

PLETHYSMOGRAPHIC RECORDINGS OF SKIN PULSES

III. Effect of Corticosteroids, Dithranol and Tar in Psoriasis

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Abstract. The vascular action of betamethasone-17-valerate, hydrocortisone acetate, dithranol and tar was measured by means of photoelectric and piezoelectric pulse plethysmography in patients with psoriasis. A distinct difference in vascular effect was demonstrated. Continued occlusive therapy by daily application of hydrocortisone acetate and betamethasone-17-valerate normalized the pulsating cutaneous blood flow within 16 and 7 days, respectively. The time needed for dithranol and Goeckerman's method was 8 and 42 days, maximum. The results corresponded with the clinical improvement of the disease. Marked reduction in vascularization was also observed following a single application of betamethasone-17-valerate. The effect produced by hydrocortisone acetate was of much lower degree and great variations were observed. The report provides additional information concerning the vascular action of steroids and indicates that plethysmographic measurements are of value in studies of percutaneous absorption of substances acting on the dermal vessels.

The purpose of the present investigation was to study the effect of betamethasone-17-valerate, hydrocortisone acetate, dithranol and tar on the vascular changes in psoriatic skin by means of pulse plethysmography. Illig (7), by using capillary microscopy, distinguished between functional and organic vascular changes in psoriasis and observed that the capillary dilatation as a functional disorder disappeared prior to the organic changes such as capillary elongation, vessel growth, coiling and network formation. He also observed that the residual erythema was due to dilatation of the subpapillary veins. Persistence of abnormal capillaries after treatment with cignoline, tar and steroids have been described by many authors using histochemical methods (1, 2, 11, 12, 17). The only difference which was observed histochemically between the various treatments was the rate of normalization.

Plethysmographic measurements from psoriatic lesions during continued therapy have not been

reported thus far. In a previous paper (19) dealing with piezoelectric and photoelectric pulse recordings in psoriasis it was reported that betamethasone-17-valerate applied under plastic occlusion caused vasoconstriction and reduced the pulsating blood flow in the skin. After conclusion of the occlusive dressing therapy the skin vessels dilated as indicated by an increase of the pulse amplitude. It was thus suggested that the vascular effect of the steroid was mainly functional and of temporary character, although an organic and permanent regression of the psoriatic vascularization takes place during continued therapy. It is proposed that this regression is secondary to the epidermal normalization, suggesting that vessel growth in psoriasis develops parallel to the primary demand of epidermal metabolism (13). The following investigation was designed to explore this possibility by studying the normalization of the cutaneous blood flow during various antipsoriatic treatments.

Furthermore, pulse plethysmography permits investigation of percutaneous absorption, since the method measures vasodilatation and vasoconstriction induced by various substances after penetration of the epidermal barrier. Vasodilatation as a biologic reaction was utilised by Stoughton et al. (16) to measure penetration through the normal epidermis. Nicotinic acid and related derivatives were studied and the penetration was evidenced by the observed erythema. A wide variation in percutaneous absorption was found. In the present study the vasoconstrictive effect of hydrocortisone acetate and betamethasone-17-valerate was utilised to investigate penetration through psoriatic skin. This allows one to attempt correlation between absorption differences in normal and diseased skin.

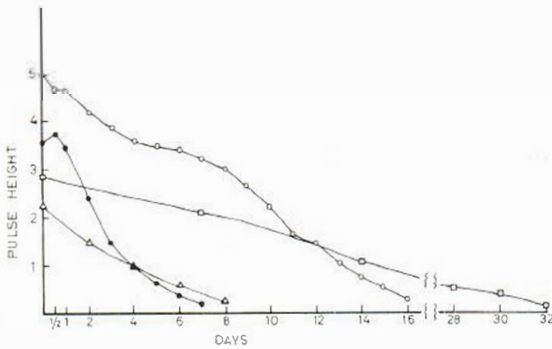


Fig. 1. Effect of treatment with hydrocortisone acetate 1%, betamethasone-17-valerate 0.1% in paste, and Goeckerman's therapy on cutaneous blood flow in psoriasis. Average of values obtained. ○, hydrocortisone acetate; △, dithranol in paste; ●, betamethasone-17-valerate; □, Goeckerman's method.

MATERIAL AND METHODS

Fifty-two lesions in 19 patients (aged 22-50 years) presenting an active, previously untreated psoriasis, were investigated during continued therapy until disappearance of pulsations. Measurements were performed on two or more lesions in each patient. The sites used in the investigation were the upper or lower extremities. Twenty lesions (10 patients) were investigated during Goeckerman's therapy,¹ twelve lesions (3 patients) during treatment with dithranol 0.1% in paste,² and ten lesions each (6 patients) during occlusive treatment with betamethasone-17-valerate 0.1%³ and hydrocortisone acetate 1% in Petrolatum, respectively. The lesions treated with steroids were examined daily before application of ointment which was spread over measured areas of lesion (4 cm²), the first examination being performed after 12 hours. Goeckerman's ointment and dithranol paste were applied daily and measurements were performed every second day during treatment with the latter. During Goeckerman's therapy, measurements were performed weekly for the first 3 weeks and later every second day. The applications were removed half an hour prior to the investigation.

In addition 4 patients, aged 25-30 years, were submitted to investigation with 0.1% betamethasone-17-valerate in ointment and 1% hydrocortisone acetate in petrolatum, each ointment being applied as a single dose on ten lesions, respectively. The lesions were reoccluded after each examination which was performed daily without further application of steroids in order to study an eventual reservoir effect. The first measurement was made after 12 hours.

The vascular effect of a single application of hydrocortisone acetate was also measured on six lesions every second hour during 24 hours. By this investigation it was

¹ Sulph.med. and pyrrol-lithantr. aa 2% in petrolatum—combined with ultraviolet light and soap baths.

² Oxyd.zinc. 40% in petrolatum.

³ Betnovate®.

postulated that further information concerning the absorption of hydrocortisone acetate in the first 24 hours could be obtained.

The pulse meters used in this study have been described in previous papers (18, 19). As the light reflection of the photoelectric device might be influenced by the tar ointment and dithranol in paste, these therapeutics were investigated by the piezoelectric apparatus which is light-independent. The piezoelectric crystal is only influenced by the pulsating skin surface and transforms the pressure into an electric charge which is recorded as a pulse wave. The photoelectric pulse meter receives light due to reflection and measures variation in the amount of blood in the skin. Recently the relationship between the photoelectric pulse and the cutaneous blood flow has been established (15); a reduction in flow will reduce the pulsations accordingly. Furthermore, vasoconstriction is characterized by a distinct decrease in pulse height and dilatation by an increase (19). In the photofield-effect transistor the current varies proportionately to the intensity of the reflected light. A 0.5 W lamp is used as light source and a lens concentrates the light before it reaches the skin. The heat production of this device is very low and has influence only when the skin is radiated for a prolonged period of time. No such effect was observed in the present investigation. The output of the photoelectric cell was considered constant as the experiments were performed under almost identical environmental conditions. The pulse height was measured in all plethysmograms and an increase or decrease was noted.

RESULTS

Marked variation in pulse height was observed between the individuals, and to a lesser degree between the various lesions in the same subject. The results obtained by each therapy, however, were uniform. The lesions treated with betamethasone-

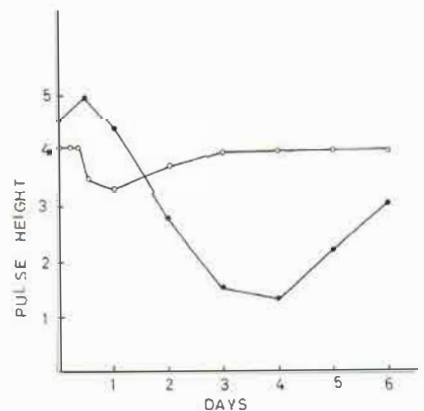


Fig. 2. Effect of a single application of hydrocortisone acetate 1% (○—○) and betamethasone-17-valerate 0.1% (●—●) on the cutaneous blood flow in psoriasis. Average of values obtained.

17-valerate appeared paler than those treated with hydrocortisone acetate. At 12 hours occlusion with betamethasone-17-valerate an increase in pulsations was recorded whereas hydrocortisone acetate produced a reduction (Fig. 1). After 24 hours a small reduction in pulse height was also observed after treatment with betamethasone-17-valerate. The vascular effect of hydrocortisone acetate remained constant at this moment. A marked reduction in pulse height was recorded during continued treatment with betamethasone-17-valerate and the pulse waves disappeared after 7 days, although the lesions were not entirely healed and residual erythema and slight infiltration persisted. Continued treatment with hydrocortisone acetate produced a gradual reduction in pulse height paralleling the clinical regression of the lesions. No pulsations could be recorded after the sixteenth day but a wide variation in vascular effect from one skin area to another was observed. Three to four days after conclusion of the treatment many lesions relapsed, showing an increase in pulse height. This was to a lesser degree also observed after treatment with betamethasone-17-valerate. The vascular effect of dithranol in paste and Goeckerman's therapy was measured by the piezoelectric method. A gradual reduction in pulse height following the regression of lesions was recorded by both treatments. Only a small change of the pulsating blood flow was observed by Goeckerman's therapy during the first 7 days of treatment.

The period of time needed for therapy until disappearance of pulsations varied from 12 to 16 days for hydrocortisone acetate, 5 to 7 days for betamethasone-17-valerate, 6 to 8 days for dithranol and 21 to 42 days for Goeckerman's method.

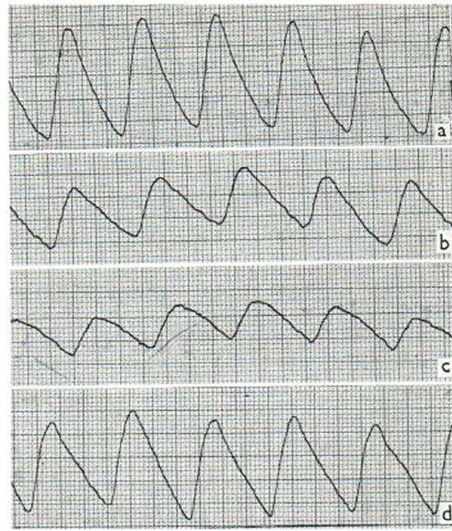


Fig. 3. Pulse recordings from psoriatic skin during treatment with hydrocortisone acetate 1%. (a) Before treatment; (b), (c) and (d) after 16, 20 and 48 hours' occlusion, respectively.

These periods corresponded with the clinical improvement of the disease. According to Wilcoxon rank sum test is $P < 0.01$ for the difference between the first and the sixth day for the various treatments (the first and the seventh day for Goeckerman's method).

Fig. 2 shows the results obtained after a single application of hydrocortisone acetate 1% and betamethasone-17-valerate 0.1% ointment, respectively. A clear difference in vascular action was demonstrated: $P < 0.01$ for the first to the sixth day. As mentioned above, the effect of the two ointments differed in that hydrocortisone acetate reduced the pulse height at 12 hours' occlusion

Table I. Effect of hydrocortisone acetate 1% ointment on the cutaneous blood flow in psoriasis (mean values)

Time	Left side		Right side	
	Pulse height (3 lesions)	Hours of occlusion	Pulse height (3 lesions)	Hours of occlusion
15.00	7.5	0	—	—
19.00	7.5	2	—	—
21.00	6.4	6	4.7	0
23.00	7.4	8	5.0	2
7.00	5.3	16	5.0	10
9.00	5.1	18	3.5	12
11.00	4.3	20	3.7	14
13.00	4.8	22	3.6	16
15.00	5.0	24	3.2	18

whereas betamethasone-17-valerate produced an increase. However, during the next 4 days a marked reduction was produced by the latter while the induced blanching disappeared within 1–2 days. Hydrocortisone acetate induced a much weaker vasoconstriction than did betamethasone-17-valerate and distinct reduction in pulse height was not constantly obtained. After treatment with the former substance the pulse waves increased to their previous height within 3 days (Fig. 2). After a single application of betamethasone-17-valerate under occlusion an increase in pulsation was noted from the fourth day but at the sixth day they had not yet reached their previous height.

Table I shows the effect of occlusive treatment with hydrocortisone acetate 1% as measured every second hour during 14 hours. The pulse height remained almost constant during the first 10 hours whereas a distinct reduction was recorded at 12 hours. The largest effect was observed after 18 to 20 hours (Fig. 3).

DISCUSSION

Percutaneous absorption of substances depends upon such factors as concentration, type of vehicle, solubility characteristics of the penetrating substance and the temperature. Furthermore, damage to stratum corneum by disease will result in a more rapid penetration from the surface to the dermis. An increase in cutaneous blood flow as observed in psoriasis, will maintain a large concentration drop across the skin favouring penetration. This will in part be counteracted by an induced vasoconstriction. Although most topical therapeutics are applied to diseased skin, little work has been done on penetration through the epidermis of patients with various dermatoses.

The variation in results observed in the present study between the various lesions may be associated with an uneven distribution of ointments under the occlusion, and with a variation in epidermal barrier and vascular reactivity. The latter shows individual and interindividual variations and must be considered when evaluating the data obtained. The blanching of the lesions observed after 12 hours of occlusive treatment with betamethasone-17-valerate is presumably related to decongestion of the papillary capillaries and reduction of the oedema in epidermis (14). The increase in pulsations recorded at this moment pro-

vides substantial evidence for this interpretation (19). After 24 hours treatment with betamethasone-17-valerate some reduction in pulse height occurred suggesting that constriction of the dermal vessels had already taken place.

The difference in vascular effect between hydrocortisone acetate and betamethasone-17-valerate is clearly illustrated (Fig. 2), the vasoconstrictive action of betamethasone-17-valerate being much stronger and of longer duration. No final conclusions concerning differences in percutaneous absorption can, however, be drawn from the present results.

Feldman & Maibach (5) using occlusive application of radioactive hydrocortisone on stripped skin, observed that the rate of urinary excretion of ^{14}C reached a peak during the first and second 14 hours and then gradually declined. Malkinson (10) found a very high and rapid loss of surface ^{14}C activity after application of radiolabelled hydrocortisone on stripped skin. Between 60 and 80% was absorbed within 4–6 hours when the steroid was covered with perforated aluminium eye patches.

Presumably, stripped skin may be compared with psoriatic skin although it is probable that more of the epidermal barrier is present in the latter condition. In the present study a lag time of 12 hours was observed for hydrocortisone acetate. Later a distinct vascular effect was recorded, indicating that the steroid had penetrated the epidermal barrier and reached the dermal vessels. The vascular action was almost constant during the second 12 hours and then gradually diminished during the next 2 days.

The reduced cutaneous blood flow observed in the first days during continued application of hydrocortisone acetate may be associated with constriction of the dilated dermal vessels as a primary effect of the steroid per se (8) or metabolites, occurring before regression of the epidermal changes takes place. After the fourth day there was a more gradual reduction in pulsatile blood flow parallel with the clinical improvement. This may be related to both (a) the normalization of the epidermis with a secondary regression of the vascular changes, and (b) the vasoconstrictive effect of the steroid. In favour of these considerations are the results obtained with betamethasone-17-valerate.

Following a single application of the latter

steroid, an increasing vasoconstriction was induced during 4 days' occlusion, suggesting a reduction in blood flow and a normalizing effect. On the fifth day the effect was brought to an end despite continued occlusion. These results clearly indicate a prolonged effect of the steroid and that vasoconstriction was in part responsible for the reduced vascularization. These data further support the interpretation of an increase in concentration of steroid or metabolites, adjacent to the pulsating vessels of the upper part of the papillary dermis. Vickers (21) using the vasoconstriction test, found no evidence of a reservoir in patients with psoriasis. This accords with the rapid disappearance of the blanching observed in the present study. Accordingly the induced pallor must be due to decongestion of non-pulsatile vessels.

Butler (3) measured the urinary excretion of radioactivity in 2 patients with psoriasis and in 1 with pemphigus after occlusive treatment with tritium-labelled betamethasone-17-valerate. Increasing amounts were found during the second and third day. These results are compatible with the increased vasoconstriction observed plethysmographically on the second and third day in the present study. Furthermore, the present findings accord with the results obtained by Des Groseillier et al. (4) after topical application of ^3H -betamethasone-17-valerate in the domestic pig. These authors reported the highest concentration of radioactivity in the plasma at the end of 72 hours.

Continued therapy with daily application of betamethasone-17-valerate normalized the pulsating cutaneous blood flow within a week. This data can be related to the microscopic findings described by other authors. Histologic examinations during occlusive therapy have revealed a persistence of the capillary changes (11, 12), but a distinction between functional and organic changes was not possible. Illig (7) using capillary microscopy, demonstrated persistence of capillary tortuosity without dilatation even in clinically blanched skin. This observation supports the hypothesis that the reduced vascularization observed during the first days was mainly of a functional character and due to the vascular effect of the steroid. This is all in accordance with the observed vasodilatation which occurs even within 24 hours of the conclusion of occlusive dressing therapy on the third day (18, 19). This assumption does not exclude the influence of an incipient nor-

malization of the epidermal changes. This influence is probably for the most part responsible for the rapid and gradual reduction in cutaneous blood flow observed within a week during occlusive treatment with betamethasone-17-valerate.

The question whether the reduced cutaneous blood flow recorded during the conservative treatments with dithranol and Goeckerman's method was primarily due to a vasoconstrictive effect of the therapeutics or was secondary to the normalization of the epidermis, might be debatable. It is possible that vasoconstriction was responsible in part for the effect obtained by dithranol, which almost equalled betamethasone-17-valerate in time required for clearing of the lesions. The action of coal tar, however, is still uncertain. Vasodilatation and hyperemia in the skin of tar-painted white mice have been observed by light microscopy (9). But owing to the fact that neither vasodilatation nor constriction could be demonstrated in the present study, it seems justifiable to relate the reduced vascularization observed during Goeckerman's therapy to the epidermal effect of the coal tar only. This interpretation is consistent with the small change observed during the first days of treatment. Further evidence is provided by the fact that the lesions did not relapse shortly after the therapy was discontinued.

The results obtained in the present study accord with the view that psoriatic vascularization follows the epidermal changes but no final conclusions can be drawn related to the site of the primary process.

Previous investigations (19) have shown that only small pulsations can be reported from normal skin adjacent to the psoriatic lesions by the photoelectric pulse meter used in this study. The increase in pulsatile flow observed in psoriatic skin is theoretically caused by dilated arterioles, metarterioles, open precapillary sphincters and the capillary changes. It is tempting to speculate whether the functional and organic changes of the papillary capillaries can be recorded plethysmographically and be separated from each other and from dilatation of the other dermal vessels. If the capillaries were pulsating one could expect a distinct reduction in the pulse amplitude after 24 hours' occlusive treatment. This would be even more evident on piezoelectrically recorded pulse waves which are induced by the pulsating skin surface and consequently by the arteriolo-

capillary pulse pressure. As described previously, the observed reduction in pulse height was very small, and constriction of pulsating capillaries would probably produce a larger reduction. Decongestion of non-pulsating capillaries, however, without constriction of the dermal vessels would induce an increase in pulse height (19). Since this did not occur, the pulsations in psoriatic capillaries may be neglected.

Our knowledge of what happens to the steroids in the period of time from skin traverse until measurements of radioactivity in the urine, leaves much to be desired. Periodic observations of residual activity of radioactive substances on the skin surface are valuable, but some percentage of error must be taken into account. Plethysmographic measurements are related to the vascular action of steroids occurring after penetration of the epidermal barrier and before they are removed by the blood stream. The results obtained in the present study are characteristic for psoriatic skin. A clear difference in action was demonstrated for hydrocortisone acetate and betamethasone-17-valerate, respectively, and it was also shown that the results obtained by a single application differed from those obtained by continued therapy. The two steroids were applied in different bases. Presumably this does not influence the penetration so much as the difference between the steroid molecules (6).

Photoelectric plethysmography on normal skin using a more sensitive photo-cell, has at present time been performed by the author (20). Further results to be described in a subsequent paper will presumably yield additional information concerning percutaneous absorption of steroids and the results can be correlated with the data already available.

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