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SYSTEMIC EFFECTS OF TOPICALLY APPLIED CORTICOSTEROID HORMONES

C.-G. HERDENSTAM

The increased use of new, potent corticosteroid hormones in the local treatment of many dermatoses, especially psoriasis, has given importance to the possible systemic side-effects due to absorption of the steroid through the skin.

In clinical and experimental research many parameters have been considered relevant as to a pituitary-adrenal suppression: (1) Eosinophil cell count in circulating blood. (2) Determination of the blood sodium and potassium levels. (3) Determination of the 24-hour excretion of urinary electrolytes. (4) Estimation of the 24-hour urinary excretion of 17-ketosteroids (17-KS), 17-hydroxycorticosteroids (17-OHCS) and 17-ketogenic steroids (17-KGS). (5) Determination of the 24-hour urinary dehydroepiandrosterone excretion. (6) Determination of the plasma level of free cortisol.

The *neutral 17-ketosteroids* in urine, which are characterized by a keto-group at C 17, consist mainly of androsterone, etiocholanolone, dehydroepiandrosterone and 11-oxysteroid metabolites. The first two steroids derive primarily from the testicles, while the last two substances merely originate from the adrenal cortex. Hence, the excretion of 17-ketosteroids does not simply reflect the adrenal function. The 24-hour urinary excretion of 17-ketosteroids is approximately 15 mg in male and 10 mg in female subjects, under normal conditions.

The *17-hydroxycorticosteroids*, characterized by the typical hydrocortisone side-chain at C 17, are represented by a limited number of corticosteroid hormones of great biologic importance. They are usually determined by the Porter-Silber method, which gives a normal 24-hour excretion of 2–10 mg. The urinary 17-hydroxycorticosteroid excretion may be of value in the diagnosis of adrenal cortex insufficiency.

The *17-ketogenic steroids* constitute a large and heterogenic group of corticosteroids, which according to Norymberski's technique can be converted into 17-ketosteroids. In this group glucocorticoid metabolites are found, deriving from cortisone and cortisol (hydrocortisone). The urinary 17-ketogenic steroid excretion reflects the total adrenal corticoid production with an average 24-hour excretion of 6–25 mg. A drawback of this method is the impossibility to separate the endogenic 17-ketogenic steroids—originating from the adrenal cortex—from the exogenic steroid metabolites. A conversion of corticosteroid hormones, absorbed through the skin, into urinary 17-ketogenic steroids might thus interfere with the excretion of adrenal corticoids and even camouflage a suppression of the adrenal activity.

With regard to the drawbacks in using the abovementioned urine assays, the determination of the urinary *dehydroepiandrosterone* excretion seems more adequate when evaluating the systemic side-effects of topical steroid treatment. The dehydroepiandrosterone is almost exclusively of adrenal origin and is not a product of intermediate metabolism. The wellknown difficulties in collecting 24-hour urine specimens quanti-

Department of Dermatology, Södersjukhuset, Stockholm, Sweden.

tatively makes, however, even this method somewhat demanding.

Comparative studies of *plasma cortisol levels* and urinary excretion of corticoids during local treatment with some of the new steroid ointments has definitely shown the plasma cortisol level to be a more sensitive and reliable indicator of pituitary-adrenal suppression (7). The decreased levels of plasma cortisol during steroid treatment are supposed to be due to suppression of pituitary corticotropine secretion. By administration of metopirone to patients with pituitary-adrenal suppression following local steroid treatment, the normal response two weeks after cessation of the treatment suggests that the pituitary suppression is temporary and reversible.

The introduction of the *occlusive dressing technique* as a powerful tool in the treatment of psoriasis, which markedly facilitates the percutaneous absorption of the steroid, initiated the first investigation in Scandinavia in this field of dermatologic basic research work: the study performed by Kirketerp (9), where the conclusion was drawn that fluocinolone acetonide in cream base applied under plastic film in psoriatics was absorbed in considerable amounts. These remarkable results were achieved in spite of the fact that the steroid cream was applied to apparently normal as well as to diseased psoriatic skin. In a more recent study, where the pituitary-adrenal function was appropriately investigated after application under plastic film of different steroid ointments merely to diseased skin, the suggestion was made that, under certain circumstances, the percutaneous absorption of steroids might be much higher than previously suspected and that a given steroid dose might even be more potent when administered percutaneously than when given intermittently by the oral route (18). A similar view was held by Taylor *et al.* (21) after investigation of the pituitary-adrenal suppressive effects of small doses of triamcinolone acetonide applied topically to psoriatic skin under occlusive dressings. In this study it was assumed that topical application of steroids with occlusion probably provides a continuous inward passage of steroid hormones followed by prolonged or cumulative elevation of the blood steroid levels. This condition might thus be analogous to continuous low-dosage intravenous infusion.

The occlusive dressing technique now seems to be less often used in Sweden than earlier mainly due to side-effects such as severe skin infections (17), skin atrophy (e.g. 5) and atrophic striae (1) but also because of the introduction of a new potent corticosteroid, betamethasone valerate with a marked effect in psoriasis even without occlusion (3). Consequently, the main interest is linked to the possible pituitary-adrenal suppressive effects of the newer corticosteroid ointments used *without occlusive dressings*.

Regarding the mechanism of corticosteroid absorption into the skin, the conditions in the normal skin seem fairly well elucidated. According to Scott and Kalz (19) the passage through the skin occurs mainly via the transepidermal and transappendageal routes, the latter implying absorption essentially through the pilosebaceous apparatus. Among the many factors affecting the absorption from a steroid ointment, the vehicle in which the steroid is dispersed and the concentration of the steroid play dominant roles. Moreover, increased skin temperature and hyperemia with increased blood flow facilitates the percutaneous absorption. Occlusive dressings might act in the same way by enhancing the absorption by interference with local heat loss and a certain degree of vasodilation. Rate-limiting factors are, however, also involved in the absorption mechanism. First, the epidermal barrier has been regarded as a rate-controlling step located in the stratum corneum (4). The existence of an epidermal barrier has been confirmed by stripping experiments, where up to 80 % of topically applied C^{14}-hydrocortisone was found to enter the stripped skin within some hours in sharp contrast to the much lower absorption in normal skin (12). Furthermore, a reservoir, from which topically applied steroids can be slowly released, has been shown to exist in the nor-

mal stratum corneum (22).

In the diseased skin, as for example in psoriasis, the situation is, however, quite different. First of all we do not know to what extent the epidermal barrier is damaged. Secondly, the enormous dilation and increased tortuosity of the capillaries in the psoriatic skin, which probably makes the vessels less responsive to vasoconstriction, might enhance the uptake of corticosteroids in the blood stream. According to a recent investigation of the NaI^{131}-clearance from psoriatically involved skin, a significantly higher than normal exchange of metabolites between blood and tissue was found; this finding was supposed to be related to the capillary abnormalities with extensive transendothelial exchange (2). Moreover, other morphologic changes in diseased skin—as for example the parakeratosis or the spongiosis in eczema—may also influence the percutaneous absorption.

Early clinical and experimental investigations failed to reveal any systemic effects after application of hydrocortisone to large areas of normal or diseased skin. After the introduction of C^{14}-labeled hydrocortisone a percutaneous absorption of less than 2 % was, however, found to occur in normal skin (10). A much higher penetration of the skin was registered when using fludrocortisone, with subsequent inhibition of the pituitary-adrenal function (11). After withdrawal of this ointment the literature on systemic effects of topical use of corticosteroid ointments without occlusion has been rather fragmentary. Yet, it was demonstrated by Livingood (10) that in inflammatory dermatoses as much as up to 15 % of C^{14}-labeled hydrocortisone was absorbed.

It seems reasonable that in certain skin disorders, e.g. psoriasis, the epidermal barrier might be almost as damaged as in stripping experiments, thus promoting the absorption of the steroid. When evaluating the possible risks for systemic effects after topical use of a steroid ointment we must, however, consider the fact that different corticosteroid compounds behave in quite different ways in this respect. It was mentioned above that fludrocortisone was found to penetrate the skin very easily with subsequent pituitary-adrenal suppression. On the other hand, flumethasone pivalate[1] and flurandrenolone acetonide[2] have not been found to exert any systemic effects after topical use even on very extensive areas of the skin under plastic occlusion (6, 8, 13). With regard to betamethasone valerate,[3] which steroid as pointed out earlier is a most potent anti-psoriatic drug (3), any data indicating a pituitary-adrenal suppression have not yet been reported after topical use without occlusion.

The penetrability and relative potency of different steroid compounds may simultaneously be determined by the vasoconstriction test developed by McKenzie and Stoughton (16). The vasoconstriction produced in normal skin by topically applied steroid dilutions appears to be a physiological response to the permeation of the steroid through the skin. It is, however, not known whether the corticosteroids produce vasoconstriction directly or whether this effect is mediated via catecholamines. According to Solomon *et al.* (20) the steroids may be capable of releasing noradrenaline from cutaneous stores.

By comparing the vasoconstriction effect of a series of 20 steroid preparations it has been shown by McKenzie (15) that acetates are better absorbed than the parent alcohol and that, in the case of triamcinolone, the synthesis of the acetonide promotes a greatly enhanced percutaneous absorption. In the same investigation flurandrenolone proved to be 10 times more effective than hydrocortisone acetate on weight-to-weight basis, while the acetonide of triamcinolone and fluocinolone were 100 times more active.

From a clinical point of view it is emphasized that the usual adverse effects of steroid therapy with Cushingoid changes, peptic ulceration or osteoporosis not have

[1] Locacorten®, Ciba.
[2] Drocort, Lilly.
[3] Celestona Valerate, Schering corporation.

been noted to date after topical steroid therapy (14). This might perhaps be explained by metabolization of the steroid absorbed in the skin or by inactivation of an active steroid compound before it has reached other organs. The fact that untreated contralateral skin lesions do not improve significantly following topical application of potent steroid ointments to certain areas in the same patient indicates, finally, that systemic effects are of minor importance after topical use of corticosteroid hormones. Conversely, the mentioned reports concerning obvious pituitary-adrenal suppression after topical application of steroids with occlusion, necessitates further investigations of the pituitary-adrenal function in the treatment of skin disorders with more and more potent steroid preparations even if occlusive dressings are avoided.

SUMMARY

A survey is made of published reports concerning pituitary adrenal suppression after topical use of corticosteroid hormones. The different laboratory assays for demonstration of systemic side-effects of topically applied corticosteroid hormones are discussed in detail.

It appears to be generally accepted that application of steroid ointments under occlusive dressings may enhance considerably percutaneous absorption of steroids. This type of treatment should therefore not be prescribed indiscriminately, especially since other side-effects can also be produced by this treatment. Topical use of the newer corticosteroid preparations—even without occlusion—may also have pituitary-adrenal suppressive effects.

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