REVIEW ARTICLE

Frontiers of rapid itch relief: a review of methylprednisolone aceponate

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Abstract

In a paediatric population, the successful management of childhood atopic dermatitis (AD) should include the careful evaluation and selection of available therapies, based not only on demonstrated safety and tolerability in small children and infants, but also on their evidence-based, anti-pruritic benefits. Moreover, the speed of anti-pruritic effect should be considered a significant parameter in treatment selection. The fourth-generation topical corticosteroid (TC) methylprednisolone aceponate (MPA) is a potent anti-inflammatory agent with a demonstrated fast and effective itch relief profile in children and infants (as young as 2 months) with AD. Compared with traditional TCs, MPA has a significantly improved therapeutic index; that is, increased potency without a proportionate increase in side effects. In addition to its established efficacy, the once-daily application and broad range of available formulations make MPA an optimal choice for acute and maintenance therapy in paediatric patients with AD-related pruritus.

The successful management of childhood atopic dermatitis (AD) requires an integrated treatment approach that addresses the multidimensional aspect of pruritus in AD, the unique challenge implicit in treating infants and children, as well as the most recent findings related to disease pathophysiology and targeted treatment. From a pharmacological standpoint, this includes the careful evaluation and selection of available therapies for their evidence based, anti-pruritic benefits in a paediatric population. Moreover, speed of anti-pruritic effect should be considered a significant parameter when choosing appropriate pharmacological therapy, for the patient's sake and due to the need for early anti-pruritic interventions that disrupt the itch-scratch cycle.

An improved approach to pruritus treatment in atopic dermatitis

The fourth-generation topical corticosteroid (TC) methylprednisolone aceponate (MPA) is a potent anti-inflammatory agent with a fast and effective itch relief profile in children and infants with AD. In addition to MPA, this newest class of TCs indicated for treating the symptoms of AD includes compounds such as: aclometasone propionate, hydrocortisone aceponate, hydrocortisone-17-butyrate-21-propionate, mometasone furoate and prednicarbate. Relative to other TCs, these fourth-generation agents are designed to provide effective treatment of inflammation and minimize side effects. MPA is a newest-generation TC, which offers a significantly improved therapeutic index (TIX) through increased potency without a parallel increase in side effects.[1]

Unique characteristics of methylprednisolone aceponate

MPA is highly lipophilic, and therefore, rapidly absorbed into the skin. Unlike other fourth-generation TCs, MPA is hydrolysed primarily in the epidermis and dermis by esterases leading to an active metabolite, methylprednisolone propionate (MPP). MPP has a high binding affinity to the corticosteroid receptor. After functional binding and subsequent dissociation from the glucocorticoid receptor, MPP is then rapidly deactivated by glucuronic acid. The inactive metabolite is then excreted in the urine, resulting in the overall low systemic exposure of MPA (Fig. 1).[1,2]

Rapid and long-term itch relief in children

An evidence-based review of a robust body of clinical studies with MPA 0.1% (Advantan®, Intendis, Berlin, Germany) demonstrated efficacy and safety in infants as young as 2 months and children, in both acute and maintenance phases of AD (Table 1).[1,3] In large-scale studies with adults and children, a majority of patients experienced distinct or complete improvement in objective (erythema, vesiculation, weeping, crusting, scaling and lichenification) and subjective (itching, burning and pain) symptoms within 1 week of treatment with MPA 0.1%.[4,5] With longer (up to 3 weeks) MPA treatment, this proportion increased to >90% and was comparable to the effects of prednicarbate and betamethasone valerate.[6,7]

Especially in children with AD, fast onset of activity to control itching is essential. MPA 0.1% treatment demonstrated significant relief of symptoms and signs (especially itching and redness) in

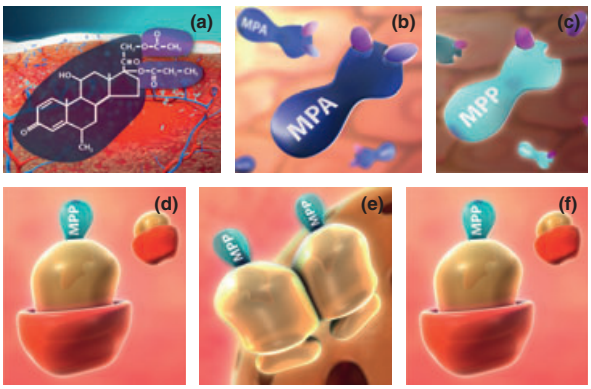

Figure 1 Illustration of the local activation process for methylprednisolone aceponate (MPA). (a) The active agent MPA is non-halogenated and has an excellent liposolubility because of its double esterification. (b, c) In the skin, esterases transform MPA into methylprednisolone propionate (MPP), which has a 2.4-fold higher binding affinity to the glucocorticoid receptor, compared with MPA. This results in a fast action of Advantan®. (d) Binding of MPP activates glucocorticoid receptors located in the plasma of many cells. (e) After dimer formation, the active receptor complex moves into the cell nucleus, where it binds either to specific DNA sequences or directly to transcription factors. This triggers biological effects, such as the inhibition of cytokine mediated T-cell activation. (f) After a minute amount of MPP reaches the bloodstream, it is quickly conjugated with glucuronic acid in the liver and cleared via the kidneys. Because of this, the effects of Advantan® are mainly limited to the desired site of action in the skin.

most patients (65%) within 2–3 days, with 97% of patients achieving significant improvement or cleared signs and symptoms by end of treatment (Fig. 2).[5] In a further study, 21 of 27 patients aged <4 years treated with a milk formulation of MPA 0.1% (Advantan) experienced complete healing after only 7 days.[8] In comparison with a daily application of tacrolimus 0.03%, children treated with MPA achieved comparable levels of treatment success for improvement in pruritus and sleep quality. Once-daily application of MPA 0.1% (Advantan) was statistically superior to twice-daily treatment with tacrolimus 0.03%.[9] From another comparative standpoint, MPA 0.1% (Advantan) ointment once-daily was as efficacious as the twice-daily application of another fourth generation TC, prednicarbate 0.25% ointment,[6] and better at preventing maintenance-phase relapse (over 16 weeks) and maintaining itch-related quality of life (QoL) compared with emollients alone.[10] In the vast majority of patients, MPA 0.1% was very well tolerated with low incidence of local or systemic effects.[11]

The improvement of itch by TCs is thought to result from the inhibition of inflammatory processes; however, recent studies in animal models indicate that there may be additional mechanisms of anti-pruritic action. In mice, for example, corticosteroids suppressed scratching behaviours induced by different pruritogenic agents [i.e. histamine, serotonine, substance P and protease-activated receptor-2 (PAR-2)]. This observed anti-pruritic effect was associated with inhibition of phospholipases A2 and Cβ3, and a pathway that was independent of transient receptor potential vanilloid-1 (TRPV-1) C-fibers.[12]

Flexibility through formulation

The galenic formulation is crucial for both the optimal release of active ingredients and to ensure suitability for the prevailing skin condition and clinical stage of AD. Moreover, diversity in galenic formulation range drives use and optimal adherence in children. Especially in the paediatric population, choice of vehicle should be tailored to clinical stage, skin condition, localization of disease and patient/caregiver preference. MPA 0.1% (Advantan) is available in four different once-daily formulations – fatty ointment, ointment, cream and milk – enabling change in vehicle type without sacrificing consistency in concentration of active principle and efficacy. All formulations of MPA 0.1% (Advantan) can be applied interchangeably and simultaneously. Specifically, the milk formulation is suitable for infants as young as 4 months.[8] MPA 0.1% (Advantan) cream is effective for face, neck and skin flexures with weeping eczema and oedema.[13] MPA 0.1% (Advantan) ointment has been shown effective and appropriate in dry skin with inflammation, infiltration and lichenification.[13] Regardless of formulation, patients treated with MPA 0.1% (Advantan) experienced rapid relief of pruritus and erythema within days (<1 week), with a majority achieving complete remission within 2–3 weeks.[4,5,8,9,11] Although treatment with other topical agents, such as topical calcineurin inhibitors, has shown similar efficacy in children compared with low-to-moderate strength TCs, to date, topical calcineurin inhibitors have not offered the same patient-oriented flexibility through formulation as highly potent new-generation TCs, especially for infants as well as for treatment of particular areas of the body.[3]

The effective use of topical therapies is a common challenge for caregivers of children with skin diseases, such as AD. Unlike oral therapies in the form of a pill or capsule, the dose of topical agents can vary based on the amount applied to the skin, the size of the affected surface and the frequency of application. Treatment success in AD depends in a large proportion, on the regular and appropriate application of topical therapies. For topical ointments, such as MPA 0.1% (Advantan), a validated Finger-Tip Unit System provides a practical guide to parents and doctors caring for children of all different ages, with varied disease localization (Fig. 3).[14,15] This system helps to take the guesswork out of topical therapy dosing, in an effort to improve adherence to therapy and clinical outcomes in children and infants.

Rapid itch relief as a treatment goal

Early, not just effective, intervention is important for preserving QoL in young patients with AD. Rapid itch relief also leads to earlier disruption of the itch-scratch cycle, and therefore, to the prevention of the associated negative physical and psychological

Table 1 Comparisons of levels of evidence* for efficacy and safety of MPA in children with AD

Description of study	*N*	Ages of children	Level of evidence	References
Multicentre, double-blind RCT with MPA 0.1% ointment QD vs. tacrolimus 0.03% ointment BID in acute severe AD; duration ≥2 weeks, ≤3 weeks; endpoints based on changes in EASI, IGA, DLQI and CDLQI	129 vs. 136	2–15 years	I	9
Multicentre, double-blind RCT with MPA 0.1% cream twice weekly vs. emollient only, in stabilized acute severe to very severe AD; duration 16 weeks	112 vs. 109	>12 years	I	10
Multicentre, double-blind RCT with MPA 0.1% cream BID vs. PC 0.25% cream BID in AD; duration ≤21 days	38 vs. 40	3–14 years	I	11
Multicentre, double-blind RCT with MPA 0.1% ointment QD plus vehicle QD vs. PC 0.25% ointment BID in AD; duration ≤21 days	55 vs. 53	4 months–14 years	I	43
Multicentre, double-blind, randomized safety study with MPA 0.1% ointment BID vs. HCB 0.1% cream BID in AD; 12-day study with 2-day run-in phase, 7 days on treatment and 4-day wash-out phase	10 vs. 10	6 months–12 years	I	43
Multicentre, open-label, prospective, randomized, comparative study with MPA 0.1% cream QD vs. MMF 0.1% cream QD in acute or subacute mild or moderate AD; duration ≥1 week, ≤4 weeks	69 vs. 68	2–14 years	I	17
Double-blind, non-randomized bilateral safety study with MPA 0.1% cream BID vs. PC 0.25% cream in AD BID; duration 3 weeks	38 vs. 40	3–14 years	IIi	18
Double-blind, non-randomized bilateral safety study with MPA 0.1% fatty ointment vs. BMV ointment in AD; duration 4 weeks	40 vs. 40	3–14 years	IIi	18
Single centre, open-label, uncontrolled study with MPA 0.1% ointment QD; patients stratified as having mild, moderate or severe AD; duration ≤ 21 days depending on disease severity; final analysis based on changes in SCORAD	51	6 months–15 years	IIii	19
Single centre, open-label, uncontrolled study with MPA 0.1% ointment QD in mild, moderately severe or severe AD†; duration 2–4 weeks; final analysis was based on physician assessment	28	4 months–12 years	IIii	20
Multicentre, observational open-label, uncontrolled study with MPA 0.1% ointment, 0.1% cream and 0.1% milk in AD; duration 3 weeks with cream and ointment, 2 weeks with milk; final analysis based on subjective and objective patient/carer and physician assessment	443	<15 years	IIii	5
Single centre, open-label, uncontrolled study with MPA 0.1% milk QD in acute or subacute AD; duration ≤14 days; final analysis based on parent's assessment	27	2 months–4 years	IV	8

*Evidence as supported by (I) at least one properly designed randomized, controlled trial; (IIi) well-designed controlled trials without randomization; (IIii) well-designed cohort or case control analytic studies, preferably from >1 research centre or group; (III) opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees; or (IV) evidence inadequate as a result of problems of methodology (e.g. sample size, length, comprehensiveness, follow-up and conflicts in evidence).

†Patients with moderately severe or severe AD received concomitant oral anti-histamines, sedatives and tar-based ointments.

AD, atopic dermatitis; BID, twice per day; BMV, betamethasone valerate; CDLQI, children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HCB, hydrocortisone-17-butyrate; IGA, Investigator's Global Assessment; MMF, mometasone furoate; MPA, methylprednisolone aceponate; PC, prednicarbate; QD, every day; RCT, randomized controlled trial; SCORAD, SCORing Atopic Dermatitis.

Table adapted with permission from Blume-Peytavi and Wahn (2011).[3]

complications and sequelae. As discussed elsewhere, integrated strategies, involving paediatric, dermatologic and psychological expertise, are necessary to meet the clinical needs of young patients with AD. Consistent with this goal, more standardized, patient-focused methods of evaluating itch are needed to facilitate the selection of optimal therapy.

In recent years, the emerging relationship between pruritus and QoL in children has shifted the therapeutic focus towards effective

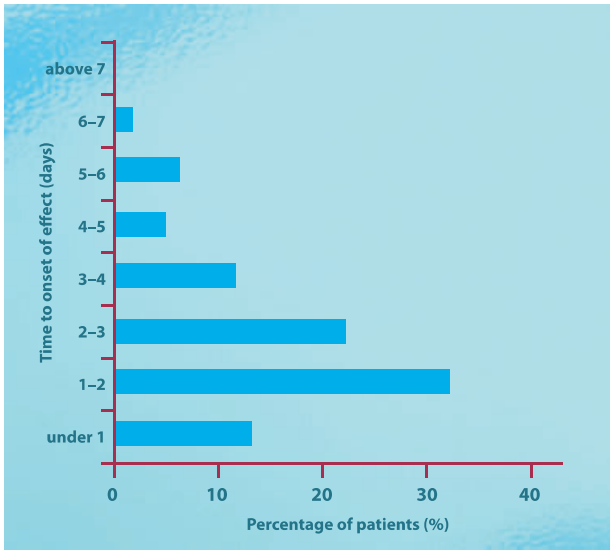

Figure 2 Patient-assessed onset of effect with MPA 0.1% treatment – atopic dermatitis subset only (*N* = 443). Figure adapted with permission from Niedner and Zaumseil, 2004.[5]

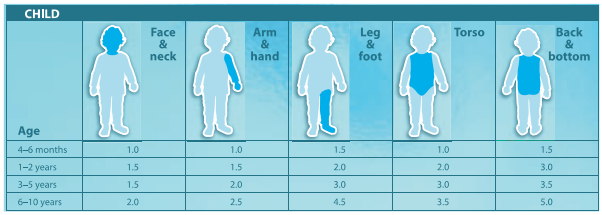

Figure 3 The Finger-Tip Unit (FTU) System is a practical guide for parents and doctors to measure the amount of topical ointment required to effectively cover a discrete area of a child's body. The figure above shows the required number of FTUs adjusted for the age of the child and location of the affected skin area. One FTU is the amount of ointment expressed from a tube with a 5-mm diameter nozzle, applied from the distal skin-crease to the tip of the index finger. Figure adapted with permission from Long and Finlay (1991) and Long *et al.* (1998).[14,15]

alleviation of itch in the short term. However, the thorough characterization of rapid-onset anti-pruritic effects of topical agents has been limited by study design. Traditional measures of pruritic effectiveness assess symptom reduction over days and weeks – not hours – immediately following treatment, and thus, do not inform the urgent clinical needs of paediatric patients.

The optimization of short-term pruritus relief assessment is an area of active clinical investigation, which utilizes models of inducible itch and currently available topical anti-inflammatory agents. Although preliminary results with MPA 0.1% (Advantan) are encouraging, more research is necessary to characterize the rapid-onset effects of these agents in various chronic skin conditions.[16] Indeed, there is a need for clinical trials that examine the potential of topical agents to provide pruritus relief in children in the hours immediately following treatment.

The use of topical treatments that effectively manage AD symptoms and facilitate rapid relief of itch is a necessary part of an integrated treatment approach for AD-associated pruritus. The selection of anti-pruritic agents should be driven by evidence of demonstrated rapid onset of effect, a proven safety profile in children and infants, and the availability of galenic formulations that enable physicians to meet the unique needs of paediatric patients.

Conflicts of interest

LGP is an employee of Bayer HealthCare. UE is an employee of Intendis.

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