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0.25 % Prednicarbate cream and the corresponding vehicle induce less skin atrophy than 0.1 % Betamethasone-17-valerate cream and 0.05 % Clobetasol-17-propionate cream

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Summary. The atrophogenic potential of medium-potent topical glucocorticoids is still controversial. In a double-blind controlled trial 24 healthy volunteers either applied 0.25 % prednicarbate cream or the corresponding vehicle to one and 0.1 % betamethasone-17-valerate cream or 0.05 % clobetasol-17-propionate cream to the other forearm twice daily. Skin thickness was regularly assessed during the six week period of application and for further three weeks thereafter, using both the B- and A-mode of a 20 MHz ultrasound scanner.

Both betamethasone-17-valerate and clobetasol-17-propionate cream significantly reduced skin thickness as compared to cream base while prednicarbate cream did not.

Given that 0.1 % betamethasone-17-valerate- and 0.25 % prednicarbate cream are reported to be about equipotent in the treatment of atopic eczema the latter preparation shows an increased ratio between its desired anti-inflammatory and its unwanted atrophogenic effect.

Key words: Skin atrophy, Prednicarbate cream; ultrasound, betamethasone-17-valerate-cream, clobetasol-17-propionate cream, adverse effects, skin atrophy

Skin atrophy resulting from the topical application of fluorinated glucocorticoids was described by Epstein et al. in 1963 [1], and since then the induction of skin atrophy has been considered to be one of the major local adverse effects due to glucocorticoids [2]. In the early days the wanted and unwanted effects of topical glucocorticoids were thought to be closely linked, subsequently new congeners were developed that showed dissociation of these effects. The frequently used topical glucocorticoid betamethasone-17-valerate is an early result of this type of work [3].

Attention has now been switched to esterified rather than fluorinated glucocorticoids in the search for new potent congeners [4]. Prednisolone-17-ethyl carbonate-21-propionate, i.e. prednicarbate, belongs to this new type of steroidal drugs. In a controlled clinical trial 0.25 % prednicarbate cream and 0.1 % betamethasone-17-valerate cream were found to be about equally potent both in atopic and contact eczema [5], but it was suggested that prednicarbate did not induce skin atrophy when applied twice daily to normal forearm skin over a period of 12 months [6]. This finding was based on macroscopy and microscopy. Ultrasound investigations were also done to evaluate the atrophogenic potential of prednicarbate, initially proposed by Tan et al. [7]. Current evidence is conflicting; according to Dykes et al. [8], 0.25 % prednicarbate cream did not reduce skin thickness more than the corresponding vehicle, or significantly less than 0.1 % betamethasone-17-valerate and 0.025 % fluocinolone acetonide cream. Lubach and Gryter [9] found that 0.25 % prednicarbate cream reduced skin thickness about as much as 0.1 % amcinonide cream and markedly more than white vaseline. Both trials were based on measurements made with early ultrasound equipment, with which only A-mode imaging was possible.

A controlled trial has now been done comparing prednicarbate cream, its vehicle and other potent glucocorticoids for their skin thinning potential using more advanced equipment and B-mode images.

Materials and methods

In this double-blind controlled trial, based on a design approved by the local Ethical Committee and complying with the requirements of the Helsinki declaration, 24 healthy adult volunteers (12 m, 12 f, aged 24 to 34 y, mean age 29.5 (4.75) y) applied two out of a total of four different glucocorticoid or base preparations to their forearms.

The four treatments were:

A) 0.25 % prednicarbate cream,

B) corresponding vehicle (cream base composed of paraffin oil, octyldodecanol, polysorbate 60, sorbitan monostearate, lactic acid, edetic acid, purified water, benzylalcohol and stearic acid),

C) 0.1 % betamethasone-17-valerate cream,

D) 0.05 % clobetasol-17-propionate cream.

Each volunteer applied either Preparation A or B to one forearm and Preparation C or D to the other, according to a partially balanced incomplete block design. Allocation of treatments to the left and right forearms was at random. Thus, each treatment modality was applied to the right forearm of six and the left forearm of six additional volunteers. Both in the morning and in the evening about 0.1 g of the test preparation was applied to an area of 4 × 4 cm, on the flexor side of the forearm close to the elbow. To dispense the drug 1 cm cream was extracted from its container and distributed

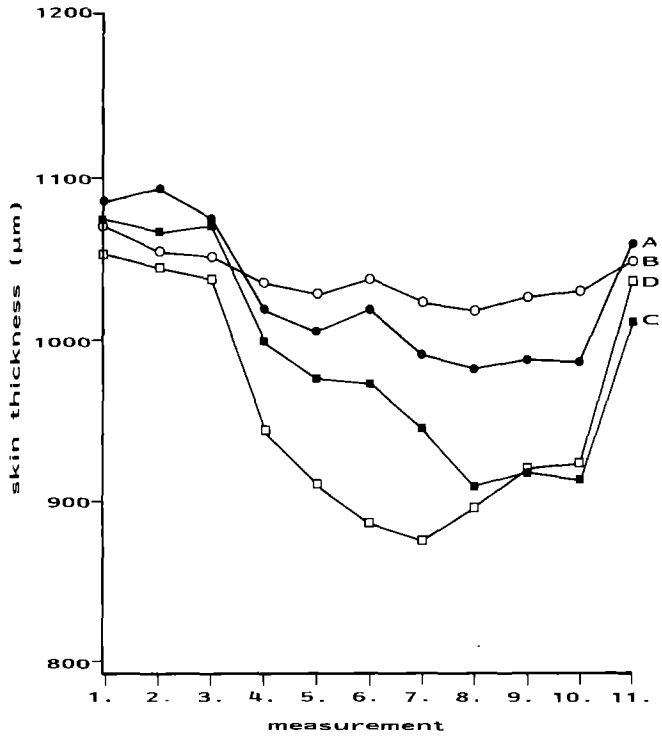

Fig. 1. Skin thickness before, during and after application of prednicarbate cream *(A)*, its corresponding base *(B)*, betamethasone-17-valerate cream *(C)* and clobetasol-17-propionate cream *(D)* as assessed by ultrasound. ● Predicarbate cream (0.25%) ○ corresponding vehicle ■ betamethasone-17-valerate cream □ clobetasol-17-propionate cream

evenly over the test area, using the index finger protected by a disposable glove. The test area was left uncovered for 10 min and it was not cleansed for the following 2 h. The treatment period comprised 6 weeks. Both test areas were inspected on Days 0 (before treatment), 4, 7, 14, 21, 28, 35, 42 (end of treatment) and 63. Analysis included both visual assessment of skin thinning and other potential adverse effects, such as telangiectasia and dryness (exsiccation). Skin thickness was assessed using ultrasound. For safety reasons the application of a treatment modality was discontinued as soon as skin thinning, telangiectasia or marked dryness were seen on inspection, or as soon as the reduction in skin thickness exceeded 40%. The trial design by and large reflected that described by Tan et al. [7].

To assess skin thickness ultrasonic A- and B-scanning were combined [10], using the DUB 20 system (Taberna pro Medicum, Lüneburg, FRG). The system comprises an applicator with a 20 MHz transducer (straight line 12.8 mm), a 20 MByte personal computer to store 10 images each on a 1.2 MByte floppy disc, and a 28 × 21 cm monitor (resolution 640 × 480 pixels) giving seven different pseudocolour images representing 256 different shades. When applied to the skin surfaces the system scanned a straight line of 12.8 mm with an axial resulution of 8 mm. The straight line investigated lay in the middle of the test area, parallel to the axes of the forearm. At each time the B-mode image was used to select five different spots where A-mode images were analyzed for skin thickness, which was defined as the thickness of both the epidermis and corium. These two layers were not analysed separately.

For statistical analysis the mean and standard deviation of the five values were calculated for each time point. The data were subjected to bi-variate analysis for independent samples. $P < 0.05$ was considered significant.

Results

Whilst skin thickness was similar at the sites investigated before treatment, it came to differ markedly after to weeks according to treatment (Tab. 1). Both 0.05% clobetasol-17-propionate cream and 0.1% betamethasone-17-valerate cream reduced skin thickness more than either 0.25% prednicarbate cream or the corresponding vehicle. Although the reduction in skin thickness was larger after clobetasol-17-propionate 0.05% cream than betamethasone-17-valerate cream, and after prednicarbate cream than the corresponding vehicle, these differences were not significant (Table 2). The evolution of skin thickness relative to its initial value under the different treatment modalities is shown in Fig. 1. A characteristic B-mode image in a volunteer who had applied prednicarbate cream for six weeks is illustrated in Fig. 2. The corresponding appearances after betamethasone-17-valerate cream for six weeks are shown in Fig. 3.

Analysis was generally based on the data obtained from 12 volunteers using each treatment. With clobetasol-17-propionate, however, the application had to be stopped before the end of the intended 6 weeks period in 10 out of 12 individuals (in 1 on Day 14, and in 9 on Day 21). Treatment was stopped once be cause of the ap-

Table 1. Time course of mean skin thickness mm with (standard deviation) before, during and 3 weeks after the application of prednicarbate cream, its corresponding base, betamethasone-17-valerate cream and clobetasol-17-propionate cream in healthy volunteers

Order of measurement	Group A	Group B	Group C	Group D
1st	1.075 (0.131)	1.051 (0.100)	1.072 (0.104)	1.037 (0.111)
2nd	1.019 (0.083)	1.035 (0.102)	1.00 (0.099)	0.944 (0.105)
3rd	1.005 (0.077)	1.028 (0.121)	0.976 (0.084)	0.910 (0.121)
4th	1.019 (0.120)	1.037 (0.102)	0.973 (0.095)	0.886 (0.116)
5th	0.991 (0.081)	1.023 (0.144)	0.945 (0.073)	0.875 (0.132)
6th	0.982 (0.078)	1.018 (0.109)	0.909 (0.079)	0.896 (0.109)
7th	0.988 (0.069)	1.027 (0.120)	0.918 (0.079)	0.919 (0.132)
8th	0.986 (0.069)	1.030 (0.118)	0.914 (0.079)	0.923 (0.141)
9th	1.060 (0.069)	1.049 (0.118)	1.013 (0.079)	1.036 (0.141)

Table 2. Analysis of variance comparing skin thickness before and after three and six weeks treatment with prednicarbate cream, its corresponding base, betamethasone-17-valerate cream and clobetasol-17-propionate cream

Comparison	Day 1	Day 21	Day 42
A/B	NS	NS	NS
A/C	NS	NS	*
A/D	NS	*	*
B/C	NS	*	*
B/D	NS	*	*
C/D	NS	*	NS

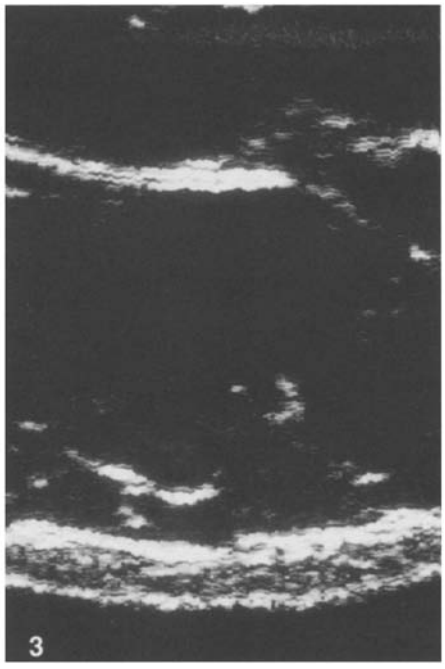

Fig. 2. B-mode image after application of prednicarbate cream for 6 weeks

Fig. 3. B-mode image after application of clobetasol-17-propionate cream for 6 weeks

pearance of initial telangiectasia and striae distensae, and in the other cases severe dryness was found.

Discussion

According to the present findings, open application of conventional potent, fluorinated, single-esterified topical glucocorticoids, such as betamethasone-17-valerate and clobetasol-17-propionate, markedly reduce the thickness of normal human skin when given twice daily for six weeks, whereas prednicarbate does not do so, all the glucocorticoids being used in conventional concentrations and (cream) preparations. This supports the findings of Dykes et al. [8]. Given that 0.25% prednicarbate cream is about as potent as 0.1% betamethasone-17-valerate cream in atopic eczema [5], it must be concluded that prednicarbate has an increased therapeutic index, at least in atopic eczema, i.e. an increased ratio between the desired anti-inflammatory action and the unwanted effect on skin thickness. To substantiate this conclusion further it would be helpful to perform a meta-analysis of previous experiences of both drugs in controlled trials. Skin atrophy should also examined by ultrasound in a comparative clinical trial in patients with atopic eczema.

Ultrasound analysis of skin thickness using both the B- and A-mode in general appears valuable in assessing changes in skin thickness in the presence of xenobiotics.

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