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Skin atrophogenic potential of methylprednisolone aceponate (MPA)

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Abstract

The most prominent and most discussed local side effect of topical corticosteroids is the thinning of the skin. Therefore, the atrophogenic potential is an important indication of the quality of a new corticosteroid. Several studies have been conducted to investigate this parameter. In rats, the effect of breaking strength of the skin, the most appropriate model for evaluating atrophogenicity in animals, showed that MPA and prednicarbate (PC) reduced the breaking strengh only slightly compared to clobetasol propionate (CBP). These results indicate that MPA could be classified as a corticosteroid with low local atrophogenic potential. This was confirmed in humans by a placebo controlled double-blind study comparing intra/interindividuals MPA (cream, ointment and fatty ointment) and bethamethasone-17-valerate (BMV), CBP and PC (cream only) under occlusive dressing over 6 weeks. Three different parameters were assessed (dermal atrophy (clinical picture), surfometric measurement of the dermatoglyphic pattern, visual evaluation of telangiectasia). In all three formulations, MPA is of lower atrophogenic potential than CBP. While there is no statistical difference between BMV and MPA, the atrophogenic potential of MPA is low. In order to reflect more the clinical use of topical corticosteroids, MPA preparations (cream 0.1% and fatty ointment) has been evaluated in comparison to BMV in an 8-week non-occluded application test. MPA was applied once a day (5 days a week) and BMV twice in 20 healthy subjects according to a double-blind randomized design. Assessment of atrophogenic potential was performed weekly using clinical scores (atrophy and telangiectasia) as main criteria and skin thickness measurements (ultrasound imaging) as a second criterion. BMV cream gives higher numbers of telangiectasia than MPA preparations and vehicles. From the skin thickness measurements, MPA treatments once a day has a lower thinning potential than BMV twice a day. These findings were confirmed by clinical trials. In 1145 patients suffering from various types of eczema who used MPA in cream and ointment, mild atrophy of the skin was observed in only one patient. Moreover, clinical signs of atrophy were present in only two out of a group of 673 patients (590 adult and 83 children) treated with MPA fatty ointment. In a group of 66 patients who used this same MPA

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fatty ointment during 3–4 months, no signs of skin atrophy were observed. Considering animal and human studies, MPA can be classified as a corticoid with low atrophogenic potential.

Key words: Skin atrophy; Topical corticotherapy; Ultrasound imaging; Methylprednisolone aceponate

Introduction

It is well known that topical corticoids may cause unwanted effects in the skin at the site of application, especially after long-lasting treatment. The most prominent and most discussed of these local side effects of topical corticosteroids is the thinning of skin (atrophogenic effect) [1–3]. The skin becomes shiny and transparent with highly dilated and blunt blood vessels. The appearance is so typical that an experienced physician would immediatly ask: 'which corticosteroid did you use and for how long?' [4].

If treatment is stopped after the first evidence of skin atrophy, the thinning is usually completely reversible. Extensive steroid-induced skin atrophy is clear evidence of unskilful treatment either by the physician or by self-administration by the patient. Therefore the atrophogenic potency in an important indication of the quality of a new corticosteroid.

Advantan is a new potent corticoid preparation that has been specially developed for the local treatment of corticoid-responsive dermatoses. The active ingredient is methylprednisolone aceponate (MPA). Three different formulations have been developed: cream, ointment and fatty ointment each containing 0.1% MPA. The preclinical toxicology of MPA does not reveal significant drug toxicity [5].

The question of an atrophogenic potential of MPA has been investigated extensively in animals, in healthy volunteers and in patients. This paper summarizes the results of the different studies to evaluate the atrophogenic potentials of MPA in animals and in humans.

Animal studies

In rats, the effect on the breaking strength of the skin allowed discrimination between MPA and other corticosteroid preparations in respect of their local unwanted effects after long-lasting treatment: MPA and PC (PC) reduced the breaking strength only slightly compared with clobetasol-17-propionate (CBP). The effect of hydrocortisone-17-butyrate (HCB) was even weaker than those of MPA and PC. These results indicate that MPA can be classified as a corticoid with low local atrophogenic potential.

Human studies

Healthy volunteers

Occluded application test In 60 healthy volunteers, 0.1% MPA was applied in the three formulations on the unchanged skin over a period of 6 weeks under occlusive conditions. These investigations were performed in comparison to CBP, BMV and PC in cream and fatty ointment formulations, and the vehicles of MPA. A comparison with PC was not possible because of the discontinuation of its application as a result of severe local adverse reactions.

The following assessment criteria were used: visual (atrophy, telangiectasia), measurement of dermatoglyphic pattern. In all three formulations, MPA developed a significantly lower atrophogenic potential than the product used containing CBP. The results showed an atrophogenic potential of MPA comparable to that of BMV under Duhring chamber occlusive conditions.

Iterative open test

The aim of this study was to characterize the atrophogenic potential of MPA under the conditions of usual clinical practice by means of an 8-week non-occluded application test. In this double-blind randomized and controlled study, MPA 0.1% cream and fatty ointment once a day were compared to BMV 0.1% cream and (fatty) ointment twice a day.

The treatments were applied on six test zones per person, three on each forearm (volar side) in 20 healthy volunteers. For each subject, the zones (2 cm diameter, 3–14 cm^2) were outlined on a transparency sheet, as well as the natural marks such as veins, scars and naevi. This system allows the perfect reproducibility of the site of application day after day. Each treatment was applied to a zone according to a schedule given in the legend of Fig. 1.

The two daily opened applications were realized 5 days a week during 8 weeks. Each product was applied (10 μl) by gently massaging with a gloved finger. Assessment of atrophogenic potential was performed weekly using clinical scores as main criterion, and skin thickness measurements (ultrasound imaging) [6] as secondary criterion.

Telangiectasia and atrophy were evaluated

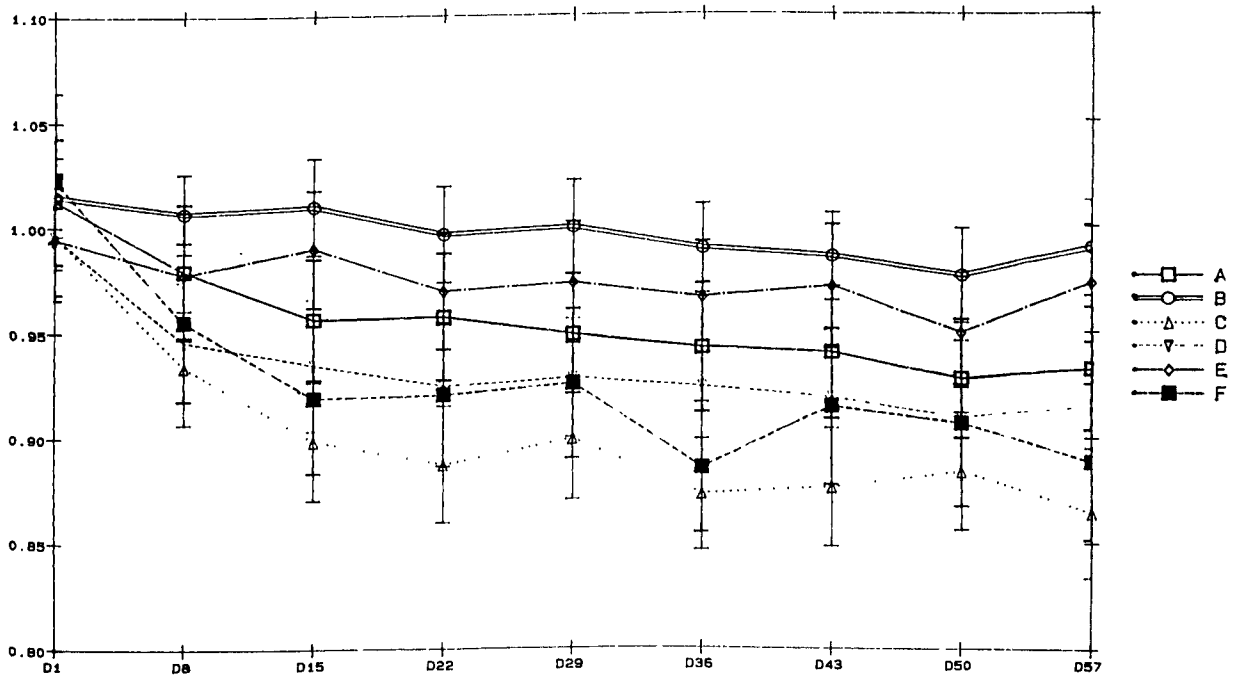


Fig. 1. Results of skin thickness measurements.

Morning	Evening
A = Vehicle cream	MPA Cream
B = Vehicle cream	Vehicle cream
C = BMV cream	BMV cream
D = Vehicle fatty ointment	MPA fatty ointment
E = Vehicle fatty ointment	Vehicle fatty ointment
F = BMV (fatty) ointment	BMV (fatty) ointment

by inspection of the skin through a stereomicroscope (Zeiss) according to a 5-point scale. The skin thickness of the six tested zones was measured using B-scan, ultrasound imaging. Skin thickness was determined on the ultrasound image (echography) by image analysis. The skin thickness is the mean of 100 lines scanned in the image.

Clinical evaluation (main criteria)

During the first 5 weeks of treatment, the presence of telangiectasia was noted ten times. From week 6 to 9, the number and intensity of telangiectasia increased. Significant difference ($P < 0.0034$) between treatment is obtained at week 8 where the score

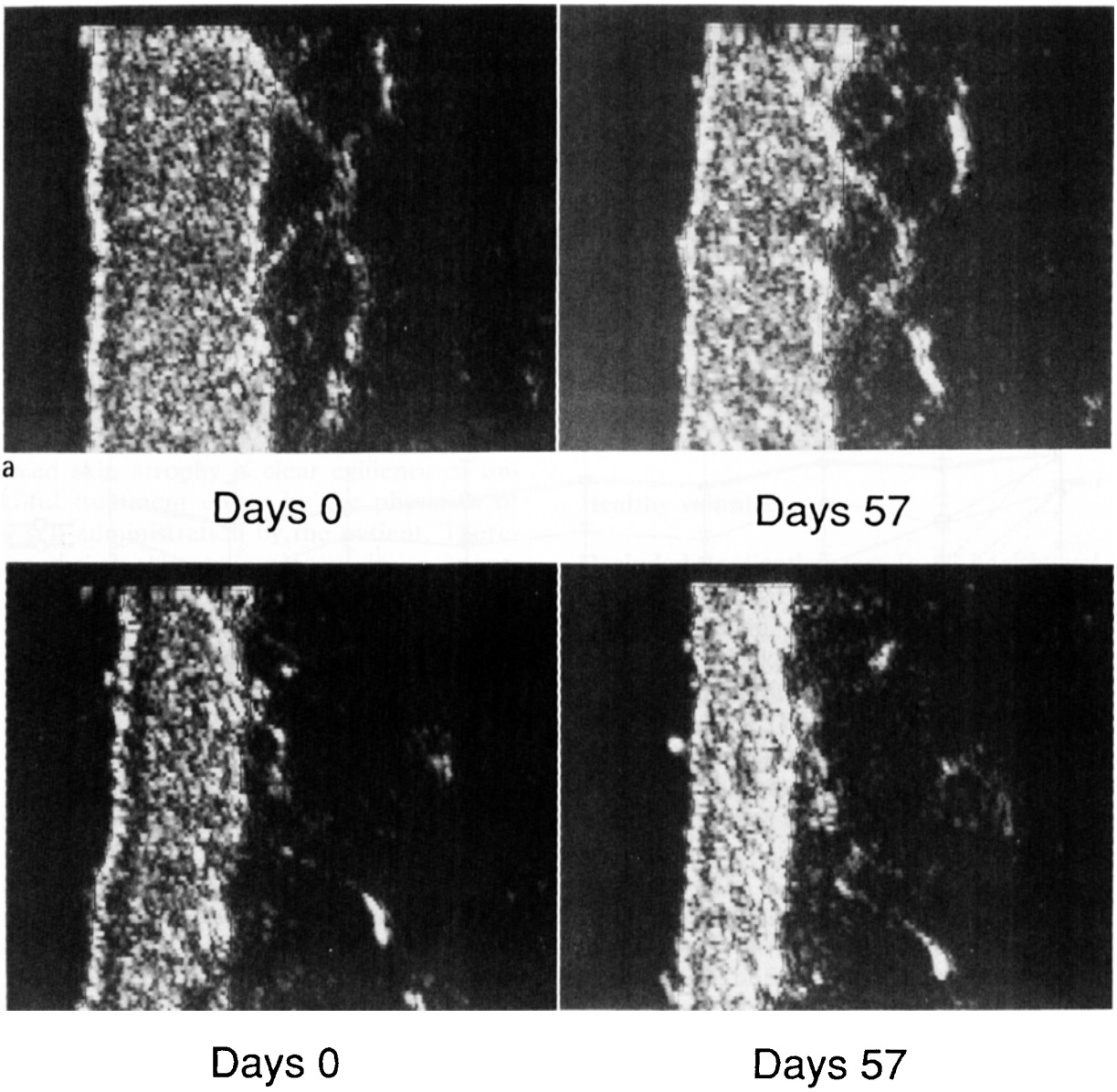
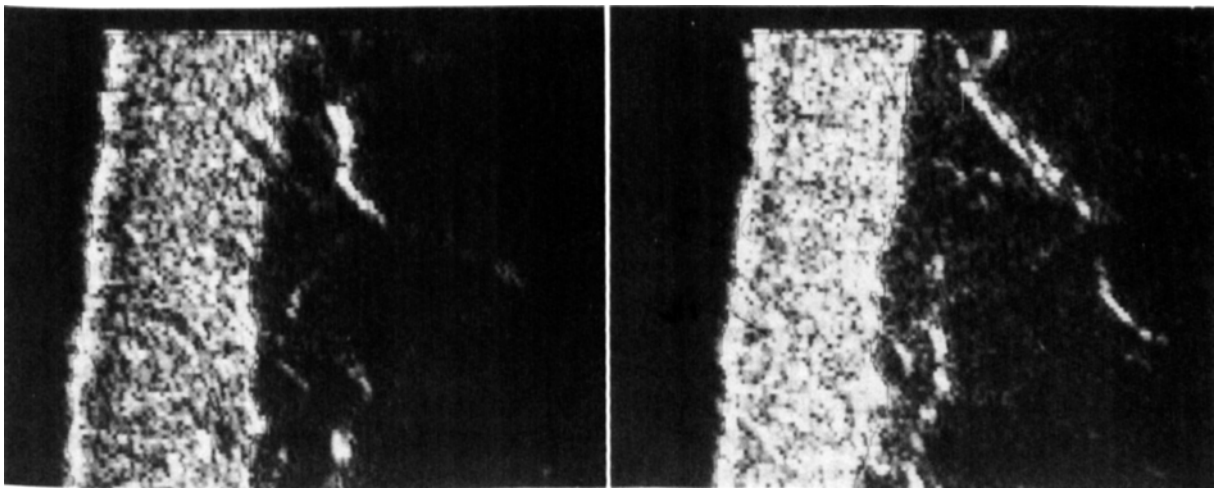


Fig. 2. Skin thickness measurement by ultrasound imaging. Decreased skin thickness between day 0 and day 57: (a) BMV cream; (b) BMV fatty ointment; (c) MPA cream.



C

Days 0 Days 57

Fig. 2 (continued).

for BMV cream is greater than that assigned to vehicle cream.

From the total cumulated score of telangiectasia the treatments can be classified (not statistically) as follows: Betamethasone cream > Betamethasone (fatty) ointment > Methylprednisolone cream > Methylprednisolone fatty ointment > Vehicle fatty ointment > Vehicle cream.

Signs of clinical atrophy observed in this study were rare ($n = 12$) and evenly distributed among treatments. Thus, no conclusion can be drawn from this parameter.

Concerning the skin thickness, an analysis of the data reveals large differences among treatment schedules at all weeks ($P < 0.01$). At the endpoint (week 9), the following statement can be made (under the control of a 5% overall error rate): Betamethasone cream and (fatty) ointment, methylprednisolone fatty ointment < Vehicle cream and fatty ointment and Betamethasone cream < methylprednisolone cream.

Moreover, for a given molecule, cream and ointment are never significantly different. Based on the thickness data, detailed analysis of products comparison can lead to the possible descriptive ranking: Betamethasone cream < betamethasone (fatty) ointment < Methylprednisolone fatty ointment < Methylprednisolone cream < Vehicle fatty ointment < Vehicle cream.

Under the experimental conditions of this study, no clear-cut conclusion can be drawn from the clinical evaluations excepting the fact that BMV cream induced more telangiectasia than vehicle cream (week 8) and that BMV preparations gave higher scores for telangiectasia than MPA preparations and vehicles. Moreover, from the skin thickness measurements, it can be concluded that MPA treatments (cream and fatty ointment, once a day) have a lower skin thinning potential than BMV treatments (cream and (fatty) ointment, twice a day).

Patients

In the six therapeutic tests with MPA in cream and ointment formulation in 1145 patients suffering from various types of eczema, in only one patient did such a corticoid-specific local adverse effect occur: in an 18 year old patient, mild 'atrophy' was observed

within the third week of MPA cream therapy. The patient had been suffering from his disease for 9 years and has been treated with various corticoids on a number of occasions. In the clinical trials with MPA fatty ointment formulation in 590 adult patients and 83 children suffering from atopic dermatitis and psoriasis vulgaris, clinical signs of atrophy were recorded in two out of the 673 patients.

Slight telangiectasia of the trunk was observed in one 57-year-old male patient who had been suffering from atopic dermatitis for 30 years. In that long period of time the patient had been treated repeatedly and for extended periods with various corticoids including potent and very potent corticosteroids. The telangiectasia occurred in the first week of treatment under both preparations, MPA and BMV respectively, which suggests an unmasking of pre-existing changes, secondary to the healing process. Mild skin atrophy of the lower legs was observed in a 58-year-old male patient who had been treated with MPA once daily on one side and MPA twice daily on the other side with an occlusive dressing on both sides. The signs of atrophy became visible in the third week of treatment after most symptoms had faded away. It is probable that in this case also pre-existing atrophy was unmasked by the therapy in this trial.

In an additional long-term study with MPA fatty ointment in 66 patients suffering from various dermatoses – mostly from psoriasis vulgaris, chronic lichenified eczemas or atopic dermatitis – no signs of corticoid-typical (or non-specific) local adverse effects were observed after a 3–4-month therapy period.

Conclusion

Topical corticosteroids are still the mainstay of dermatological therapy. Local and systemic side effects are undesirable and there is still room for optimization. With respect to safety [7], it may be concluded that MPA 0.1% preparations are safe. In the case of telangiectasia or atrophy, long-standing disease or repetitive courses of earlier treatment were responsible for the findings in the population studied (more than 360 healthy volunteers and 1887 patients evaluated, aged 3–90 years). This does not exclude the possibility of local damage by MPA. As was found in the Duhring chamber test (occluded application test), atrophy can be caused by MPA 0.1% formulations when applied for long enough under occlusion conditions. This implies that the development of atrophy/telangiectasia and the duration of treatment will have to be closely monitored and therapy modified accordingly. With respect to the atrophogenic potential, the MPA preparations compared well with the commonly used BMV preparations.

Considering the good local tolerance of MPA preparations together with their good therapeutic efficacy and their low systemic activity, the risk/benefit ratio is very favourable for these compounds.

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