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EFFECT ON PLASMA CORTISOL LEVEL AND URINARY CORTISOL EXCRETION, IN HEALTHY VOLUNTEERS, AFTER APPLICATION OF THREE DIFFERENT TOPICAL STEROID OINTMENTS UNDER OCCLUSION

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Abstract. The systemic effect of the topical glucocorticoid ointments budesonide 0.025% (Preferid®), hydrocortisone-17-butyrate 0.1% (Locoid®) and betamethasone-17,21-dipropionate 0.05% (Diproderm®) was studied in 9 healthy volunteers. Five g ointment was applied on about 13% of the total body surface, using occlusive technique for three consecutive nights. The cortisol values in plasma and urine were measured before, during, and 3 days after applications. Although budesonide and betamethasone-17,21-dipropionate are equipotent drugs from a therapeutic point of view, the halogenated betamethasone-17,21-dipropionate caused significantly greater decrease in both plasma- and urinary cortisol levels. Between the two non-halogenated glucocorticosteroids, budesonide and hydrocortisone-17-butyrate, no significant difference was found despite the large difference in anti-inflammatory effects. The results indicate that it is possible to improve the ratio between the local therapeutic effect and the systemic activity of a glucocorticosteroid. Budesonide represents such an improvement.

Key words: Budesonide; Hydrocortisone-17-butyrate; Betamethasone-17,21-dipropionate; Ointment; Healthy volunteers; Adrenal suppression; Cross-over study

During the development of glucocorticosteroids, increased potency has been achieved by substitution with one or several halogen atoms in the steroid skeleton, but at the cost of increased systemic activity. The use of potent, topical steroids has therefore focused attention on the systemic side effects (6, 11). Recently, a non-halogenated glucocorticosteroid, budesonide (Fig. 1), was synthesized (14). Pharmacological, pre-clinical, and clinical studies indicate that budesonide is a potent glycocorticosteroid (1, 5, 7, 8, 13) and can be classified as a group III steroid (2).

For a true comparative systemic effect study between several drugs, it is necessary to use a cross-over design. Only normal skin is suitable for this type of trial; the barrier does not alter under test conditions as it does in the diseased skin. The investigation time should be kept to a minimum to avoid any risk of damage to the HPA axis of the volunteers. We therefore administered the ointment at night when the ACTH release is most sensitive to suppression (12) and used occlusive bandage to enhance the penetration.

In the present study, we compared the cortisol-suppressive effect of three drugs: the non-halogenated budesonide (BUD) 0.025% ointment which is therapeutically equipotent (group III) with the halogenated betamethasone-17,21-dipropionate (BDP) 0.05% ointment (5). As a reference we used another non-halogenated but clinically less potent steroid (group II) hydrocortisone-17-butyrate (HCB) 0.1% ointment which has a relatively mild systemic effect (9).

This investigation aimed at finding whether the separation of anti-inflammatory and systemic effects found in the pharmacological investigations with budesonide is also relevant in man (4).

MATERIALS

Eleven healthy male volunteers participated in the study; mean age 26 years (range 21–37), mean weight 74 kg (range 59–89). Before the study, they underwent a thorough clinical and laboratory investigation. Written consent was obtained. The participants were instructed to avoid stress of any kind, to arrive at the clinic 30 minutes before the blood test, to avoid medication and alcoholic drinks, to keep a constant sleep–wake cycle, and to avoid warm, humid, or cold environment.

The proprietary ointments tested were obtained commercially: Diproderm® 0.05% (betamethasone-17,21-

* A subsidiary of AB Astra, Sweden.

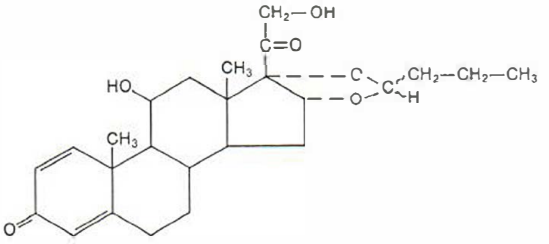

Fig. 1. Structural formula of budesonide [16α, 17α-(22R,S)-propylmethylenedioxypregna-1,4-diene-11β,21-diol-3,20-dione].

dipropionate) ointment; Schering Corp., USA. Locoid® 0.1% (hydrocortisone-17-butyrate) ointment; Gist-Brocades, The Netherlands.

Preferid® 0.025% (budesonide) ointment, containing mineral oil, propylene glycol, white petrolatum and white wax; Tika, Sweden. Placebo ointment, with the same components; Tika, Sweden.

METHODS

Plasma cortisol was analysed with two different techniques: Radioimmunoassay (RIA) (NEN, New England Nuclear, North Billerica MA 01862, USA) was used for immediate determinations. Gas chromatography–mass spectrometry (GC–MS) was used because of its specificity for the final evaluation of plasma- and urinary cortisol. A separate comparative study between these two techniques was made (10).

After a medical investigation, the basal plasma- and urinary cortisol levels of 14 volunteers were tested on 2 days in succession.

To be able to compare the ability of the topical glucocorticosteroids to suppress cortisol production, the dose used should not suppress the cortisol completely but only sufficiently for reliable calculations.

The first part of the investigation was to establish whether 10 g of ointment was an appropriate dose. Ten g of each preparation was applied under occlusion for one night. Plasma- and urinary cortisol were measured before and after the treatment. Two out of 4 subjects treated with BDP showed a marked cortisol suppression (44 and 47 nmol/l, normal values: 150–700 nmol/l). The results indicated that 10 g of ointment would be too much for a 3-night period.

Eleven of the 14 subjects participated in the second part of the investigation. Nine subjects received the same topical steroid as before but with only 5 g, while 2 received placebo ointment. Applications were made on three consecutive nights (4 p.m. – 8 a.m.). After a wash-out period of 11 days, a new application of ointment was made with another preparation. The first application day for each preparation was always the same day of the week (Tuesday).

The cross-over design for 9 of the volunteers was made in the following order (3 subjects in each group): I: BUD, BDP, HCB; II: BDP, HCB, BUD; III: HCB, BUD, BDP. Two subjects were treated with placebo ointment at every application. The trial was kept blind for the volunteers, i.e. single blind.

Five g of ointment was evenly dotted out on about 13% of the body surface and smeared (Fig. 2). The area was covered with polyethene wrap and elastic bandage (Surgifix) for 16 hours. At 8 a.m. after the blood test, all ointment was removed with a washing-up detergent (pH 7) as emulgator. The ointment was rinsed away under a warm shower. Blood samples were drawn at 8 a.m. ±5 min (Tuesday–Sunday) from each subject. A skilled nurse applied the needle. The plasma was sampled for immediate cortisol analysis (RIA), and for GC–MS determinations. The rapid RIA technique made it possible to withdraw, if necessary, volunteers with severe cortisol suppression. 24-hour urinary collections, started in connection with the first ointment application at 4 p.m., were sampled until 4 p.m. next day. The urine samples were stored at −20°C until the trial was over.

The statistical calculations were analysed with two-sided Student's *t*-test.

RESULTS

Fig. 3 shows the results of the plasma- and urinary cortisol determinations. BUD and HCB caused less decrease of the plasma cortisol level (at the most 50%) than the halogenated BDP (at the most 96%). BUD and HCB were not significantly different at any time. Six volunteers out of 9 had to be withdrawn after 2 nights' treatment with BDP because of too low cortisol values. They are accounted

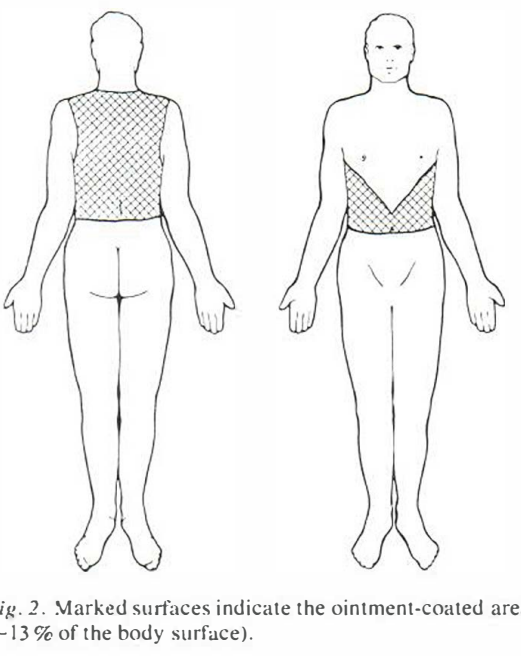

Fig. 2. Marked surfaces indicate the ointment-coated area (~13% of the body surface).

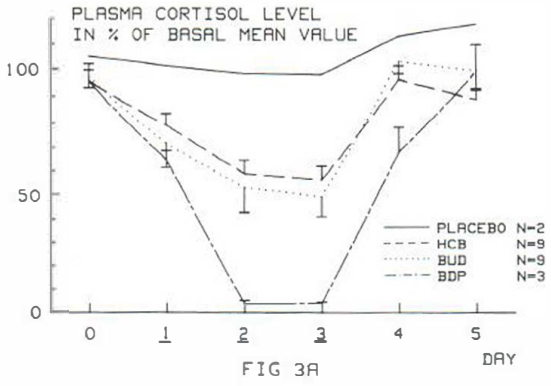

FIG 3A

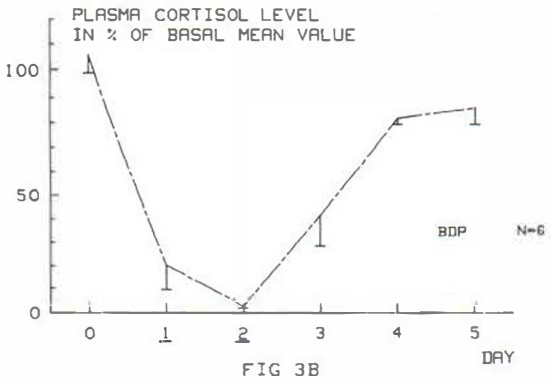

FIG 3B

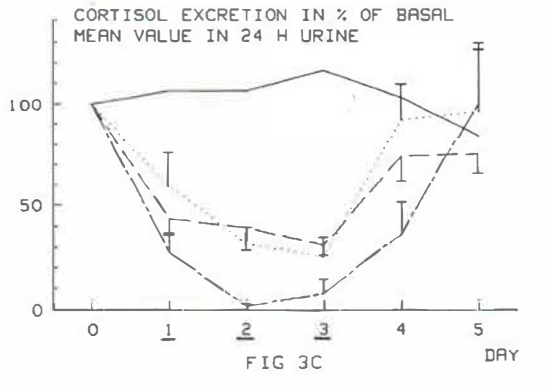

FIG 3C

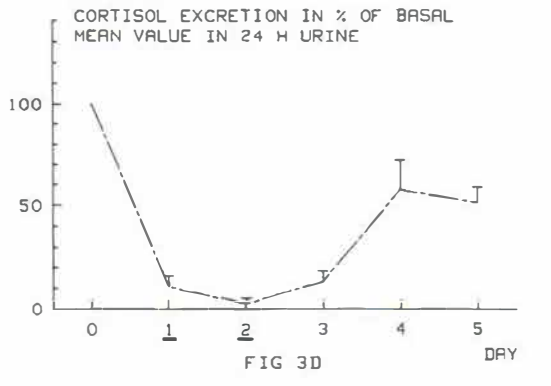

FIG 3D

Fig. 3. Changes in plasma- and urinary cortisol as percentage of basal mean value after 1–3 nights of occlusion (A, C), and after 1–2 nights' occlusion with Diproderm (B, D). Starting values for plasma cortisol were taken and are marked in A and B with S.E.M. values (day 0). Underlined days indicate treatment days. In C, $N=8$ on day 5 for budesonide and hydrocortisone-17-butyrate.

for separately in the figure. A comparison of the plasma cortisol suppression between BDP and BUD for the first 2 days' occlusion (N=9) showed that the difference after both 1 and 2 days' occlusion was statistically significant ($p<0.001$ and $p<0.01$ respectively). A corresponding comparison between BDP and HCB gave $p<0.01$ and $p<0.001$ respectively.

A satisfactory recovery followed within 3 days for BDP after 2–3 days' occlusion and within one day for BUD and HCB after 3 days' occlusion (Fig. 3 A and B).

The 24-hour urinary cortisol excretion was significantly lower with BDP ($N=9$) on the second occlusion day compared with both BUD and HCB ($p<0.01$). The 6 volunteers with only 2 days' occlusion with BDP had very low cortisol excretions from the first occlusion day to one day after the treatment. They had not recovered on the fifth day of the trial ($p<0.01$).

The normal cortisol synthesis can easily be affected by stress of different kinds. The occlusion in itself is perhaps a contributing factor. The 2 volunteers who only received placebo ointment throughout the trial acted as a control of this stress factor. However, their cortisol values indicate that no such stress occurred from the occlusion.

DISCUSSION

The antipsoriatic effect of budesonide is documented in studies with betamethasone-17,21-dipropionate and hydrocortisone-17-butyrate as reference drugs (5, 8 and four reports to be published). These clinical studies have indicated that budesonide is superior to hydrocortisone-17-butyrate and at least as effective as betamethasone-17,21-dipropionate.

The relation between local therapeutic effect

and systemic activity for different steroid drugs has until now been hard to evaluate due to the lack of cross-over design in the studies. The suppressive effect, however, is documented separately for both betamethasone-17,21-dipropionate and hydrocortisone-17-butyrate (6, 9).

It must be emphasized that comparative studies (cross-over) cannot possibly be performed in patients suffering from any type of steroid-sensitive dermatosis because of gradual alteration of the barrier, and also intra- and inter-individual variations of the lesions.

The present study was performed in healthy volunteers and presumably their skin barrier function is normal. The relevance of this study for diseased skin is not known. In some respects, the occlusive technique imitates a defective barrier. The large decrease in plasma cortisol in 6 out of 9 subjects already after one night's occlusion with betamethasone-17,21-dipropionate clearly demonstrates the inter-individual variations resulting in differences in the percutaneous absorption of steroids.

The object of topical steroid therapy is to deliver a therapeutically effective dose of steroid to the target organ with the least possible disturbance to other parts of the body. The present results show that it is possible to improve the ratio between local therapeutic effect and systemic activity.

An explanation of this favourable relation is the rapid liver biotransformation rate of budesonide which has been verified with in vitro experiments in both rat and human liver (3).

To conclude: Preferid is the first non-halogenated potent (group III) steroid with an improved ratio between local therapeutic effect and systemic activity.

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