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REVIEW ARTICLE

Balancing efficacy and safety in the management of atopic dermatitis: the role of methylprednisolone aceponate

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Abstract

Although emollients can be sufficient to manage mild atopic dermatitis (AD), acute flares resulting in moderate-to-severe symptoms require treatment with anti-inflammatory agents, such as topical corticosteroids (TCs) and topical calcineurin inhibitors (TCIs). This review examines the role of a member of the newest class of TCs, the fourth-generation compound methylprednisolone aceponate (MPA) in AD management, with reference to the chemical structure, pharmacokinetics, efficacy in AD, safety assessed in preclinical and clinical trials and dosing considerations. MPA has an optimized efficacy/safety profile with minimal local or systemic adverse effects. In addition, it offers the opportunity for once-daily dosing, which provides benefits in terms of patient compliance with treatment.

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Keywords

anti-inflammatory agents, atopic, corticosteroids, dermatitis, eczema, emollients

Conflicts of interest

In the past 3 years I have been paid as a consultant by a company with a vested interest in the product being studied, on issues related and unrelated to the product being studied.

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Introduction

Background

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by dry skin (xerosis) and increased transepidermal water loss caused by breakdown of the skin's normal barrier function. A key symptom is itching; in the acute phase erythema, papules, vesicles, crusts, weeping and oedema can be present, while thickening, lichenification and scaling of the skin are characteristic of the chronic phase.

Emollients form the basis of treatment for acute and chronic AD, but most patients also require anti-inflammatory therapy with either topical corticosteroids (TCs) or topical calcineurin inhibitors (TCIs) for management of acute flares. TCs have remained the gold standard anti-inflammatory treatment since the introduction of hydrocortisone, the first TC, in the 1950s. Adaptations to the basic molecular structure have been made to optimize the anti-inflammatory and immunosuppressive capacities of TCs, while minimizing unwanted adverse effects. Balance between efficacy, potency and safety remains a key therapeutic goal. This review examines the properties and role of a member of the newest class of TCs, the fourth-generation compound methylprednisolone aceponate (MPA) in AD management.

The use of emollients and anti-inflammatory agents in treatment of AD

Routine use of emollients is the basis of treatment for AD. Ointments, fatty ointments, lipocreams, creams and lotions soothe irritation, rehydrate the skin and help to keep the skin barrier intact (Fig. 1).

Ointments have a high ratio of fat to water and do not require the addition of (potentially allergenic) preservatives. They are most efficient in keeping the skin hydrated.[1] Creams contain a higher proportion of water than ointments, making them easier to

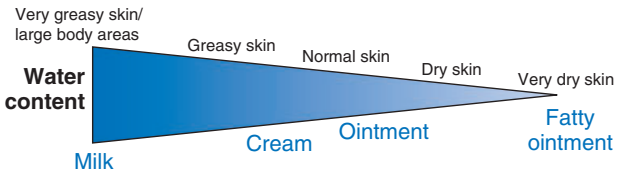

Figure 1 Use of emollients should be tailored to the skin type of the affected area.

spread, and can be applied liberally and frequently. Lotions have the highest water content of any emollient and therefore are rapidly absorbed. While they can soothe the irritation rapidly, they are less efficient as moisturizers.

Emollients can be sufficient for the management of mild AD, but acute flares resulting in moderate-to-severe symptoms require treatment with anti-inflammatory agents (Fig. 2). TCs have remained the gold standard of anti-inflammatory therapy in AD for more than 50 years, even after the introduction of the TCIs (pimecrolimus and tacrolimus) for mild-to-moderate cases. TCs induce their effects via several mechanisms, including effects on gene expression and on the cells of the immune system. Whilst it is recognized that management of AD commonly requires concomitant use of emollients and anti-inflammatory agents,[2] recent research has confirmed that, in children with AD, continued use of emollients after treatment with corticosteroids has ceased can help to maintain clinical improvements in xerosis and itching.[3]

The choice of vehicle used for TCs is important. Ideally, the selected vehicle should enhance lipophilicity and/or hydrate the stratum corneum to optimize absorption by the skin and facilitate release of the active ingredient into keratinocytes. These attributes increase the bioavailability of the topical therapy and can influence the tolerability and ease of application of a TC.[4] For instance, stiff, occlusive ointments are unsuitable for application to weeping skin, but are suitable for application to the soles of the feet; creams are the vehicle of choice for acute and sub-acute dermatoses in moist or intertriginous areas.[5]

Optimizing corticosteroid structure for use in AD

Many variants of the basic steroid structure (seventeen carbon atoms in four fused rings, with further carbon atoms contained in side chains) have been produced in an attempt to improve absorption, efficacy and potency, while minimizing side-effects (Table 1).

Such modifications can increase intrinsic potency (e.g. by methylation at C-6 or halogenation at C-9), improve lipophilicity (by esterification of alcohol residues) and increase metabolic resistance.[6–8] Modifications that dramatically affect potency can often be accompanied by an increase in adverse events, however.[7,8] Researchers have sought to optimize the balance between potency and safety of TCs – this is particularly important in patients with chronic AD, and in paediatric patients. Corticosteroids are classified according to potency; the British classification scheme has four groups while the American scheme uses seven.[9] Table 1 shows the potency ranking of TCs based on the British scheme. A relatively small group of compounds combine optimum efficacy with minimum side-effects (Fig. 3). Newer molecules – e.g. mometasone furoate (MM), hydrocortisone-17-butyrate-21-propionate, prednicarbate and MPA – demonstrate favourable risk–benefit ratios with respect to anti-inflammatory effects, acceptability and convenience for patients, weak atrophogenicity and lack of cross-sensitivity reactions.[7,10]

Mode of action of TCs in AD

Corticosteroids act via a number of pathways to reduce inflammation.[11,12] Firstly, they exert differential control of gene expression via activation of nuclear receptors in target cells, which then regulate gene transcription.[13,14] On entering T lymphocytes, for instance, the drug molecule binds to specific glucocorticoid

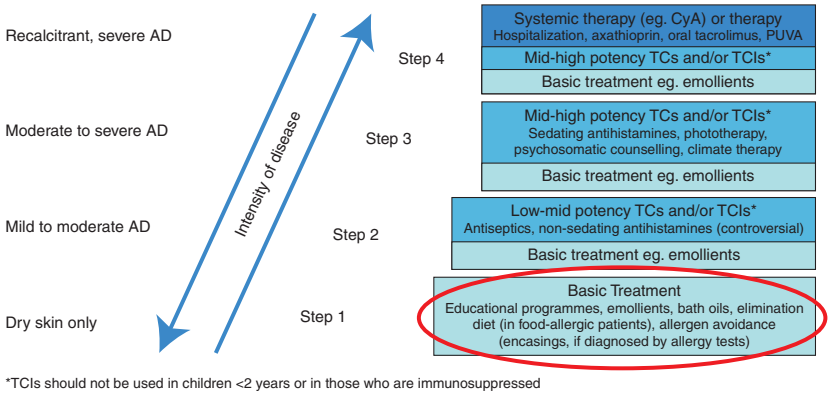

Figure 2 Stepwise management of AD. Treatment should be escalated according to the severity of AD symptoms. AD, atopic dermatitis; CyA, cyclosporin A; PUVA, psoralen and UVA treatment; TCs, topical corticosteroids; TCIs, topical calcineurin inhibitors. Reproduced from Akdis *et al.*[2]

Table 1 Structure and potency of some corticosteroid preparations used in AD

Corticosteroid	Structural modifications	Formulations
Very potent		
Betamethasone dipropionate	6α-methyl; 9α-chloro; 16β-methyl; 17,21-dipropionate	Ointment (0.05%); cream (0.05%)
Clobetasol propionate	6α-methyl; 9α-fluoro; 16β-methyl; 17-propionate	Ointment (0.05%); cream (0.05%)
Diflorasone diacetate	6α-fluoro; 9α-fluoro; 16β-methyl; 17,21-diacetate	Ointment (0.05%)
Halobetasol propionate	6α-fluoro; 9α-fluoro; 16β-methyl; 17-propionate; 21-chloro	Cream (0.05%)
Potent		
Amcinomide		Ointment (0.1%); lotion (0.1%)
Betamethasone valerate	6α-methyl; 9α-fluoro; 16β-methyl; 17-valerate	Ointment (0.01%)
Desoxymethasone	9α-fluoro; 16α-methyl	Ointment (0.25%); cream (0.25%); gel (0.05%)
Diflorasone diacetate	6α-fluoro; 9α-fluoro; 16β-methyl; 17,21-diacetate	Ointment (0.05%); cream (0.05%)
Fluocortolone		Cream (0.25%)
Fluocinonide	6α-fluoro; 9α-fluoro; 16,17-acetonide; 21-acetate	Ointment (0.05%); cream (0.05%); gel (0.05%)
Fluticasone propionate	6,9α-difluoro; 11β-hydroxy; 16α-methyl-3oxo; 17β-carbothioate	Ointment (0.005%)
Halcinonide	9α-fluoro; 16,17-acetonide; 21-chloro	Ointment (0.1%); cream (0.1%)
Methylprednisolone aceponate	6α-methyl; 17-propionate; 21-acetate	Ointment (0.1%), cream (0.1%), milk (0.1%)
Mometasone furoate	9α-fluoro; 16α-methyl; 17-furoate; 21-chloro	Ointment (0.1%)
Triamcinolone acetonide	9α-fluoro; 16,17-acetonide	Ointment (0.5%, 0.1%); cream (0.5%)
Moderately potent		
Betamethasone dipropionate	6α-methyl; 9α-chloro; 16β-methyl; 17,21-dipropionate	Lotion (0.05%)
Betamethasone valerate	6α-methyl; 9α-chloro; 16β-methyl; 17-valerate	Cream (0.01%); lotion (0.01%)
Desoxymethasone	9α-fluoro; 16α-methyl	Cream (0.05%); gel (0.05%)
Fluocinolone acetonide	6α-fluoro; 9α-fluoro; 16,17-acetonide	Ointment (0.025%); cream (0.2%, 0.025%); oil (0.01%)
Flurandrenolide	6α-methyl; 6α-fluoro; 11,21 dihydroxy; 16,17-(1-methylethylidene)bis-oxy	Ointment (0.05%); cream (0.05%)
Fluticasone propionate	6,9α-difluoro; 11β-hydroxy; 16α-methyl-3oxo; 17β-carbothioate	Cream (0.05%)
Halcinonide	9α-fluoro; 16,17-acetonide; 21-chloro	Ointment (0.1%); cream (0.1%)
Hydrocortisone butyrate	17-butyrate	Cream (0.1%)
Hydrocortisone valerate	17-valerate	Cream (0.025%)
Mometasone furoate	9α-fluoro; 16α-methyl; 17-furoate; 21-chloro	Cream (0.1%)
Triamcinolone acetonide	9α-fluoro; 16,17-acetonide	Ointment (0.1%); lotion (0.1%)
Less potent		
Alclometasone dipropionate	7α-chloro; 16α-methyl; 17,21-dipropionate	Ointment (0.05%); cream (0.05%)
Betamethasone valerate	6α-methyl; 9α-chloro; 16β-methyl; 17-valerate	Lotion (0.05%)
Desonide	16,17-(1-methylidene)bis(oxy)-pregna-1,4-diene-3; 20-dione	Cream (0.05%)
Dexamethasone	9α-fluoro; 16α-methyl	Cream (0.1%)
Fluocinolone acetonide	6α-fluoro; 9α-fluoro; 16,17-acetonide	Cream (0.01%); solution (0.01%)
Methylprednisolone	6α-methyl	Cream (1%)
Prednicarbate	17-ethylcarbonate; 21-propionate	Cream (0.1%)
Triamcinolone acetonide	9α-fluoro; 16,17-acetonide	Cream (0.1%)

Adapted from Hengge et al., 2006[5] and Brazzini, 2002[7].

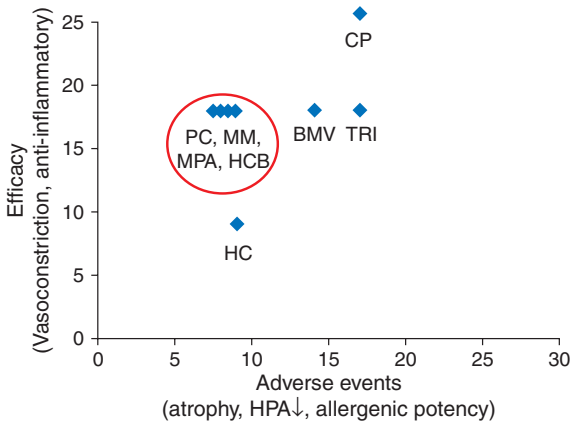

Figure 3 Efficacy versus side-effects of corticosteroids. A representation of efficacy versus adverse events [therapeutic index (TIX)] for a number of topical corticosteroids. The clinical compounds (PC, MM, MPA, HCB) have a TIX of 2.0 indicating a very favourable efficacy to adverse events rate. BMV, betamethasone valerate; CP, clobetasol propionate; HCB, hydrocortisone butyrate; PC, prednicarbate; HPA, hypothalamic-pituitary-adrenal; MM, mometasone furoate; MPA, methylprednisolone aceponate; HC, halcinonide; TRI, triamcinolone acetonide. Adapted from Luger *et al.*[10]

receptors (GR) in the cytoplasm to form a complex which then translocates to the cell nucleus and binds to specific DNA-responsive elements. The end result is downregulation of production of pro-inflammatory cytokines such as tumour necrosis factor α (TNFα), interleukin-1α (IL-1α), IL-3, IL-5, granulocyte-macrophage colony stimulating factor and upregulation of other molecules including annexin 1.[7,9,12,13,15,16] Increased concentrations of the proinflammatory cytokines IL-1β, IL-6 and TNFα in the cytoplasm sensitize the GR, increasing the rate of corticosteroid binding.[17] Secondly, corticosteroids also reduce inflammation by reducing synthesis of pro-inflammatory mediators such as prostaglandins and leukotrienes.[18]

The overall effect of corticosteroid treatment is to suppress the release of arachidonic acid,[19] impair the function and maturation of dendritic cells [20,21] inhibit the migration of leucocytes to sites of inflammation,[7] suppress eosinophil maturation,[22] diminish microvascular leakage in inflamed skin,[23] and reduce collagen synthesis.[24]

Adverse effects of TCs

The most common adverse effects of corticosteroids are local. Rarely, absorption of corticosteroids into the systemic circulation can give rise to systemic effects,[25] reflecting the fact that their mode of action is non-specific.

Local adverse effects result mainly from mineralocorticoid antiproliferative effects on keratinocytes and fibroblasts, leading to epidermal and dermal thinning.[26] Treatment with TCs may also inhibit epidermal lipid synthesis as well as lipid layer formation and alter stratum corneum integrity, resulting in an impaired epidermal barrier function.[27,28] However, disturbed epidermal expression of involucrin, loricrin, filaggrin and keratins in patients with AD was improved upon treatment with TCs.[28]

Changes in gene transcription can lead to adverse events, mainly related to actions on electrolyte and water balance; neoglycogenesis and tissue repair; and inhibition of adenohypophyseal function.[7,13] Concern about serious adverse events associated with corticosteroids can lead in some cases to 'corticosteroid phobia'.[29]

Skin atrophy, evidenced by thinning of the skin and the presence of telangiectasias and striae in areas of dermis subject to mechanical stress,[5,9,17] is, perhaps the best known adverse event associated with TC use. Inhibition of the pituitary-adrenal axis is the most serious.[17,30] Atrophy involves epidermal, dermal and sub-cutaneous tissue and is caused by changed viscoelasticity in those glycoproteins and proteoglycans responsible for interfibrillar adhesion of collagen.[9,17,31] These changes can occur after a few months of topical therapy and also contribute to the widening of blood vessels.[7] Epidermal thinning is caused by a reduction in cell size and is in part reversible. This is not always true of atrophy in deeper skin layers.[32] Striae represent a permanent type of skin atrophy and consist of visible, scar tissue.[5] From the patient perspective, they are, therefore, an important local adverse event associated with long-term TC use, particularly when they occur in highly visible areas.[33]

Small numbers of patients experience either hypersensitivity or resistance to corticosteroids – probably as a result of mutations in the GR.[9,30] Perioral dermatitis, tinea incognito, corticoid acne, rosacea, hypertrichosis and hypopigmentation are distressing to patients and can affect compliance. 'Steroid face' is a term used to describe erythema, telangiectasia and rosacea-like symptoms that may develop after prolonged treatment of facial AD. Corticosteroids probably induce degeneration of the follicular epithelium, causing exit of follicular contents.[7]

The most recent generation of corticosteroids – the non-halogenated corticosteroid diesters – balances potent anti-inflammatory activity with reduced systemic toxicity and weak atrophogenicity.[7,34] The remainder of this review concentrates on one member of this group, MPA.

Use of MPA in AD

Adaptation of chemical structure to meet the needs of patients

As shown in Fig. 4, MPA has a methyl group at C-6 and both of the alcohol residues attached to the five-membered ring are esterified (a propionate group at C-17 and an acetate group at C-21). Methylation at C-6 increases receptor binding – and therefore potency – while double esterification significantly increases lipophilicity, facilitating rapid and efficient penetration of the stratum corneum and increased bioavailability.[35,36] Unlike other potent

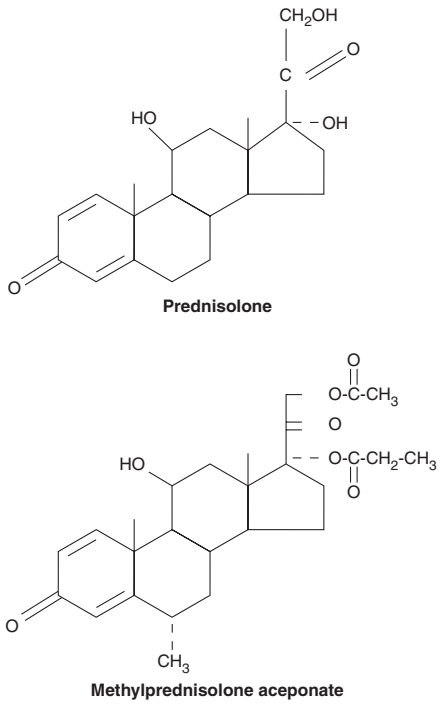

Figure 4 Structures of prednisolone and methylprednisolone aceponate.

corticosteroids, MPA does not contain a halogen at C-9; this contributes to a high degree of dissociation between topical and systemic activity.[36]

MPA is metabolized rapidly by esterases within the epidermis and dermis. Under physiological conditions, the acetate group is preferentially removed to produce the key metabolite methylprednisolone-17-propionate (MPP), which binds three times more strongly to the GR than does MPA.[35,36] This local activation process has been shown to take place more rapidly in inflamed skin than in normal skin, because of the increased concentrations of esterases and therefore the active metabolite is concentrated in damaged skin.[31] MPP undergoes a rearrangement (acyl migration) of the propionate group from C-17 to C-21, forming methylprednisolone-21-propionate. Once in the skin, methylprednisolone-21-propionate is easily hydrolysed and rendered relatively inactive. Any MPP entering the systemic circulation is rapidly inactivated by conjugation with glucuronic acid, reducing the potential for systemic side-effects.[37]

Efficacy of MPA in AD

The onset of activity of MPA is very rapid. A majority of AD patients (50–80%) experience complete or distinct improvement in objective (erythema, vesiculation, weeping, crusting, scaling and lichenification) and subjective (itching, burning and pain) symptoms within 1 week of treatment according to patients' and physicians' global assessments.[38,39] This proportion improves to >90% of patients with longer (up to 3 weeks) treatment.[37,38,40] In particular, MPA provides fast and effective relief from itching and reddening, especially in patients with severe symptoms.[39]

Once-daily MPA has demonstrated good efficacy, with rapid onset of activity in a wide range of patients with AD.[41–43] In infants aged <18 months, 85% treated with a milk formulation of MPA experienced complete remission or significant improvement of AD after 3 weeks.[41] Vesiculation was completely absent after 1 week of treatment and no patient had exudation after 3 weeks.[41] More than 90% of patients with AD on the hairy part of the scalp experienced complete remission or significant improvement in symptoms (patients' and physicians' global assessment) after ~2 weeks' treatment with once-daily MPA (0.1%) solution.[43] Among patients with severe AD flares, 67% of patients were clear of or experienced significant improvement in symptoms (according to Investigator's Global Assessment) after 3 weeks of treatment with MPA 0.1% ointment applied once daily, the same percentage as in patients treated with tacrolimus 0.03% ointment twice daily.[42] A notable ~70% improvement [mean visual analogue scale score (VAS)] in itching was reported after 7 days' treatment, which was reflected in better quality of sleep and a 90% improvement in Eczema Area and Severity Index (EASI) scores by end of treatment. Indeed, MPA was superior to tacrolimus in terms of itching, EASI score and sleep quality.[42] The authors of this study therefore concluded that these advantages recommended the use of MPA as first line treatment in AD. Patients who recovered from AD flares had a 3.5-fold lower risk of relapse with maintenance therapy of twice-daily emollient applications plus MPA (0.1%) ointment (applied once daily at weekends only) than with emollient alone.[44] During 16 weeks of maintenance therapy with MPA, small increases in VAS for intensity of itching (~5 mm) and EASI (~0.5 points) were recorded, but no signs of skin atrophy were observed and no other adverse events were reported.[44] A similar study with intermittent tacrolimus treatment in children with AD also indicated that maintenance therapy can reduce the incidence of flares[45] – this is significant because tacrolimus is not universally licensed for continuous use because of concerns over its long-term safety. Two of 59 children in the study did experience serious immunosuppression-related events; however, more work would be required to address the concerns raised in the US FDA's black box warning for tacrolimus (see http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm151161.htm).

In healthy volunteers, a comparison of MPA with MM confirmed that, while both fourth-generation TCs were equally effective in reducing UVB light-induced skin erythema, there were important differences in safety parameters. Atrophogenicity, incidence and severity of telangiectasia and incidence of serum cortisol level suppression were all markedly higher with MM.[46]

Once-daily application

Most topical anti-inflammatory medications for AD are applied twice daily. The safety (see below) and efficacy of MPA permit once-daily administration.[36,38,40,42,47,48] As routine skin care products (such as emollients, oils, moisturizers) have to be applied regularly at times that do not interfere with the dosing schedule for medication, once-daily dosing is a great advantage when encouraging patients to comply with the regimen.[42,47] MPA has a very rapid onset of activity, offering the potential to curtail duration of treatment; the low incidence of systemic side-effects may also appeal to patients with 'corticosteroid phobia'.[14,38–43,49] Finally, MPA is available in a wide range of formulations, including two ointments, a cream, a lotion and a milk, of equal efficacy that suit the needs of different patient age, skin condition, location of lesions and disease severity.[39,40,49]

Safety of MPA in AD

A number of studies involving animal models, healthy volunteers and patients have demonstrated that the incidence and severity of adverse effects with MPA are significantly lower than that with other corticosteroids of comparable efficacy, and are similar to those of some less potent corticosteroids.[46,48–50]

Short-term local events

MPA is very well tolerated in the majority of patients: the incidence of adverse events is around 5%.[36] Adverse events are almost always mild-to-moderate in severity,[39,40] and rarely result in treatment discontinuation.[40,48,50] The most common local adverse events are mild erythema, sensation of burning, dryness, scaling and rash.[39,40] These result from non-specific irritation of the skin and may be attributed to excipients in the formulation rather than to MPA.[50]

Longer-term local events

The long-term safety of MPA has been studied in animals, healthy volunteers and in clinical studies.

Animal models. Experiments in animal models indicate that the atrophogenic potential of MPA is low.[36,51] In naked Wistar rats, MPA caused greater skin thinning than did vehicle, but significantly less ($P < 0.05$) than MM after 19 days' treatment.[52] The incidence of telangiectasias was also significantly less ($P < 0.05$) with MPA than with MM.

Healthy volunteers. The atrophogenic potential of MPA (0.1%) in cream and ointment preparations under occlusive conditions was found to be significantly less than that of clobetasol 17-propionate or MM [46,50] but similar to that of betamethasone 17-valerate (BMV).[36,50] Under clinical conditions, treatment with MPA (0.1%) cream and fatty ointment twice daily for 8 weeks resulted in a greater incidence of telangiectasias than with vehicle alone but a lower incidence than with BMV[50] or MM.[46] Most (80%) telangiectasias resulting from MPA treatment were rated as 'slight'.[46] Daily MPA treatments over an 8-week period reduced skin thickness (as measured by ultrasound imaging); this reduction was slightly more noticeable with the fatty ointment.[50] Treatment with MPA (0.1%) cream affected skin thickness less than did MPA (0.1%) fatty ointment or either formulation of BMV. There were no differences observed between the cream and fatty ointment formulations of MPA in terms of atrophogenic potential[50] or incidences of telangiectasias and skin thinning.[51]

Clinical studies. In pooled study results from 1145 patients with AD, only one heavily pretreated patient had signs of skin atrophy.[40] In pooled results from more than 600 patients with AD, two patients experienced atrophy and one developed telangiectasias – although in one case each, the atrophy and telangiectasias appeared within days of starting treatment, suggesting that treatment was unmasking pre-existing conditions.[50]

The range and severity of skin irritation events were similar between patients treated with long-term maintenance therapy (two doses per week) and acute therapy, but the incidence of events was higher in the MPA group (15%), although not higher than with emollient alone (24%).[44]

Systemic events

Absorption of corticosteroids into the systemic circulation can cause a number of specific and non-specific symptoms. Non-specific symptoms include hyperglycaemia, hypertension, leucocytosis and potassium and sodium shifts.[5] The rapid onset of action of MPA, followed by inactivation of its metabolites following absorption, confers a lower risk of unwanted systemic effects. No non-specific systemic events were observed in patients treated with MPA (0.1%) ointment for 3 months.[50]

The most concerning systemic effect of corticosteroids is suppression of the hypothalamic-pituitary-adrenal (HPA) axis. In humans, this is measured as reduction in serum cortisol concentrations, and anomalies in the circadian rhythm. Degree of adrenal suppression is dependent on duration of treatment, drug potency, area of skin covered and condition of the skin.[31]

Animal models. In rats, MPA did not suppress cortisol, as assessed by measuring the weight of the thymus, even after 43 days of treatment.[36]

Healthy volunteers. In one small study using occlusive treatment with MPA (0.1%) ointment over 60% of the body surface,[46] 5 of 10 healthy volunteers experienced changes neither in serum cortisol levels nor in circadian rhythm after 6 days, two had suppressed circadian rhythm but no cortisol changes and the remainder had depressed cortisol levels and altered circadian rhythm.

In another study in 100 healthy volunteers using 40 g topical MPA (0.1%) applied daily over 60% of the body surface, with skin

dressed with cotton or occluded for 22/24 h per day, no changes were observed over 8 days.[49,50]

Clinical studies. Four adult patients with AD involving 40–60% of the skin surface treated with 30 g MPA (0.1%) fatty ointment (15 g twice daily) for 7 days similarly experienced no effects on the HPA axis. A long-term study of MPA fatty ointment (1–3 times daily application) in chronic dermatoses showed no evidence of suppressed endogenous cortisol secretion in 45 adult patients over a 4-month period.[50]

Safety in children

AD is more prevalent in children than in adults. Children's smaller size, increased vulnerability of the skin (particularly in infants) and the potential necessity for long-term treatment means that the safety of medications is of greater concern in this population. Systemic effects are of most concern because over-use can result in restricted growth and development in children.[41] Nevertheless, the effects of topical steroids are marginal, in comparison with the influence of extent of the disease.[53]

Several formulations of MPA, including a milk, are indicated for use in young children. In clinical trials, no adverse events were recorded in children younger than 4 years of age who received once-daily applications of the milk formulation of MPA for up to 14 days.[41] In a range of trials ($N = 213$) with children aged 4 months to 15 years with mild, moderate or severe AD treated once-daily with MPA (0.1%) ointment for up to 21 days, adverse events were mostly absent. Some cases of mild burning sensation were recorded and very few children experienced infectious skin diseases.[48,54,55] There were no discontinuations because of adverse events in these trials. Cortisol levels remained at baseline concentrations in children treated with MPA for 1 week.[48]

Conclusions

While emollients are an important basis for treatment in AD, management of acute exacerbations requires the additional use of anti-inflammatory therapy to treat flares and alleviate symptoms such as itching. Corticosteroids have been the gold standard treatment for AD for over 50 years, providing rapid relief of symptoms and a reduction in inflammation. The most recent generation of corticosteroids balances high potency with low incidence of local adverse events and absence of systemic events. MPA – with increased lipophilicity and binding affinity for the GR – typifies this new, optimized generation. Its local activation in the skin, followed by rapid inactivation of metabolites, minimizes the risk of systemic adverse effects. The rapid onset of activity of MPA, high efficacy and potency and very low incidence of adverse events in patients treated with a range of formulations of MPA (0.1%), together with availability of once-daily dosing, a major benefit for patient acceptability and compliance with treatment, make MPA an effective and well-tolerated choice for a wide range of patients with AD. In addition, the recently proposed intermittent use of topical corticosteroids – proactive treatment – with a favourable safety profile such as MPA provides a novel, safe and effective approach to control AD.

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