

DOSE-DEPENDENT EFFECT OF TOPICAL CORTICOSTEROIDS ON BLOOD FLOW IN HUMAN CUTANEOUS TISSUE

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Abstract. In seven healthy subjects the dorsum of the hand was treated with beta-methasone valerate cream in increasing concentrations, from 0.1 to 1.0%, and with hydrocortisone butyrate 0.1% with or without plastic occlusion. Under conditions of controlled room temperature, blood flow in treated, placebo-treated, and untreated cutaneous tissue was measured using the local ^{133}Xe wash-out technique. Placebo creams did not affect cutaneous blood flow, but beta-methasone valerate 0.1% reduced blood flow and 1.0% increased it. An increase in blood flow was also observed after use of hydrocortisone butyrate under plastic occlusion. The results indicate a dual effect of potent corticosteroids on cutaneous blood flow.

Key words: Topical corticosteroids; Corticosteroids; Blood flow; Cutaneous tissue

Local corticosteroid application causes cutaneous blanching, an effect which, though insufficiently explained, has been extensively used as an index of percutaneous absorption of corticosteroids (7). Recent reports have demonstrated tachyphylaxis to the blanching effect (1, 4). This finding has supported the theory that topically applied corticosteroids act indirectly by releasing endogenous noradrenalin from sympathetic nerve fibres and or by influencing the recapture of noradrenalin by inhibiting the "noradrenalin pump", as with guanethidine (8, 12).

The purpose of the present study was to investigate the dose-dependent effect of local corticosteroid application on blood flow in human cutaneous tissue.

MATERIAL AND METHODS

The experiments were conducted in 7 healthy volunteers, 4 women and 3 men, aged 22-34.

1. Application of corticosteroid

Five persons received topical application of β -metasone valerate in a cream base (Celeston-valerate®, Scherring Corporation). Concentrations of steroid were 0.5 and 1.0%. Control experiments with the cream base alone and with a steroid concentration of 0.1% were carried out. The cream was applied four times at 6 hour intervals in a total amount of 100 mg to an area of 4 cm diameter on the dorsum of a hand. Two hours after the last application, cutaneous blood flow was measured.

All 7 persons received topical application of hydrocortisone butyrate 0.1% in cream (Locoid®, Gist-Brocades), applied in the same way as with β -metasone valerate. In 6 persons, the effect of applying 100 mg hydrocortisone butyrate under occlusive plastic for 6 hours to an area of 4 cm diameter on the dorsum of a hand was investigated. In 2 persons, control experiments were performed with the cream base alone under plastic occlusion for 6 hours. Blood flow was measured 2 hours after the last application or 2 hours after removal of plastic.

Room temperature was kept at $22 \pm 1^\circ\text{C}$ throughout the experiments. Skin temperature was measured with thermocouples before and after each experiment. The range was $32 \pm 1^\circ\text{C}$. No significant difference in temperature between treated and untreated locations on the dorsum of the hand could be detected by the present method. There were no reports of subjective sensation of heat or cold, nor of sweating.

2. Measurement of blood flow in cutaneous tissue

Blood flow in cutaneous tissue was measured by the local ^{133}Xe wash-out technique (11). ^{133}Xe (20 mCi/ml) dissolved in 0.01-0.04 ml saline was injected intracutaneously using needles with an outer diameter of 0.25 mm. In order to test the effect of the injection trauma, control experiments were performed in 3 cases using the atraumatic epicutaneous labelling technique of Sejrsen (10). The ^{133}Xe gas was deposited over the skin in a chamber formed by the skin and a mylar membrane. The gas remained in the chamber for 3 minutes to allow diffusion into the skin and was then withdrawn, after which the membrane was lifted and any excess gas removed by blowing on the skin surface.

The measurements were started immediately after the

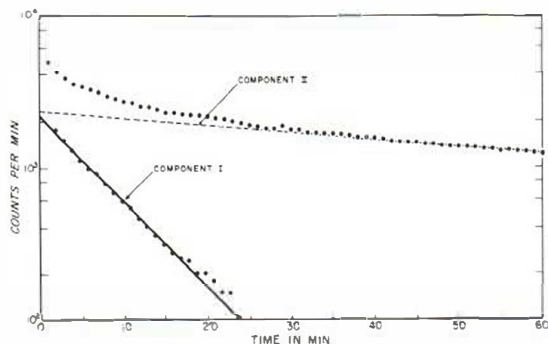


Fig. 1. Wash-out curve from untreated skin after epicutaneous labelling, showing the principle of biexponential resolution. (For details, see text.)

application of ^{133}Xe and lasted about one hour. The γ -emission of ^{133}Xe was detected by a NaI (Tl) scintillation detector placed 10 cm above the radioactive field. The pulses were fed into a gamma spectrometer (meditronic®, Denmark) with a window set around the 81 keV photopeak of ^{133}Xe . The activity was recorded in one-minute intervals and the count values were printed out without delay.

3. Calculations

According to Sejrsen (10) the wash-out of atraumatically applied ^{133}Xe to the skin follows a biexponential course where the fast monoexponential component reflects cutaneous blood flow and the slow monoexponential component reflects blood flow in subcutaneous tissue. The perfusion coefficient, f , was calculated from the Kety formula, $F = k \cdot \lambda \cdot 100 \text{ ml}/100 \text{ g} \cdot \text{min}$ (5), where k is the wash-out rate constant in min^{-1} and λ the tissue-to-blood partition coefficient in ml/g (9). A λ -value of 0.7 ml/g was used for cutaneous tissue and 10 ml/g for subcutaneous tissue (11). The logarithmically transformed count values corrected for background activity were plotted against time (Fig. 1). The slow monoexponential tail part of the curve (component II) was extrapolated to time zero and subtracted from the initial part of the curve. Thus, the fast monoexponential component I was constructed. In the experiments with intracutaneous injection of ^{133}Xe , the initial 10 minutes of the curve was omitted in order to rule out the influence of the injection trauma (11).

4. Intact diffusion barrier to ^{133}Xe

Inflation of a cuff placed on the upper arm to 250 mmHg completely stopped the wash-out of ^{133}Xe from a hand treated with β -methasone valerate 1%. This indicates that the local steroid treatment did not affect the cutaneous diffusion barrier to ^{133}Xe .

5. Statistics

Student's t -test for paired samples was used.

RESULTS

In Fig. 2, a representative example of ^{133}Xe wash-out from skin treated with β -methasone valerate 1.0% is shown. It is evident that the slow monoexponential tail part (component II) starts earlier than in untreated skin (Fig. 1) and that component I is steeper. Results of resolution of the wash-out curves obtained in β -methasone valerate experiments are shown in Fig. 3. Control and placebo values are the same, but application of β -methasone valerate 0.1% caused a reduction in blood flow ($p < 0.05$). After application of the 0.5% concentration, no deviation from the control could be detected in the mean results, but 1.0% β -methasone valerate caused a significant increase in cutaneous blood flow ($p < 0.05$). In Fig. 4, results of hydrocortisone butyrate experiments are shown. There was no detectable change in blood flow values following application of hydrocortisone butyrate for 24 hours, but application under plastic occlusion for 6 hours resulted in a significant increase in cutaneous blood flow.

Control experiments with placebo under plastic occlusion in 2 persons gave no detectable change from control values, which were 10.9 and 10.2 $\text{ml}/100 \text{ g} \cdot \text{min}$, respectively. The epicutaneous labelling technique did not affect the test values. In experiments with β -methasone valerate 1.0%, the

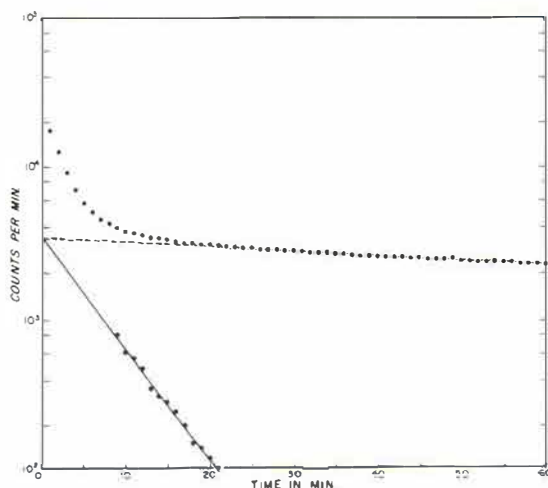


Fig. 2. Wash-out curve from skin treated with β -methasone valerate cream 1.0%. After resolution of this curve, a change in component I is revealed. Intracutaneous labelling data points from the first 10 minutes are not used (injection trauma).

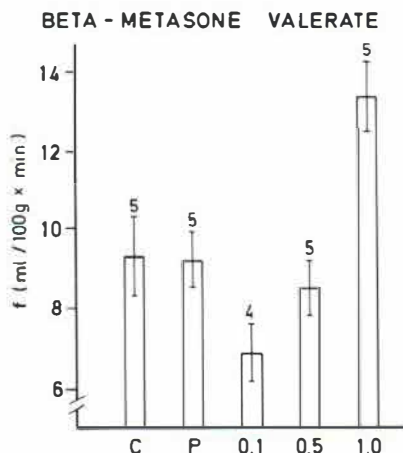


Fig. 3. Cutaneous blood flow after treatment with various concentrations of β -methasone valerate. C: control; p: placebo cream; 0.1, 0.5, and 1.0%: concentration of corticosteroid. Numbers of experiments and standard errors of the mean are shown. 0.1 and 1.0 are significantly different from control ($p < 0.05$).

control value was 11.1, the test value after intracutaneous labelling 11.7, and the test value with epicutaneous labelling, 12.0 ml/100 g·min. In occluded hydrocortisone butyrate experiments on 2 persons, control values were 10.9 and 10.2, intracutaneous test values 9.8 and 17.5 ml/100 g·min, respectively. The subject who responded with a decreased blood flow was the only person who also responded with a decrease during treatment with β -methasone valerate 1.0%. No change in subcutaneous blood flow was detected during experiments with β -methasone valerate or hydrocortisone butyrate.

DISCUSSION

The main finding of the present study is that β -methasone valerate 0.1% reduced the blood flow in cutaneous tissue after four applications within 24 hours, thus confirming the results of a previous study (6). Hydrocortisone butyrate 0.1% did not affect cutaneous blood flow. However, by using higher concentrations of β -methasone valerate and by using hydrocortisone butyrate under plastic occlusion, an increase in cutaneous blood flow was demonstrated.

The mechanisms responsible for the decrease in vascular tone following applications of corticosteroids in substantial amounts might be the

result of a liberation and depletion of catecholamines from the sympathetic nerv ending, as proposed by Solomon (12). Another possibility could be a direct effect on vascular smooth muscle, reducing intrinsic vascular reactivity. The theory of catecholamine liberation and depletion is compatible with the finding of tachyphylaxis to the skin blanching action of topically applied corticosteroids (1, 4). Tachyphylaxis has been found following repeated applications of all tested corticosteroids, including non-fluorinated compounds (1). One might expect that tachyphylaxis would be reached earlier when using the more potent steroid preparations, but according to published results this seems not to be the case (1).

The catecholamine liberation hypothesis is further supported by the observation that the pressure effect of noradrenalin can be potentiated by hydrocortisone, using isolated arterial preparations in vitro (3). The constrictor actions of both adrenalin and noradrenalin on mesenteric arterioles in rats was potentiated by systemic administration of corticosteroids (2). Reis (9) conducted experiments on human bulbar conjunctiva, demonstrating that local steroid application induced increased sensitivity to noradrenalin, but that it also altered the basal morphology of the vessels towards an arteriolar constriction and emptying of capillaries without the addition of noradrenalin.

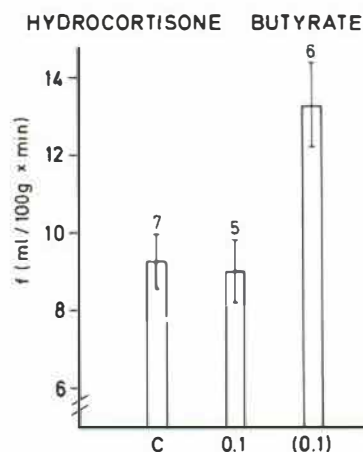


Fig. 4. Cutaneous blood flow in hydrocortisone butyrate experiments. C: control; 0.1% concentration of corticosteroid; (0.1): corticosteroid applied under occlusion for 6 hours. (0.1) significantly different from control ($p < 0.01$).

The following conclusion can be drawn from the present results. If the bioavailability of a local corticosteroid is low, the result can be an unaltered or a decreased blood flow, but after application of the steroid in a high concentration or under the influence of factors which facilitate percutaneous penetration, blood flow will increase. The cause of this is unexplained, but the possibilities include catecholamine depletion and/or interference with the intrinsic reactivity of smooth muscle cells. These possibilities are currently under investigation.

REFERENCES

1. Altmeyer, P. & Zaun, H.: Ergebnisse reflexionsphotometrischer Bestimmungen der Vasoconstriction nach topischer Steroidapplikation. V. Vasoconstrictionsphänomene und Tachyphylaxie nach wiederholter Steroidapplikation. *Arch Derm Res* 255: 51, 1976.
2. Altura, B. M.: Role of glucocorticoids in local regulation of blood flow. *Am J Physiol* 211: 1393, 1966.
3. Besse, J. C. & Bass, A. D.: Potentiation by hydrocortisone of responses to catecholamines in vascular smooth muscle. *J Pharmacol Exp Ther* 154: 244, 1966.
4. du Vivier, A. & Stoughton, R. B.: Acute tolerance to effect of topical glucocorticosteroids. *Br J Dermatol* 54, suppl. 11: 25, 1976.
5. Kety, S. S.: Theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol Rev* 3: 1, 1951.
6. Kristensen, J. K. & Wadskov, S.: Studies on ^{133}Xe wash-out from human skin. Quantitative measurement of blood flow in normal and corticosteroid treated skin. *J Invest Dermatol* 68: 196, 1977.
7. McKenzie, A. W. & Stoughton, R. B.: Method for comparing percutaneous absorption of steroids. *Arch Dermatol* 86: 608, 1962.
8. Mitchell, J. R. & Oates, J. A.: Guanethidine and related agents. I. Mechanism of the selective blockade of adrenergic neurons and its antagonism by drugs. *J Pharmacol Exp Ther* 172: 100, 1970.
9. Reis, D. J.: Potentiation of the vasoconstrictor action of topical norepinephrine on the human bulbar conjunctival vessels after topical application of certain adreno cortical hormones. *J Clin Endocrin* 20: 446, 1960.
10. Sejrnsen, P.: Blood flow in cutaneous tissue in man studied by wash-out of radioactive xenon. *Circ Res* 25: 215, 1969.
11. Sejrnsen, P.: Measurement of Cutaneous Blood Flow by Freely Diffusible Radioactive Isotopes. Thesis. Copenhagen, 1971. *Dan Med Bull*, suppl. 18, 1971.
12. Solomon, L. M., Wentzel, H. E. & Greenberg, M. S.: Studies in the mechanism of steroid vasoconstriction. *J Invest Dermatol* 44: 129, 1965.

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