Percutaneous Absorption of Hydrocortisone during Exacerbation and Remission of Atopic Dermatitis in Adults

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Percutaneous absorption of hydrocortisone was studied in 18 young adults during and after the acute phase of atopic dermatitis using the direct hydrocortisone absorption test. In the acute phase the post-application increase in serum cortisol concentration ranged between 18 and 711 nmol/l (median 125 nmol/l). In remission the increase in serum cortisol ranged between 0 and 114 nmol/l (median 16 nmol/l), which was significantly lower than the rise in the acute phase. In the acute phase of dermatitis, topical hydrocortisone treatment has both a local and a systemic effect, due to percutaneous absorption. *Key words: Hydrocortisone; Percutaneous absorption; Atopic dermatitis.* (Received January 11, 1988.)

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The main barrier to the percutaneous absorption of drugs is the stratum corneum (1–6). Stripping of the horny layer is known to increase the percutaneous absorption of hydrocortisone (2). Little quantitative information is available on how the penetration is influenced by diseased skin. Feinblatt et al. (7) have suggested that percutaneous absorption of labelled hydrocortisone is higher in children with atopic dermatitis than in children with normal skin. Bronaugh et al. (8) have shown in vitro that percutaneous absorption of hydrocortisone is twice as great through eczematous skin, as through normal skin. Turpeinen et al. (9) studied the percutaneous absorption of hydrocortisone in children by a direct method. High absorption occurred more often in children with severe skin disorder than in those with mild or moderate skin disease.

The purpose of the present study was to evaluate the effect of diseased skin on percutaneous absorption of hydrocortisone, by measuring the absorption during and after the acute phase of dermatitis by the direct method. No quantitative data on this topic have been available previously in adults.

METHODS

Patients

Twenty-four patients, 17 females and 7 males, with chronic atopic dermatitis were selected for the study. The age range of the patients was 16 to 44 years (mean = 25.2 years). The patients had been admitted to hospital because of exacerbation of the dermatitis. The state of the skin was scored by grading the erythema and excoriations separately: 0, none; 1, mild; 2, moderate; and 3, severe. The sum of the scores varied from 2 to 5 (mean = 4.0) in the acute phase of dermatitis. The extent of skin involvement was determined using the rule of nine, and it varied from 45 to 100% (mean = 75%) in the acute phase. The absorption test was performed twice on 18 patients: on the 3rd day after admission to hospital, and after the treatment, when the acute phase had subsided. The treatment consisted of 1% hydrocortisone cream and topical chlorhexidine and systemic antimicrobials, if infection was suspected. The dermatitis

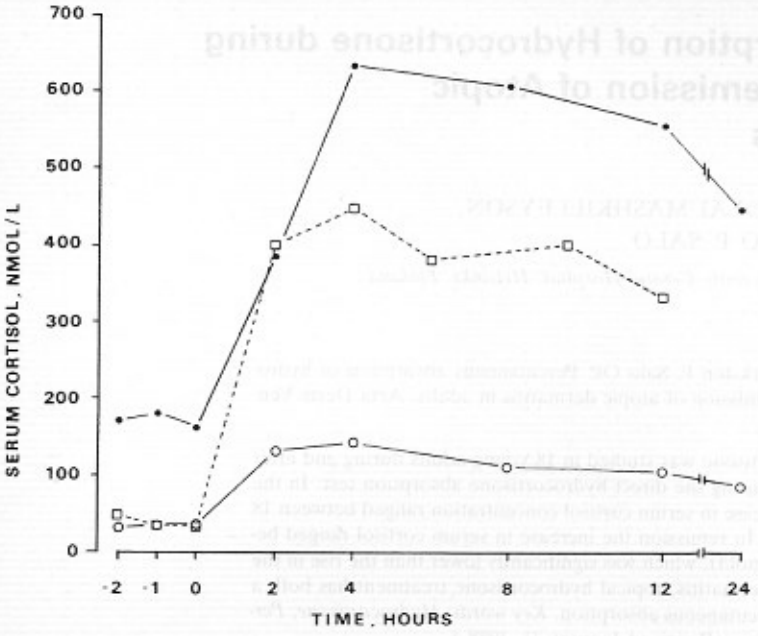

Fig. 1. Individual hydrocortisone 12 and 24 h absorption curves in the acute phase of dermatitis. Serum cortisol levels measured before (time −2, −1 and 0) and after application of 1% hydrocortisone cream. Patients: 1, ●—●; 2, ○—○; 3, □--□.

was brought to complete remission in all but one patient (no. 10: erythema 1/excoriations 0, extent 70%).

Serum cortisol determination

Serum cortisol levels were determined using [^{125}I]cortisol radio-immunoassay kit manufactured by Farmos Diagnostica, Turku, Finland. In this test the cross-reactivity with dexamethasone is less than 0.005%.

The absorption tests

Patients were hospitalized initially without topical glucocorticoid for 48 h prior to the test. The principles of the absorption test have been presented previously in an article on children (9). Endogenous secretion of cortisol was suppressed with dexamethasone. The patients received 1 mg dexamethasone p.o. at 7 p.m., 1 a.m. and 7 a.m. before the first blood sample, which was taken at 8 a.m. Thereafter dexamethasone was given every 6th hour until the last sample as taken. The blood samples for determination of serum cortisol were drawn either through an intravenous plastic cannula or through skin areas to which hydrocortisone cream had not been applied.

Hydrocortisone, 1%, was applied in a proprietary cream base containing Vaseline alb., Macrogol. 400, Cetostearol., Cetomacrogol. 1000, Methyl. parahydroxybenz. with 60% water content. No occlusion was used. The amount of cream used was 50 g during the acute phase, except for patients 3 and 4, who received 80 and 120 g, respectively. The same amount of cream was used in both tests.

In 2 patients, serum cortisol was measured during 24 h and in one patient during 12 h after application. A 4 h absorption test was developed on the basis of these findings and this was performed on the remaining 21 patients. To evaluate the effect of stress due to venipuncture during dexamethasone suppression, serum cortisol was measured 1 h and 2 h before and immediately prior to the application of 1% hydrocortisone cream. The highest acceptable basal cortisol value under suppression was 200 nmol/l (9, 10). Altogether 42 absorption tests were performed.

Statistics

Statistical comparison of the groups was performed using Wilcoxon's signed rank test for paired data and the Mann-Whitney test for unpaired data.

RESULTS

The effect of the adrenocortical suppression caused by dexamethasone is seen in the subnormal (<200 nmol/l) basal levels of serum cortisol in all the 42 absorption tests (mean 72±47

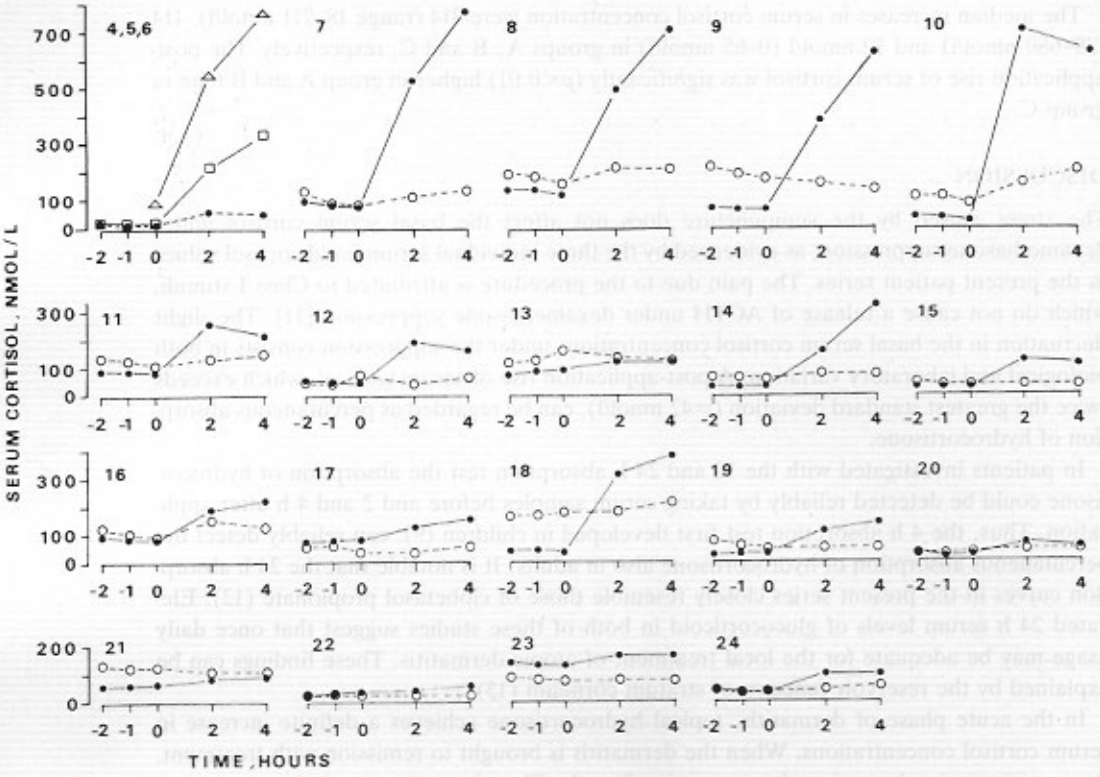

Fig. 2. Individual 4 h absorption curves. Serum cortisol levels measured before (time −2, −1 and 0) and 2 and 4 h after application of 1% hydrocortisone cream. Patients: 4, △—△; 5, □—□; 6, ●--●, in whom the test was performed only in the acute phase. In patients 7–24 the test was performed during exacerbation (●—●) and remission (○--○) of dermatitis.

nmol/l, range 20–180 nmol/l). The individual basal levels (0) are seen in Figs. 1 and 2. To evaluate the effect of stress due to venipuncture during dexamethasone suppression, serum cortisol was measured 1 and 2 h before and immediately prior to the application of hydrocortisone cream (Figs. 1 and 2). The standard deviation (SD) of these values varied between ±1 and ±21 nmol/l between the patients.

The individual 24 and 12 h absorption curves are presented in Fig. 1. The highest serum cortisol level was reached within the first 4 h. In these patients, serum cortisol 12 and 24 h after application was 2–10 times as high as the basal cortisol level. The individual results of the 4 h absorption tests are presented in Fig. 2. In 18 patients the test was performed during the acute phase of dermatitis and also after the dermatitis was brought to remission. In the acute phase the maximal post-application rise of serum cortisol varied between 18 and 711 nmol/l (median 125 nmol/l). In remission, the maximum ranged from 0 to 114 nmol/l (median 16 nmol/l) and it was significantly ($p<0.01$) lower than in the acute phase.

On the basis of the clinical characteristics of the dermatitis at the time of the absorption test, the patients were divided into three groups:

A) 18 patients with widespread (>/ = 40%, mean 78%) and high grade (the sum of erythema and excoriation scores 4–5, mean 4.4) dermatitis;
B) 7 patients with widespread (mean 61%) and low grade (score 1–3, mean 2.6) dermatitis;
C) 17 patients with dermatitis in complete remission (extent 0%, score 0).

The median increases in serum cortisol concentration were 314 (range 18–711 nmol/l), 114 (29–680 nmol/l) and 10 nmol/l (0–65 nmol/l) in groups A, B and C, respectively. The post-application rise of serum cortisol was significantly ($p<0.01$) higher in group A and B than in group C.

DISCUSSION

The stress caused by the venipuncture does not affect the basal serum cortisol under dexamethasone suppression, as evidenced by the three individual serum basal cortisol values in the present patient series. The pain due to the procedure is attributed to Class I stimuli, which do not cause a release of ACTH under dexamethasone suppression (11). The slight fluctuation in the basal serum cortisol concentrations under the suppression consists in both biological and laboratory variation. A post-application rise of serum cortisol, which exceeds twice the greatest standard deviation (=42 nmol/l), can be regarded as percutaneous absorption of hydrocortisone.

In patients investigated with the 12 and 24 h absorption test the absorption of hydrocortisone could be detected reliably by taking serum samples before and 2 and 4 h after application. Thus, the 4 h absorption test first developed in children (9), can reliably detect the percutaneous absorption of hydrocortisone also in adults. It is notable that the 24 h absorption curves in the present series closely resemble those of clobetasol propionate (12). Elevated 24 h serum levels of glucocorticoid in both of these studies suggest that once daily usage may be adequate for the local treatment of atopic dermatitis. These findings can be explained by the reservoir function of stratum corneum (13).

In the acute phase of dermatitis, topical hydrocortisone achieves a definite increase in serum cortisol concentrations. When the dermatitis is brought to remission with treatment, the percutaneous absorption decreases significantly. The absorption levels in severe and moderate dermatitis resemble those in children aged 18 months or over, while they are clearly lower than the absorption levels in children under 18 months of age (14). In complete remission of dermatitis, the absorption was very low; the post-application increase in serum cortisol was below the sensitivity limit of the absorption test in most of the patients. This is consistent with the previously observed minimal percutaneous absorption of hydrocortisone through healthy adult skin (15). The restoration of the barrier function of the skin to glucocorticoids during the treatment has also been suspected previously (16). The severalfold difference in absorption noted within the groups of severe and moderate dermatitis in the present study might partly be explained by individual differences in the skin inflammation. However, severalfold individual variation in absorption of hydrocortisone has also been found through normal adult skin (15). An additional explanation could be the different systemic or cutaneous metabolism of steroids in different individuals (17–21).

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