Review

Skin Pharmacology and Physiology

Safety and Efficacy of Fluticasone Propionate in the Topical Treatment of Skin Diseases

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Abstract

Fluticasone propionate – the first carbothioate corticosteroid – has been classified as a potent anti-inflammatory drug for dermatological use. It is available as 0.05% cream and 0.005% ointment formulations for the acute and maintenance treatment of patients with dermatological disorders such as atopic dermatitis, psoriasis and vitiligo. This glucocorticoid is characterized by high lipophilicity, high glucocorticoid receptor binding and activation, and a rapid metabolic turnover in skin. Although skin blanching following fluticasone propionate exceeds that of corticosteroids of medium strength, several clinical trials demonstrate a low potential for cutaneous and systemic side-effects, even in difficult-to-treat areas like the face, the eyelids and intertriginous areas. Even among paediatric patients with atopic dermatitis, fluticasone propionate proved to be safe and effective. These pharmacological and clinical properties are reflected by the high therapeutic index of this glucocorticoid.

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Introduction

Topical glucocorticoids are the drugs most often prescribed by dermatologists due to their anti-inflammatory, immunosuppressive and antiproliferative effects, which are thought to be their primary mechanism of action in the treatment of several skin disorders [1]. The clinical use of these drugs, however, is still restricted by the potential for adverse events. Therefore recent research has focused on the development of steroids with lower toxicity without a loss of effectiveness. The synthetic carbothioate corticosteroid fluticasone propionate (FP, Flutivate®) combines excellent clinical efficacy with minimal risk for local or systemic adverse events. It is available as a cream and ointment with similar potency, yet differing strength (0.05 vs. 0.005%) of the active agent. This article reviews the pharmacology and the safety profile as well as the use of topical FP in clinical practice, paying particular attention to the treatment and prophylaxis of skin diseases such as atopic dermatitis (AD), psoriasis and vitiligo.

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Fig. 1. Molecular structure of cortisol, FP and its inactive metabolite. Structural modifications at positions 1, 6 and 9 are activating in terms of anti-inflammatory and mineralocorticoid activity, while the two esterifications highly increase the natural lipophilicity and the drug uptake of FP. Rapid metabolization to the inactive moiety due to ester cleavage replacing the thioester moiety at position 17 by a carboxylic acid function contributes to the low systemic activity.
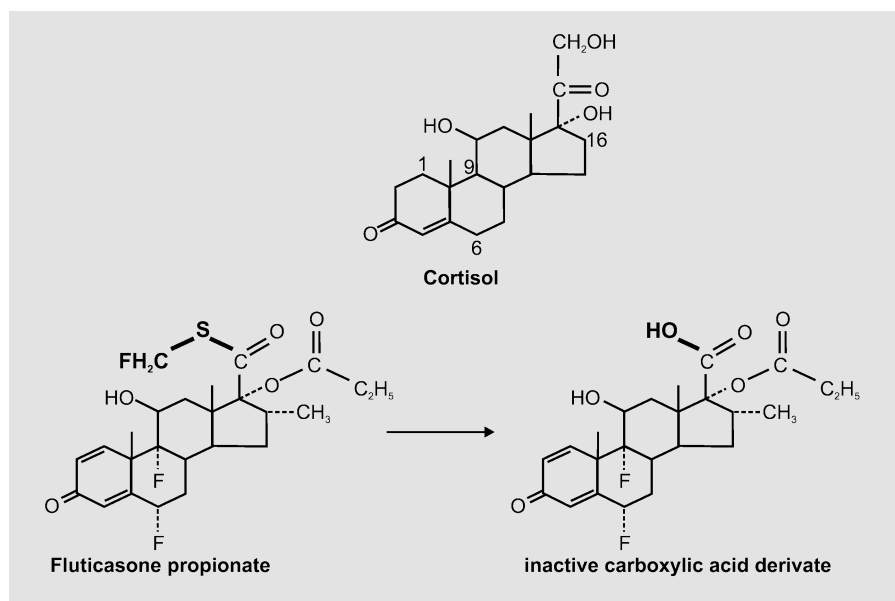
Chemical Structure and Glucocorticoid Receptor Affinity

In general, glucocorticoids have a so-called androstane structure with 17 carbon atoms arranged in three 6-membered rings and one 5-membered ring. Additional modifications to this basic skeletal structure have led to the development of highly lipophilic corticosteroids such as FP, which has been classified as a potent corticosteroid [2]. In this fluoromethyl androstane-17β-carbothioate, an extra double bond at positions 1 and 2, two fluorines at positions 6 and 9, and an α-methyl group at position 16 are additionally inserted (fig. 1). The two esterifications at position 17 (with a propionate group) and at position 20 (with a fluorized thio ester, named 'carbothioate') highly increase the molecule's natural lipophilicity, its cutaneous drug uptake and its binding to human skin tissue [3] as well as to the glucocorticoid receptor (GR), a 777-amino-acid protein member of the superfamily of ligand-receptor nuclear receptors [4]. X-ray crystallographic investigations revealed that the carbonyl of the 17β-carbothioate ester substituent lies below the plane of ring D rather than above, as observed for other corticosteroids, and might explain the rapid enzymatic hydrolysis of FP to its inactive metabolite [5].

Quantitative structure-activity relationship studies indicate that FP has a high affinity to the GR reflected by a fast association and slow dissociation rate, suggesting that the FP-GR complex will be stable [6]. Indeed, using a kinetic assay, Högger and Rohdewald [7] measured the GR equilibrium dissociation constant of FP in human lung cytosol and reported a value of 0.49 nmol/l. The receptor complex half-life exceeded 10 h, which significantly differs from dexamethasone (1 h), triamcinolone acetonide (4 h) and budesonide (5 h) [7]. Normalization of the relative receptor affinity to dexamethasone, with dexamethasone given a value of 100, resulted in a remarkable value of 1,910 for FP. Results of an equilibrium competition assay (relative receptor affinity: 1,401) are rather close [7]. Despite these receptor pharmacokinetic differences, FP provides selectivity for the GR by having only little or no affinity to progestagen, androgen, oestrogen or mineralocorticoid receptors [8]. This GR affinity can be attributed to the halogenation at the 9α position increasing both glucocorticoid and mineralocorticoid effects, presumably through an electron-withdrawing effect of the 11β-hydroxyl group [9]. Furthermore, the insertion of an α-methyl substituent at position 16 is known to eliminate mineralocorticoid activity [8].

Effects of the FP-GR Complex

GR gene regulations have been studied at the molecular level. Upon interaction with the GR, FP interferes with the effects of transcription factors such as the activating protein (AP) 1 and the nuclear factor κB [10], which are involved in the activation of pro-inflammatory cyto-

kines like interleukin (IL) 1α and IL-1β [11]. For example, AP-1-induced transactivation increases rapidly in response to mitogenic factors and tumour promoters and enhances cell proliferation and activates inflammatory signalling pathways. Like the other corticosteroids, FP potently antagonizes AP-1 effects. Inhibition of AP-1 and nuclear factor κB explains anti-inflammatory, immunosuppressive and antimitotic glucocorticoid effects in the treatment of psoriasis or eczema [11]. Genes known to be up-regulated by FP include those encoding for lipocortin I and the p11/calpactin-binding protein which are involved in the suppression of the release of arachidonic acid [11]. Furthermore, lipocortin I inhibits phospholipase A_2, reducing the amount of arachidonic acid released from phospholipids [1].

At the cellular level, the beneficial properties of FP in terms of inflammation and pathogenic hyperproliferation also become obvious from the decrease in markers of inflammation in human endothelial cells, such as the endothelial-leukocyte adhesion molecule and the vascular cell adhesion molecule [12, 13]. Furthermore, FP inhibits TNF-α-stimulated E-selectin at a concentration of 1 nmol/l in human endothelial cells, whereas 8-fold higher concentrations of budesonide are required for the same effect [12]. In vitro studies also indicate that FP directly suppresses a continuous or excessive activation of neutrophil function and might suggest a further role for this agent in the inhibition of inflammation and in the modulation of neutrophil-mediated damage of the connective tissue [14]. Furthermore, FP normalizes the increased level of mucosal mast cells in presensitized animals, reduces T cell proliferation and enhances T cell apoptosis at least partly by the inhibition of the T cell growth factor IL-2 [15]. In patients with bronchial asthma, FP reduces eosinophilia by promoting eosinophil apoptosis [16] and indirectly by a diminished production of cytokines such as IL-5, IL-8, IL-13 and the respective receptors that are involved in eosinophil maturation, recruitment and survival [15, 17, 18]. In the presence of IL-5, FP (EC_{50} = 1.7 nmol/l) was revealed to induce concentration-dependent apoptosis of eosinophils being 5 times more potent than budesonide and 10 times more potent than triamcinolone acetonide and flunisolide [19].

Vasoconstrictor Activity in Humans

When applied under occlusion to the normal skin of human subjects, potent glucocorticoids produce blanching or vasoconstriction. In this standard test, a known range of doses of the glucocorticoid is applied to the skin of the inner forearm, and the blanching due to vasoconstriction is compared visually to a laboratory standard, e.g. fluocinolone acetonide [20]. The intensity of blanching is then quantified to estimate the topical activity of corticosteroids. Subsequent studies have shown that vasoconstrictor activity is closely related to anti-inflammatory effects in skin diseases [21].

A series of vasoconstrictor studies were undertaken to compare FP to topical corticosteroids used for inflammatory diseases [22]. FP turned out to be 3 times more potent than beclomethasone-17,21-dipropionate and its active metabolite, beclomethasone-17-monopropionate, and equipotent to mometasone furoate, a synthetic 16α-methyl analogue of beclomethasone. FP was 10 times more potent than triamcinolone acetonide, flunisolide and fluocinolone acetonide, and intermediate in potency between betamethasone-17-valerate (less potent) and clobetasol-17-propionate (more potent) [22].

Safety Profile

Most topical corticosteroids are absorbed in quantities that can produce both systemic and topical adverse events. These adverse effects are related mainly to actions on electrolyte and water balance, neoglycogenesis and to an inhibitory effect on adenohypophyseal function [23].

Potential for Systemic Adverse Events

The principal systemic side-effects of glucocorticoids comprise Cushing's syndrome, hypertension, electrolyte imbalance, diabetes mellitus, pseudoprimary aldosteronism, osteoporosis or growth retardation. FP is well tolerated having a low potential to cause adverse systemic effects. Compared to first-generation topical corticosteroids such as betamethasone, the compound yields little hypothalamic-pituitary-adrenal axis effects reflecting the high quotient between topical activity and systemic activity due to its lipophilicity [24, 25] and its hepatic metabolism to the inactive moiety 17β-carboxylic acid [26, 27]. In a clinical trial investigating the propensity for systemic absorption, 25 g FP 0.05% cream were allotted twice daily under occlusion for 5 days in one group, and 12.5 g FP 0.05% cream were applied twice daily without occlusion for 21 days in the other group. Even upon application of these large doses there was no evidence of a suppressed cortisol secretion underlining the low propensity for sys-

temic absorption of FP [28]. In 120 patients with moderate-to-severe eczema, the safety and tolerability of FP 0.05% cream versus hydrocortisone-17-butyrate 0.1% cream was assessed for 3 months. After 3 months of treatment, plasma cortisol levels were not significantly affected by either agent. Among patients with changes in plasma cortisol, 56% were in the hydrocortisone-17-butyrate group and 27% were in the FP group [29]. Although the 9α-fluorination enhances all the biological activities of glucocorticoids, a concomitant increase in adverse systemic effects could not be reported [4].

Potential for Local Adverse Events

Moreover, topical steroids are as a rule capable of causing local side-effects such as skin atrophy, steroid face and teleangiectasia, pruritus, burning, perioral dermatitis, rosacea, corticoid acne, allergic contact dermatitis, hypertrichosis or hyperpigmentation [30].

Skin Atrophy
Skin atrophy as the most relevant local side-effect is expressed by flattening of the Malphigian and horny layers and of the rete ridges [31]. The decreased size of keratinocytes and of the stratum corneum, the reduced amount of melanin transferred to keratinocytes and a diminished synthesis of collagen in particular largely contribute to epidermal and dermal thinning, with resulting teleangiectasia, ecchymoses and skin fragility [32].

In the previously mentioned trial in patients with eczema, none of the subjects treated with FP experienced any major local side-effects, including cutaneous atrophy [29]. Only 8.5% of the persons treated with FP and 11.7% of the hydrocortisone-17-butyrate group observed drug-related adverse events such as folliculitis and pustules. A further randomized, placebo-controlled study with 40 healthy individuals used pulsed A scan ultrasound to characterize the extent of cutaneous atrophy due to FP 0.05% cream versus vehicle cream after once daily non-occlusive application for either 2, 4, 6 or 8 weeks. FP caused a mean decrease in skin thickness by 3% compared with placebo ($p = 0.62$) [33] while the dermal thinning potential was 15–16% for betamethasone valerate 0.1% cream and for hydrocortisone-17-butyrate 0.01% cream, and 13% for mild corticosteroids such as hydrocortisone 1.0% cream when applied twice daily [34]. The low reduction seen with once daily applied FP 0.05% cream points towards a minimal atrophogenic potential, since once daily applied fluticasone 0.05% cream has been shown to be equally effective with the twice daily application [35]. Likewise, a paediatric safety trial enrolling 51 children (aged 3 months to 5 years) with extensive moderate to severe psoriasis or eczema revealed a low skin thinning potential (2%) even after an extensive treatment with large quantities of FP 0.05% cream [36].

Eyelid/Periorbital Dermatoses and Contact Allergy
Local side-effects might in particular occur after application of topical steroids in the treatment of eyelid or periorbital dermatoses (i.e. seborrhoeic dermatitis, contact dermatitis and AD, lichen simplex and blepharitis) as a frequent cause of conjunctival sac contamination, which can lead to glaucoma, ocular hypertension, cataracts and blindness. Recently, Tan et al. [37] have evaluated the in vitro penetration of FP 0.005% ointment in samples of normal human eyelid skin by means of modified diffusion chambers and concluded that only small amounts of FP 0.005% ointment penetrate eyelid skin.

Topical corticosteroids have also been documented as a frequent cause of true, delayed-type hypersensitivity reactions leading to a disseminated or generalized eczematous reaction [38]. They were found to be the seventh most common allergen after nickel sulphate, cobalt chloride, colophony, fragrance mix, balsam of Peru and potassium dichromate. Several problems are combined with the identification of a contact allergy to corticosteroids: the clinical picture is often misleading, the patch test procedure is a subject of discussion and the diagnosis is probably not considered often enough because clinicians were rarely aware of such a possible adverse effect [39]. Concerning treatment options, non-fluorinated corticosteroids might be more likely to induce a contact allergy than fluorinated steroids since they react more rapidly with arginine than fluorinated steroids, thus inducing sensitization [40]. Further studies point towards a low potential of FP concerning hypersensitivity reactions and cross-sensitivity reactions to non-fluorinated steroids, such as tixocortol pivalate or budesonide [41]. In a recent patch test study, the allergenic potential of FP 0.05% cream was analysed both with patients who had used it to treat eczema as well as persons with a known contact allergy to other corticosteroids [42]. Of these 206 corticosteroid-allergic subjects, 118 had actually used Flutivate, and 155 were tested with an extended corticosteroid series (consisting of 63 different corticosteroids) in which it was included. As a result, only 3.3% (i.e. 7 persons) gave a clear (+ or ++) reaction to it. Most notably, only 1 of these 7 FP-allergic patients had actually been exposed to fluticasone 0.05% cream, so most of the positive reactions to it must be due

to cross-sensitivity. This observation is in line with an earlier case report indicating allergy to FP as a cross-reaction in a patient sensitive to many other topical corticosteroids [43]. Therefore, in addition to the 'classic' goals of glucocorticoid research – high selectivity and low systemic absorption – FP does not give rise to widespread corticoid sensitization and might also be used in most patients who have been previously sensitized to corticosteroids.

Treatment of AD with FP

Adults

Topical corticosteroids are the mainstay of therapy in AD. In the previously mentioned study comparing FP 0.05% cream with hydrocortisone-17-butyrate 0.1% cream, FP proved to be a both well-tolerated and effective agent in the treatment of patients with moderate-to-severe eczema [29]. Likewise, the 0.005% ointment formulation revealed to be more effective than its vehicle [44] and similar in efficacy to the high-potency drug betamethasone-17,21-dipropionate 0.05% ointment [45] in the treatment of mild-to-moderate eczema. After twice daily application for 4 consecutive weeks, no significant differences in terms of the physician's gross assessment, the severity of signs and symptoms of eczema and the patient's assessment of treatment effects were observed.

However, many clinicians are reluctant to prescribe high-potency topical corticosteroids for the long-term treatment of AD of the face and intertriginous areas because these areas are more susceptible to corticosteroid penetration due to thin skin and self-occlusion. The in vitro use of FP 0.005% ointment on surgically excised eyelid skin has already been reported to bear a low risk of cutaneous side-effects and suggests that FP might be a suitable candidate for the management of the face and intertriginous areas [37]. Hence Tan et al. [46] conducted a long-term open-label study of 21 adults with AD being treated with FP 0.005% ointment twice daily for the first 2 weeks, and then only once daily for 2 consecutive days each week for 8 more weeks. As a result, 95% of the persons with facial and intertriginous lesions responded to the treatment after 2 weeks. Furthermore, improvement was maintained in most patients over a 71-day period, patients had high remission rates of disease symptoms, and there was no development of clinical signs of unwanted effects like skin atrophy or teleangiectasia [46]. Although this clinical trial did not assess eyelid or periorbital lesions, one might conclude that FP 0.005% ointment is a safe and effective agent in the treatment of AD

on the face and intertriginous areas when tapering the dose from a twice daily application to a long-term management regimen of once daily application on 2 consecutive days every week for 8 weeks. At the same time, another research group observed that pimecrolimus 1% cream, a non-steroid inhibitor of inflammatory cytokines, might be as efficacious and safer in the long-term treatment of AD, thus reducing or eliminating the need for corticosteroid treatment [47]. However, these results do not point towards a steroid-sparing effect of pimecrolimus as indicated since the study does not refer to common therapeutic standards as the topical corticosteroid is only applied in the rare case of unacceptable itch and clinical signs like crusting, excessive scratch marks or severe erythema. After the use of the topical corticosteroid, patients had to administer pimecrolimus or vehicle depending on the group they were in, thus favouring the pimecrolimus group which is treated with an active agent for 1 week more than the placebo group. Furthermore, this study was vehicle controlled, does not explicitly refer to the treatment of sensitive areas such as facial and intertriginous skin and administers prednicarbate 0.25% cream in the event of flares. Therefore a clinical study comparing FP to pimecrolimus in the long-term management of AD of the face and intertriginous areas appears most interesting.

Children

Among the paediatric population, AD is the most common chronic disease in Europe, the USA and Japan. The 'gold standard' of therapy is a mildly or moderately potent topical glucocorticosteroid such as hydrocortisone and clobetasone butyrate, respectively, with emollients as effective adjuncts to achieve a steroid-sparing effect without compromising the anti-inflammatory efficacy [48, 49]. An observational study compared FP 0.05% cream (once daily) to clobetasone butyrate 0.05% cream (twice daily) in 21 children (3–8 years old) with moderate AD and showed that these two therapeutic regimens are both safe with FP 0.05% cream being at least as effective as clobetasone butyrate 0.05% cream [50].

An effective method of treatment with dressings in children with AD is the wet-wrap technique involving the use of open-weave cotton tubular dressings impregnated with diluted topical corticosteroids [51]. A comparative trial evaluated the efficacy of wet wraps using FP 0.005% ointment and mometasone furoate 0.1% ointment for the treatment of refractory AD in 27 children [52]. The agents were allotted once daily for 4 weeks without wet wraps or for 2 weeks without wet wraps followed by 2 weeks of application under wet wraps. Interestingly, significant

clinical improvement stagnated after 2 weeks in patients who were solely treated with the open application, while those with wet wraps continued to improve and finished the study with significantly less severe disease [52]. The low drop-out rate of 5.5% indicated that the wet wraps were well tolerated. Therefore both, FP 0.005% and mometasone furoate ointments, are effective in the treatment of AD with wet wraps as an intermittent and short-term measure being useful in further improving this skin disorder. Since the wet-wrap technique represents an occlusive and hydrating dressing on children with inflamed skin and a defective barrier, percutaneous absorption and systemic bioactivity of the corticosteroid might be increased. In order to decrease the amount of topical corticosteroid used, Wolkerstorfer et al. [53] evaluated the efficacy and safety of several dilutions of FP 0.05% cream (i.e. 5, 10, 25 and 50%) for 2 weeks. Most notably, the significant clinical improvement in children with AD was, irrespective of the FP dilution, applied under a wet wrap and occurred mainly during the first week of treatment. Taking into account that the second week of treatment only led to minor improvements, the authors concluded that 1 week of treatment with a 5% dilution under a wet wrap might suffice to achieve major improvement in the treatment of children with severe AD.

Maintenance Treatment in Adults and Children

AD is a chronic relapsing condition and requires a long-term management approach since many patients will experience recurrent exacerbations [54]. Prompt treatment of flare-ups by twice daily administered topical mid-strength corticosteroids until the inflammation subsides is recommended by many dermatologists as first-line treatment for the control of relapses, thus minimizing steroid exposure and the risk of local or systemic side-effects [54]. Several recent studies have investigated a treatment approach to the long-term management of AD with FP. A small-scale study indicated that once an acute flare-up of AD had been stabilized by daily FP 0.005% ointment, remission of AD can be maintained with regular daily use of emollients and bath oil plus FP applied twice weekly to areas of the skin that had been brought under control but were prone to relapse [55]. By this treatment strategy, the risk of relapse was reduced two- to threefold, and the relapse-free period could be extended to more than 16 weeks, while the median time to relapse was just over 4 weeks in subjects receiving intermittent vehicle plus emollients [55]. A large multicentre study comprising both adult (44%) and paediatric (66%) subjects (aged 3 months up to 65 years) with moderate to severe AD also

gave evidence of marked clinical improvement of AD due to FP 0.05% cream in terms of efficacy and safety [56]. By administration of the cream formulation, the risk of relapse was reduced sevenfold in adults and eightfold in children. Furthermore, the relapse-free period on intermittent FP/emollients was estimated to exceed 20 weeks, while the median time to relapse was just 4–5 weeks in subjects receiving intermittent vehicle plus emollients.

However, it remains puzzling that the cream formulation is more effective than the more occlusive ointment formulation found to be equipotent in the vasoconstriction assay irrespective of the differing concentration [22]. Hence these two trials were followed by a similar large-scale study only with adult patients (aged 12–65 years) exploring the efficacy and safety of both, FP 0.05% cream and 0.005% ointment, applied according to the same regimens [57]. As a result, following stabilization of a flare, the addition of regular, twice weekly FP to an emollient maintenance regimen also significantly reduced the risk of relapse in moderate to severe AD. However, FP 0.05% cream again proved to be more effective than FP 0.005% ointment with the risk of relapse being reduced sixfold and twofold, respectively [57]. The authors conclude that the potency of a topical corticosteroid preparation as determined by the human vasoconstriction/skin blanching assay as an index of percutaneous absorption of a compound might not fully reflect its performance in treating healed and active lesions of AD. Furthermore, from a cosmetic point of view, ointments are greasy and patients might feel less comfortable, which might have affected the patients' compliance with ointments. However, further studies are warranted to fully elucidate the unexpected difference between these formulations.

As already shown, most of the published data about the long-term benefits of FP in the maintenance treatment of AD focus on adults. Hence, two recent multicentre studies compared the efficacy of FP 0.05% cream versus the mildly potent hydrocortisone 1% cream and the moderately potent hydrocortisone-17-butyrate 0.1% cream, respectively, for both acute and maintenance treatment of AD in children (aged 2–14 years) [58]. The respective creams were allotted twice daily for 2–4 weeks until AD was stabilized, and thereafter treatment was stepped down intermittently as required (up to twice daily) to affected areas at the first sign of a relapse for up to 12 weeks. Patients were also allowed to use emollients as required. The total AD score combining measures of both extent and severity of AD, the diary card data and the final clinic visit of the maintenance phase indicated that FP applied twice daily was significantly more effective in

both the acute and long-term management of moderate to severe AD than hydrocortisone or hydrocortisone-17-butyrate. The treatment differences between FP 0.05% cream and hydrocortisone-17-butyrate 0.1% cream differ from the results of Juhlin [29], who reported no difference between these agents. However, the recent observations were solely made in paediatric patients and underscore that FP provides a high level of efficacy and maintenance of disease control with a tolerability similar to the mildly potent hydrocortisone 1%.

Treatment of Psoriasis with FP

Several studies compared the efficacy of FP with other agents in the treatment of psoriasis, a chronic, genetically influenced, immune-mediated skin disease characterized by abnormal proliferation and differentiation of epidermal keratinocytes as well as dermal infiltration of inflammatory components. Callen [59] discusses two double-blind, randomized, parallel-group 4-week studies that evaluated FP 0.05% cream versus betamethasone valerate 0.1% cream, also a medium potent topical corticosteroid, in the treatment of moderate-to-severe psoriasis. Concerning efficacy, no statistically significant differences could be found between the two agents. In a further 4-week study enrolling 125 patients with moderate-to-severe psoriasis, FP 0.05% cream proved to be superior to hydrocortisone-17-butyrate 0.1% cream after a duration of 3 weeks and at the end-of-treatment visit. By the end of therapy (i.e. 4 weeks), the skin of 79% of patients receiving FP 0.05% cream was rated as cleared, excellent or good versus that of 68% of patients who used hydrocortisone-17-butyrate 0.1% cream [60].

Nürnberger [61] describes a trial that compared twice daily administration of FP 0.005% ointment with hydrocortisone-17-butyrate 0.1% ointment in 115 adults with moderate-to-severe psoriasis. Most patients had psoriatic involvement of long duration with an affected mean body surface area of 17%. In this difficult-to-treat population, FP was found to be therapeutically superior to hydrocortisone-17-butyrate ointment. Fluticasone had a rapid onset of action, significantly reduced psoriatic plaque scaling and thickening after 1 week and erythema after 2 weeks of treatment. Cleared, excellent or good end-of-treatment response rates were 72% for FP compared with 68% for hydrocortisone-17-butyrate. A comparison of the efficacy between FP 0.005% ointment and a high-potency corticosteroid, betamethasone-17,21-dipropionate 0.05% ointment, revealed no significant differences while both medi-

cations were well tolerated [62]. This finding is important, since FP bears a lower risk for local and systemic side-effects and might have excellent safety for treatment of corticosteroid-responsive dermatoses, particularly those of the recurring type such as psoriasis. Furthermore, the use of FP has been associated with a low risk of cutaneous side-effects for sensitive facial and intertriginous areas [63]. FP 0.005% ointment was applied twice daily for 2 weeks of acute treatment, followed by a long-term management phase of 8 weeks, during which the dosage was decreased to once daily for 2 consecutive days every week. Most patients maintained improvement over 71 days of the study, and no patient experienced clinical signs of atrophy or teleangiectasia. Recurrence rates were low in facial and intertriginous sites and significantly lower than in non-facial, non-intertriginous areas [63].

Treatment of Vitiligo with FP

Vitiligo is an acquired skin disorder caused by the disappearance of pigment cells from the epidermis. Histology shows a complete absence of melanocytes in the lesions. Although there is no universally effective and safe therapy available, many treatment options such as photo-(chemo)therapy, autologous transplantation methods, depigmentation therapy and corticosteroid use [64] have been well established. It is assumed that corticosteroids suppress inflammatory and auto-immune processes in active progressing lesions, thus allowing melanocyte repopulation spontaneously or by UV irradiation [64].

Novel strategies include a long-term combination therapy of topical FP plus exposure to long-wave ultraviolet A radiation (320–400 nm). FP 0.05% cream allotted once daily and ultraviolet A irradiation (10 J/cm^2) performed twice weekly proved to be synergistic in repigmenting localized vitiligo lesions [65]. The combination therapy led to a better repigmentation than either treatment alone. Perifollicular and marginal repigmentation could be observed as fast as 6 weeks after the start of therapy in the treated skin. After a period of 9 months, clinical and histological examinations revealed no evidence of skin thinning or teleangiectasia in both adult and paediatric patients and indicate that FP is a well-tolerated corticosteroid with high anti-inflammatory efficacy for the long-term treatment of vitiligo.

Conclusion

The numerous clinical applications of the topical mid-potency corticosteroid FP for the treatment of AD, psoriasis and vitiligo have been described and attest to its central role in dermatological practice. In addition, potential novel indications of FP corresponding to the beneficial effect on skin barrier disruption caused by nickel-induced allergic contact dermatitis come to horizon [66, 67]. Studies about FP are accumulating, and results suggest an increased overall therapeutic potential in terms of efficacy and tolerability due to its increased affinity and improved GR pharmacokinetics.

Comparative trials indicate that this unique carbothioate combines potent anti-inflammatory effects and a low potential for unwanted systemic and local side-effects: topical activity of FP judging from vasoconstriction proved to be high [22], while skin thinning, allergenic potential and hypothalamic-pituitary-adrenal inhibitory potency are exceptionally weak. According to the guidelines of the German Dermatological Society (Deutsche Dermatologische Gesellschaft) these parameters allow the calculation of the therapeutic index as a useful marker of quality to compare the most commonly prescribed topical corticosteroids in Germany [68]. The value to be determined reaches 2.0, thus being the highest currently found. While this would not indicate a difference to other topical glucocorticoids with increased benefit-to-risk ratio, i.e. prednicarbate, methylprednisolone aceponate and mometasone furoate, FP so far looks unique when it comes to its application in particularly steroid-sensitive areas as well as in the maintenance treatment of relapse/prone chronic inflammatory skin diseases such as AD and psoriasis vulgaris.

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