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Overview of clinical experience with methylprednisolone aceponate

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Abstract

Methylprednisolone aceponate is a new potent topical corticosteroid. Chemically it is a corticoid diester that rapidly penetrates the skin. It is rapidly metabolised and then conjugated so that although potent, it does not appear to cause serious local or systemic side effects. Clinical trials indicate that once daily applications are sufficient to control most eczematous disorders and that it is suitable and effective in atopic dermatitis.

Key words: Methylprednisolone aceponate; Corticosteroid; Eczema

Introduction

Eczema is a common distinctive reaction pattern of the skin to a wide variety of injurious stimuli: chemical, physical and microbiological. It is the epidermis that predominantly, but not exclusively, responds to the stimulus with an outpouring of oedema fluid and other signs of inflammation. The redness, swelling, vesiculation and scaling that results from the above tissue response is one of the commonest problems to afflict the skin. In many of the instances in which this symptom complex develops, such as atopic dermatitis, the causative agency cannot be identified with certainty although the symptomatology and the response to treatment is broadly similar in most eczematous disorders. It is this latter issue that needs to be addressed here. Eczema can be a most distressing disorder causing distressing symptoms and considerable disability (Table 1). All the signs, symptoms and malfunctions of the skin are due to the type and particular site of inflammation. On this basis it is clear that apart from removal of the basic underlying cause (which, as has already been stated, is quite often unknown) the most appropriate way to improve the eczema sufferer's lot is to use a 'broad spectrum' anti-inflammatory agent. The corticosteroids are effective anti-inflammatory agents par excellence and when administered topically with care rather than systemically, cause relatively few serious side effects in relation to their benefits. They are certainly capable of causing a host of unpleasant side effects (Table 2) and problems arise when they are used recklessly,

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Table 1
Disability due to eczema

Type of disability	Cause	Result
1. Physical	A fissuring due to decreased extensibility of abnormal stratum corneum	Pain and lack of mobility; sleeplessness and fatigue
2. Social and emotional	Abnormal appearance	Social isolation and peer rejection
3. Economic	Appearance and physical disabilities	Unemployment and underpromotion

inappropriately and without appreciation of the potential for problems.

Modes of action of topical corticosteroids in eczema

In acute eczema, skin blood flow rapidly increases, and increased permeability of the endothelial walls of the microvasculature result in dermal oedema. At the same time the keratinocytes themselves become swollen and oedematous and spongiotic oedema fluid collects between epidermal cells. Many of these changes are mediated by the release of phospholipases from lysomes in keratinocytes with the consequent release of arachidonic acid from cell membranes and the initiation of the 'arachidonic acid cascade' with the production of 'pro-inflammatory' prostanoid molecules. Increased levels of prostanoids have certainly been detected in skin from eczematous dermatoses [1,2] but it is evident that other mediators are involved as well. Inflammatory cells accumulate within the skin tissues but the density, site and variety of this cellular infiltrate varies with the acuity, severity and type of stimulus responsible for the eczematous reaction.

The modes of action of the topical corticosteroids in the eczematous disorders are extensively, but not completely characterized. The initial part of the train of events is the release of the corticosteroid molecule from the vehicle and the penetration into the skin. In the early untreated stages of eczema, there is scarcely any stratum corneum barrier and thus no impediment to penetration.

Once within the skin the corticosteroid binds to the nuclear corticosteroid receptor

Table 2
Adverse side effects due to topical corticosteroids

Systemic		
	Isotrogenic Cushing's Syndrome Pituitary adrenolaxis suppression	From absorption of potent corticosteroid molecules
Local		
	Skin thinning Striae distensae Facial erythema and telargiectasia Bruising	Connective tissue atrophy
	Masked infection in particular tinea incognito	Due to suppression of inflammatory response to infection
	Acneiform folliculitis Perioral dermatitis	Causes unknown
	Depigmentation Hirsutes	Causes unknown

and a series of metabolic events ensue that mediate the therapeutic effects. It is possible that some of the actions are not receptor mediated, but detail and evidence on this issue is in short supply.

A major part of the anti-inflammatory effect is due to the synthesis of a group of peptide substances known as the lipocortins [3]. These peptides have effect of inhibiting the lysosomal enzyme phospholipase A_2 which after release breaks down the phospholipids of cell membranes and initiates the 'arachidonic acid cascade' with the ultimate formation of the pro-inflammatory prostanoids.

Apart from this important aspect of corticosteroid action, there are other components to the 'anti eczematous action' of the corticosteroids [4]. They have an antimitotic effect and this probably counteracts the epidermal hyperproliferation and thickening that occurs in chronic eczematous rashes. The corticosteroids also affect the movement of inflammatory cells tending to reduce the density of the inflammatory cell infiltrate [5].

In addition to these actions the topical corticosteroids have a well known vasoconstrictor action and this too probably contributes to their overall anti-inflammatory effects in eczema [6].

Topical methylprednisolone aceponate

Methylprednisolone aceponate (MPA) has been developed with eczematous dermatoses particularly in mind. It is a potent corticoid diester that because of its pharmacokinetic properties shows considerable dissociation between its actions at the site of application and its systemic activity. MPA is highly lipophilic and rapidly penetrates the skin. Once within the skin it is hydrolysed into 6-α-methylprednisolone-17-propionate that has a higher binding affinity for the corticosteroid receptor than does MPA itself. If the affinity for dexamethasone is 100, that for MPA is 59 but that for the product of hydrolysis 6-α-methylprednisolone-17-propionate is 143. These properties seem to confer a satisfactory degree of pharmacological potency (Kecskes et al., 1992) [7] and a gratifying safety profile. Ortonne [8] reported that he detected one patient only with mild skin atrophy out of 1145 patients treated with MPA in one study. Another study by the same author reported the occurrence of only 2 with a degree of atrophy out of 673 patients treated with MPA. Ortonne also reported investigations in which the pituitary adrenal axis suppressive activity of MPA was compared with that of clobetasol-17-propionate and betamethasone-17-valerate in normal human volunteer subjects. These clearly demonstrated that the clobetasol preparations produced marked adrenal suppression, but that the plasma cortisol level remained within the normal range and maintained the usual diurnal variation in those treated with the MPA preparations. The plasma cortisol of patients with atopic dermatitis and psoriasis treated with MPA preparations also did not drop to below the normal range and once again the diurnal fluctuation in the levels was maintained.

Methylprednisolone aceponate preparations in eczematous dermatoses

Pharmacological studies indicated that MPA preparations have a profile of a 'highly potent' topical corticosteroid with vasoconstrictor activity between that of betamethasone valerate and that of clobetasol propionate [9]. In addition, the results of an experiment with 20 human volunteers who had poison ivy dermatitis also indicated that MPA was very effective at suppressing this allergic eczematous disorder [10].

Kecskes [10] assessed the atrophogenicity and propensity to induce telangiectasia of MPA ointment in comparison to mometasone furoate ointment in a human pharmaco-

logical investigation. MPA caused significantly less atrophy and significantly less severe telangiectasia than mometasone furoate. In view of the established equal anti-inflammatory activity, this result proves on increased benefit to risk ratio for MPA ointment vs mometasone furoate ointment.

The inevitable and important question is 'how effective are MPA preparations for eczema in clinical practice'? A brief answer is that all results to date indicate that MPA is highly effective for this group of inflammatory skin disorders.

Haneke [11] from Wuppertal, Germany, reported the results of 3 double blind clinical trials of MPA preparations in 276 patients with atopic dermatitis. The studies were right-left comparisons with randomized assignments of 0.1% MPA fatty ointment against 0.1% betamethasone-17-valerate each used twice daily or MPA once or twice daily against betamethasone-17-valerate twice daily. At the end of the 4-week study period, there was no difference between the once-daily and the twice-daily MPA application sides with 66% complete healing and 27% marked improvement compared to 68 and 30% for the betamethasone-17-valerate twice-daily applications.

In another report, Fritsch [12] from Innsbruck in Austria describes the results of 6 multicentre controlled double-blind studies in 1723 patients with various kinds of eczema in which 0.1% MPA cream or ointment formulations once or twice daily were compared with 0.1% betamethasone-17-valerate cream applied twice daily. The treatments were applied for a 3-week period and all the treatment regimens proved equally helpful with more than 90% improvement in all groups. It should be noted that the once- and twice-daily MPA applications were equally effective as were the cream and ointment formulations.

A frequently asked question with any new corticosteroid treatment is 'how safe and effective is the preparation for use in children with atopic dermatitis?' An answer to this question is provided by a paper by Rampini [13] from Genoa in Italy in which 3 multicentre studies of 220 children with atopic dermatitis were reported. The studies compared prednicarbate 0.25% cream and ointment, with hydrocortisone-17-butyrate 0.1% fatty cream and with MPA 0.1% cream and ointment in 7- or 21-day treatment regimens. In the 7-day study in which MPA ointment was compared to the prednicarbate preparation, plasma cortisol levels were also measured. The results of these studies demonstrated response rates in excess of 95% for all 21-day treatment schedules and furthermore no significant effects on the plasma cortisol levels were recorded.

Tolerability

All the clinical studies conducted thus far indicate that the cream and ointment formulations tested are well tolerated by the patients on whom they have been used. All the preparations employed in the above studies (including MPA preparations) seem to have been responsible for minor side effects in a very small number of subjects. Redness, itchiness, scaling and the signs of folliculitis were seen in some 3–5% of the patients treated.

Conclusions

The new corticoid diester methylprednisolone aceponate has been shown to be a potent topical corticosteroid without evidence of it being able to cause serious local side effects or suppression of the pituitary adrenal axis. In clinical use once daily applications seem able to suppress eczematous inflammation in more than 95% of patients over 3–4-week periods. The agent appears suitable for use in children and to be well tolerated.

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