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Long-term treatment with 6α-methylprednisolone aceponate

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Abstract

Aim 6α-Methylprednisolone aceponate (MPA) is a new steroid double ester for topical use, the potent action and lack of untoward side-effects of which became evident in two different studies.

Background Recent studies have proved the concept that MPA is both potent and extremely well tolerated when used for a relatively short time.

Methods Two multicentre studies on patients with steroid responsive dermatoses using either MPA fatty ointment ($n = 66$) or MPA in a vehicle individually adapted to the patients' skin condition ($n = 256$) were conducted over a maximum of 4 and 6 months, respectively. Plasma cortisol levels were determined in study I ($n = 45$) to reveal potential systemic effects.

Results Complete healing and marked improvement were achieved in 86 % of 322 patients. There were no systemic side effects and no significant alteration in plasma cortisol levels during and after treatment. Minor temporary local side effects were observed in 7%.

Conclusion MPA (Advantan) is a potent antiinflammatory topical steroid virtually devoid of systemic adverse effects and with a low incidence of local side-effects.

Key words: Topical steroid treatment; Soft steroid; Methylprednisolone aceponate; Atopic dermatitis; Psoriasis vulgaris; Adverse steroid effects; Cortisone atrophy

Introduction

Corticosteroids have been the most important drugs for the majority of inflammatory skin diseases. For many dermatoses, there is hardly any alternative treatment. However, inappropriate use of both systemic and topical steroids has discredited these powerful remedies. After the detection of hydrocortisone and the development of more and more potent topical corticoid preparations, the negative effects of long-term use of steroid topicals have become known to the public and have produced an irrational, sometimes hysterical fear of 'cortisone'. It is known that all nucleated cells possess the same steroid receptor, hence the positive and negative effects cannot be dissociated. A new way had to be searched for in order to find a possibility to enhance the antiinflammatory action

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without increasing the antiproliferative effect. The introduction of one or two esters markedly improved the bioavailability of these topical steroids resulting in so-called 'soft steroids'. The aim of two long-term studies with 6α-methylprednisolone aceponate (MPA) was to prove the assumption that this new prednisolone double ester derivative would not interfere with the pituitary-adrenal axis and not induce steroid atrophy, telangiectasiae, or striae.

Material and methods

6α-Methylprednisolone aceponate (Advantan®) was tested in two multinational multicentre studies for its long-term effect on steroid-responsive chronic dermatoses. The issue of safety and tolerance was particularly stressed.

Patients of both sexes with a minimum age of 18 years and suffering from steroid-sensitive dermatoses were enrolled (Table 1). Contraindications and exclusion criteria are given in Table 2.

Patients in study I were given Advantan fatty ointment once to thrice daily for up to 4 months and patients in study II received Advantan fatty ointment, Advantan ointment, or Advantan cream once to three times daily up to 6 months. The trial medication was applied either open or under dressings. The treatment was continued until clearing of symptoms. During the following control interval of 6 weeks, the patients received the MPA-free base and were seen every other week. The trial was completed when the patients remained disease-free during this 6-week period. In case of recurrence, Advantan was re-administered until healing was achieved. The maximum treatment duration was 4 and 6 months, respectively. The clinical course was evaluated biweekly during the first 4 weeks, then monthly. All symptoms (objective: erythema, infiltration, desquamation, pustules, prurigo, lichenification, rhagades, sclerosis, haemorrhage, excoriations, atrophy; subjective: itching, burning, pain) were rated as follows: none, moderate, se-

Table 1
Patient data and diagnoses

	Study I	Study II	Σ
Number of patients	66	256	322
males	31	120	151
females	35	136	171
Mean age	52.2	42.1	
Psoriasis vulgaris	30	93	123
Atopic dermatitis	9	89	98
Chronic lichenif eczema	17	31	48
Pustulosis palm plant	6	18	24
Lichen planus	3	6	9
Lichen scler atroph	–	2	2
Chronic cut LE	1	12	13
Other dermatoses	–	5	5
Steroid damage prior to trial	4	36	40
Steroid pretreatment	40	221	261

Table 2
Contraindications and exclusion criteria

Contraindications	Exclusion criteria
Specific skin infections	Systemic steroids within 4 wks
Chicken pox	and topical steroids within 3 days
Vaccination reactions	before trial
Mycoses	Further relevant treatments
Bacterial skin infections	Pregnancy
Perioral dermatitis	Hypersensitivity to any ingredient
Rosacea	of trial medication
	Additional topical or systemic steroid

Table 3
Treatment results

	Complete		Marked		Moderate		None		Deter		Σ
	I	II	I	II	I	II	I	II	I	II	
Psoriasis vulg	15	35	10	35	4	14	1	9			121
Atopic dermatitis	9	53		28		6				2	96
Chron lich exzema	10	16	5	12		1	2	1			48
Pust palm plant	4	12	1	5			1				24
Lichen planus	3	5		1							9
LSA		2									2
Chron cut LE		9		3							13
Other dermatoses		2		2				1			5
Σ	41	134	16	86	5	20	4	11		4	322

Complete: complete healing; Marked: marked improvement; Moderate: moderate improvement; None: no effect; Deter: Deterioration; I: study I; II: study II.

vere. At the end of the study, the overall treatment result was judged as complete healing, marked improvement, moderate improvement, no effect, and deterioration.

The pituitary-adrenal function was evaluated in 45 patients of study I by examining plasma cortisol levels at the beginning, after 2 and 4 weeks and at the end of the trial.

Results

In study I, 59 patients completed the study in time, and seven patients were withdrawn. The results were generally very good with 41 (62.1%) patients healed and 16 (24.2%) markedly improved (Table 3). Six patients suffered from a recurrence during the 6-week control interval and were retreated; five showed complete healing and one was distinctively improved. Neither local nor systemic adverse effects were observed.

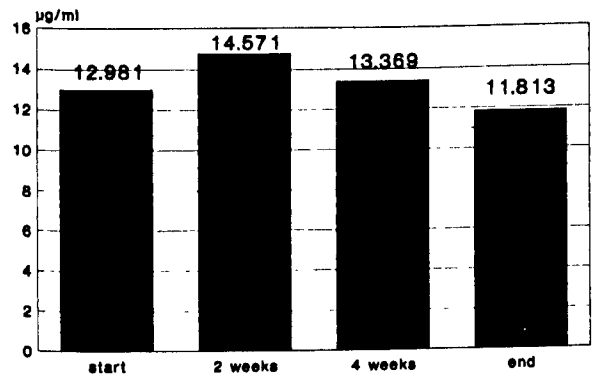

Fig. 1. Plasma cortisol levels before, during and after treatment

Plasma cortisol levels did not reveal an inhibition of pituitary-adrenal functions even after a maximal consumption of 1000 g Advantan fatty ointment (Fig. 1).

Out of 259 patients enrolled in study II, 256 could be evaluated. 227 completed the trial in time and 29 were withdrawn. The mean treatment duration was 4.8 months. The final evaluation showed healing in 134 (52.3%), marked improvement in 86 (33.6%), moderate effect in 19, no effect in four, and deterioration in four patients (Table 3). Out of 49 patients who experienced a recurrence during the control period and were retreated with Advantan, 48 showed complete healing of marked improvement.

No systemic adverse effects were observed but 22 patients experienced minor temporary local side effects such as burning (9 ×), itching (4 ×), pain (1 ×), folliculitis (2 ×), erythema, oedema, vesicles, papules, pustules, and perioral dermatitis (1 × each). Steroid-characteristic side-effects such as atrophy,

telangiectasiae, or striae did not occur and preexisting ones either remained unchanged or improved during Advantan treatment.

A total of 36 (study I, 7; study II, 29) patients (lack of efficacy 6/8, non-compliance 0/8, adverse effects 0/3, violation of protocol 0/2, other reasons 1/8) discontinued the study.

Discussion

Although a plethora of potent and ultrapotent topical steroids is on the market there is still a need for new agents [2,4–6]. What is needed in routine use is a safer rather than a more potent topical steroid. The fourth generation steroids were specifically designed to retain their antiinflammatory and antieczematous action and at the same time, to reduce their antiproliferative and systemic effects which are mainly responsible for their unwanted effect [9,10]. The new steroid diester 6α-methylprednisolone aceponate has shown that it is able to fulfil the current need for a modern steroid: to be highly effective and tolerable and lacking adverse systemic effects even after long-term administration [1–3,7–10]. Both preclinical tests and clinical trials have provided evidence of its potent action in different animal models and inflammatory skin diseases. It was comparable to betamethasone valerate and prednicarbate [1,3,7], but completely lacked their systemic actions [7,8,10]. This goal was achieved by

(1) improved penetration through increased lipophilicity of the steroid due to its double esterification,

(2) build-up of a depot in the horny layer with continuous diffusion of MPA into the epidermis, where it is

(3) activated from the prodrug (double ester) to the active drug by splitting of the C21 ester enhancing its activity threefold at the very site where its action is needed, and

(4) its inactivation by hydrolysis and removal from the skin by the blood circulation.

Acknowledgement

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