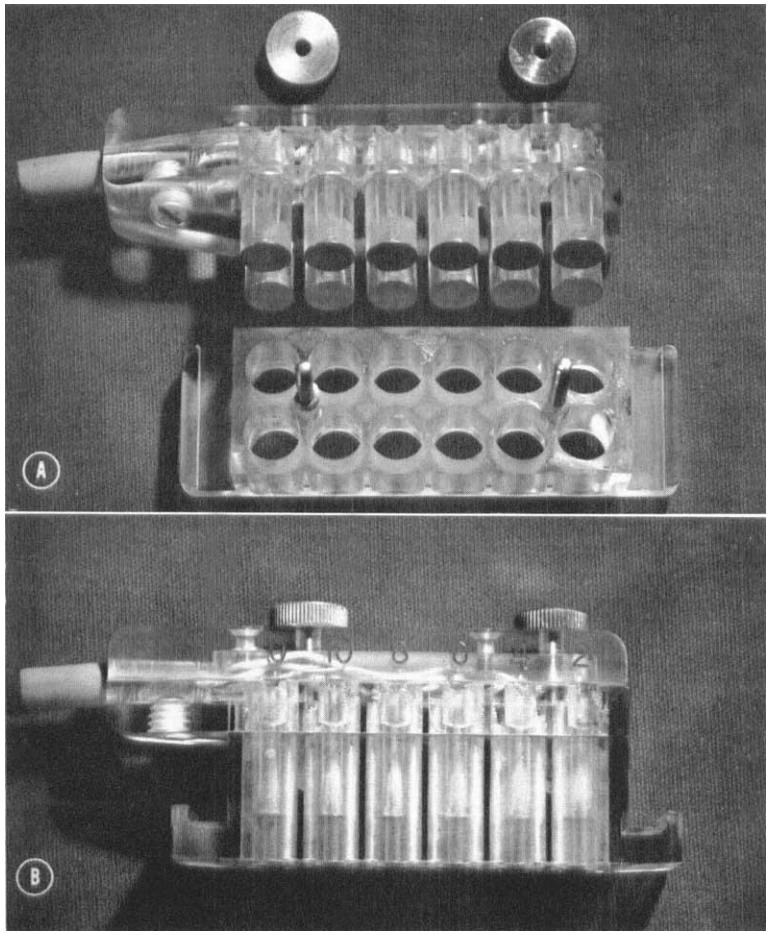

FIG. 1a and b. The anode consists of a multi-electrode unit

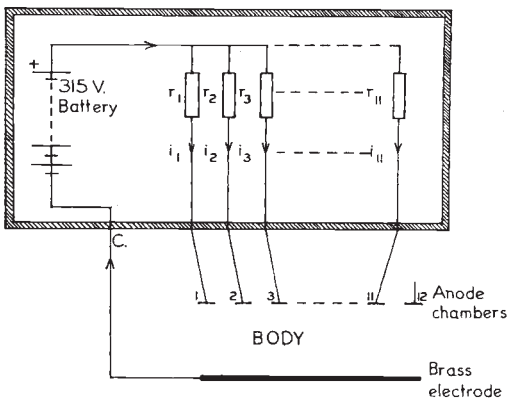

FIG. 2. Diagram of the iontophoretic circuit

with four different concentrations. Within a concentration of 10 to 500 μg/ml of the drugs, similar reactions in the skin were observed. This means that the drugs are introduced by electrophoretic mobility (iontophoresis) and not by electroosmosis, *i.e.* carried passively with the electroosmotic flow of fluid.

In the following experiments, 100 μg/ml of epinephrine or *l*-norepinephrine bitartrate dissolved in freshly prepared columnar distilled water were used. The epinephrine was prepared from a stock solution containing 1 mg epinephrine/ml (Exadrin, Astra Södertälje, Sweden).

Size and Place of Brass Electrode: The influence of the contact area of the negative brass electrode on reactions of the skin was studied by using three different sizes (20, 40 and 80 cm^2). The reactions to epinephrine and norepinephrine at the anode were found to be independent of the cathode size used. The current through each chamber was also controlled and found to be independent of the cathode size used. Therefore, differences in contact area at the cathode are of no importance.

In the following studies, the middle-sized brass electrode has been used. The site of the cathode

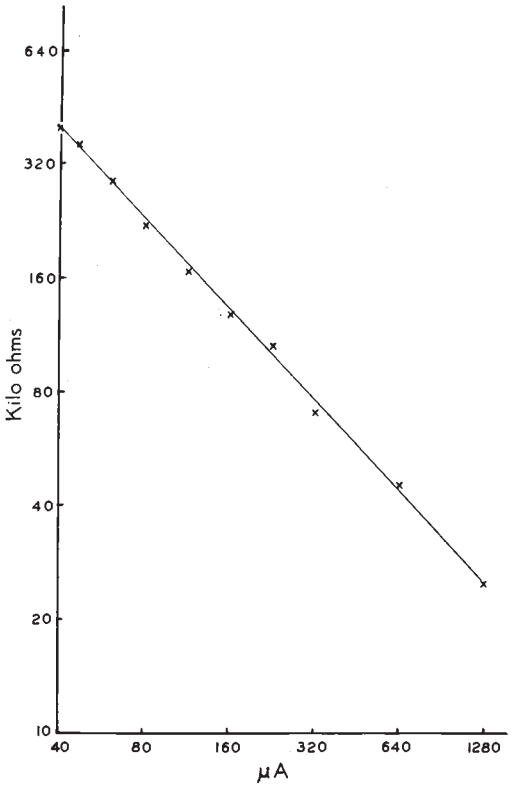

FIG. 3. The electrode resistance of the body at different amperages. Ordinate: Resistance of the body in kiloohms. Abscissa: Current (μA) through the chambers when the subject is tested.

on the body was found not to influence the skin response. The currents through the chambers were the same with the brass cathode placed on the legs or on the same or opposite arm as the anode.

Skin Thickness: The influence of the thickness of the corneal layer was tested in 21 subjects where the stratum corneum had been partly removed by applying adhesive tape 18 times, 15 minutes, 1, 4, 24 or 48 hours before the iontophoretic test. Comparison was made between the response to norepinephrine on the stripped area and the corresponding normal area on the other arm. The quotients between the doses (currents) needed to give a blanching response on stripped skin/unstripped skin are as follows:

15 minutes	0.13;	0.33;	0.50;	0.50	
1 hour	0.13;	0.25;	0.33;	0.75	
4 hours	0.33;	0.33;	0.50;	0.50	
24 hours	0.25;	0.50;	1.00;	2.00;	3.00
48 hours	0.25;	1.00;	1.00;	1.50	

In most of the subjects stripped 15 minutes to 4 hours before iontophoresis, the blanching area was not sharply limited to the area in contact with the anode solution, but a fading out of the blanching could be seen some minutes after iontophoresis. This was probably due to edema caused by the stripping. In unstripped skin, the blanching area is always sharply limited to the round anode area. No certain effect of stripping was found on the pilomotor activity.

The currents through each chamber were measured in some of the patients on the stripped skin and were found to be the same as on the unstripped skin. The increased response in stripped skin induced by norepinephrine is thus not due to a change in body resistance. It is probably due to decreased retention of the substance in the superficial skin layer, which will be discussed later.

MATERIAL

The test site consisted of grossly normal forearm skin in healthy medical students (age 19–24), and patients with the following clinical entities: 1) atopic dermatitis, 2) psoriasis, 3) various eczemas (including seborrheic dermatitis, nummular eczema, stasis dermatitis and non-specific hand eczemas). It should be emphasized that only grossly normal skin was utilized, unless otherwise noted.

RESULTS

The minimum dose of epinephrine and norepinephrine causing blanching and pilomotion in

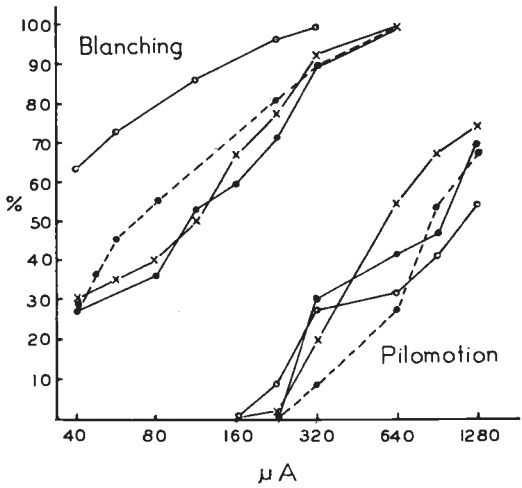

FIG. 4. The effect of iontophoretically introduced norepinephrine. Ordinate: Per cent of the subjects tested showing blanching and pilomotion. Abscissa: Minimal current (= dose) in μA causing blanching and pilomotion. •——• Normal (17 subjects), ×——× Eczema (40 subjects), ●-----● Psoriasis (11 subjects), ○——○ Atopic dermatitis (22 subjects).

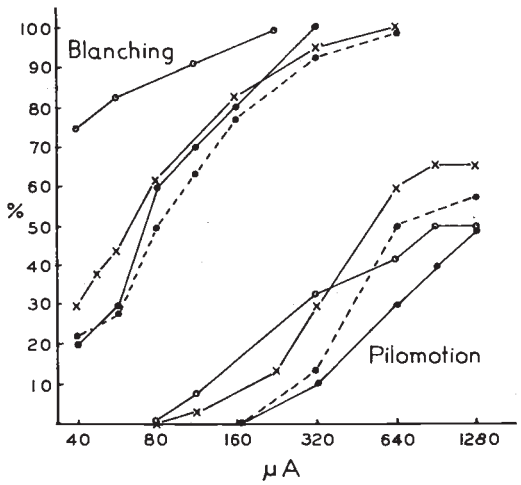

FIG. 5. The effect of iontophoretically introduced epinephrine. Ordinate: Per cent of the subjects tested showing blanching and pilomotion. Abscissa: Minimal current (=dose) in μA causing blanching and pilomotion. •——• Normal (10 subjects), ×——× Eczema (23 subjects), ●-----● Psoriasis (14 subjects), ○——○ Atopic dermatitis (12 subjects).

the skin appears in figures 4 and 5. It is concluded that decreased doses (=currents) of epinephrine and norepinephrine produce blanching in atopic dermatitis as compared with psoriasis ($P < 0.05$ resp. 0.01), eczema ($P < 0.02$), and controls ($P < 0.01$). No difference was found in the dose causing piloerection nor in the reaction to epinephrine or norepinephrine in diseased and normal-appearing skin areas in 5 patients with atopic dermatitis.

The patients reported did not receive systemic corticosteroids or local therapy in the test area. Four patients with atopic dermatitis received 0.5 mg. dexamethasone (Decadron, Merck, Sharpe and Dohme) 4 times daily. Their skin condition improved; when re-tested one week hence, the results were identical.

DISCUSSION

An increased reaction to epinephrine and norepinephrine was evidenced in patients with atopic dermatitis. Lobitz and Campbell (2) and Reed and Kierland (4) however, found normal response in atopic patients to intradermally injected epinephrine in dilution of 1/10,000 and 1/100,000. The discrepancy might be explained by their use of comparatively high doses, so that they obtained a blanching in all subjects. Since they obtained blanching in all subjects, their high doses of epinephrine obliterated finer quantitative comparisons. It should be emphasized that the results of iontophoresis and intradermal injections are not directly comparable; for intradermal injection induces not clearly defined variables such as spreading and resorption.

Since patients with atopic dermatitis tested with distilled water, saline, 48/80 or mecholyl at currents lower than 160 μA do not develop blanching, the lower currents themselves could hardly produce the increased reactions noted with epinephrine above. Nor can difference in skin thickness explain the results. On the contrary, the increased skin thickness seen in atopic dermatitis might tend to mask even a more increased sensitivity to epinephrine and norepinephrine.

In atopic dermatitis the presence of edema has been suggested in the unaffected skin (5, 6), though no increased amount of water has been demonstrated (7). Therefore, epinephrine introduced in such edematous sites may be diluted and resorbed rather than bound to the cells. Conversely, it might be assumed that epinephrine is bound to the cells in normals, therefore, it is not available to produce blanching to the same extent as in atopic subjects. This was indeed the case, as will be seen in the following paper. However, the finding of a normal pilomotor reaction in atopic patients indicates that it is the vessels which are more sensitive. We can, therefore, at the present time not state whether the increased blanching reaction found in patients with atopic dermatitis is due to an increased sensitivity of the vessels and/or a decreased binding of the drugs to the cells which they have to pass before reaching the effector organ. Each or both possibilities might be valid as an explanation for the increased tendency to vascular contractibility in atopic dermatitis.

SUMMARY

Epinephrine and norepinephrine have been introduced into the skin by a quantitative iontophoretic method. The dose of the drug is dependent on the current applied but independent of body resistance and concentration used. The minimum current applied for 30 seconds (=dose) causing pilomotion and blanching has been estimated in normals and in normal-appearing skin of patients with eczema, psoriasis and atopic dermatitis. No difference was found in the pilo-

motor reaction in the different diseases. A lower threshold for blanching after both epinephrine and norepinephrine was found in patients with atopic dermatitis. The mechanism for this increased reaction is discussed.

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