Topical Therapy I: Corticosteroids and Vitamin D Analogues

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Abstract

Psoriasis is a life-long disease that affects approximately 2 % of the population. Approximately 80 % of psoriasis patients have mild to moderate disease. Topical therapies play an important role in the treatment of patients with mild to moderate disease. Patients often start treatment with topical steroids, vitamin D3 cream or ointment or a combination of the two. This chapter will describe the pharmacokinetics and mechanism of action of topical steroids and vitamin D analogues. Long-term side effects, the importance of vehicle, potency ratings as well as combination use with other treatment modalities will be discussed.

Keywords

Psoriasis • Topical steroids • Vitamin D cream • Cutaneous atrophy • Topical treatment of psoriasis • Topical steroid side effects

Introduction

Topical corticosteroids (TCS) are a mainstay in treatment of a wide range of inflammatory dermatoses and are the cornerstone of psoriasis therapy. As long-term use of topical steroids can cause side effects, vitamin D analogues have arisen as an important adjunct to therapy for mild to moderate psoriasis.

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Topical Corticosteroids

Pharmacokinetics/Mechanism of Action

There are seven classes of topical steroids which range from superpotent (class 1) to the very low-potency topical steroids (class 7). These classes have been developed based on vasoconstrictor assays [1]. The vasoconstrictor assay involves preparing the test corticosteroid in 95 % alcohol and then applying it to the volar surface of a normal volunteer's forearm, the alcohol is left to

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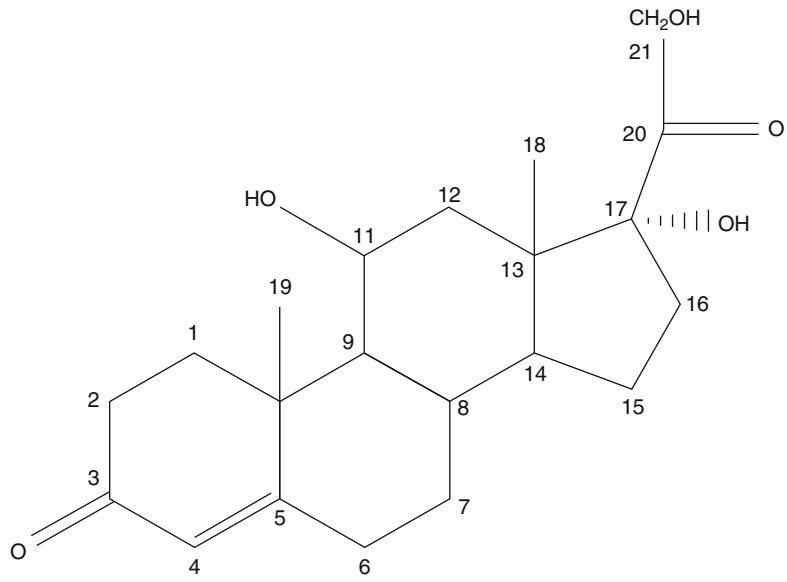

Fig. 6.1 Topical corticosteroid

evaporate and then the test area is covered with an occlusive dressing for 16 h. The area is then washed off and vasoconstriction is assessed using a statistical analysis. The vasoconstrictive assay correlates well with clinical efficacy and is reproducible.

Three factors determine the pharmacokinetics and potency of a topical corticosteroid: the structure of the corticosteroid molecule, the vehicle and the skin onto which the corticosteroid is applied [2]. Hydrocortisone is the central structure of most topical corticosteroids. Variations are formed by placing hydroxyl groups into the 11-β, 17-α, and 21 positions. Additionally, ketone groups at the 3 and 20 positions and a double bond into the 4 position of the glucocorticoid nucleus distinguish between classes. Adding or altering functional groups such as hydroxyl, hydrocarbon, ester, fluoro, chloro, acetonide or ketone at certain positions can vastly impact the molecule's pharmacokinetics [2]. The alteration of hydroxyl groups modifies the molecule's lipophilicity, solubility, percutaneous absorption and glucocorticoid receptor binding ability [2].

Glucocorticoid potency is increased by adding a double-bond at position one, additional fluorination or chlorination [2] (Figs. 6.1 and 6.2). Additionally, halogenation at the 6-α or 9-α position increases glucocorticoid receptor binding activity [2]. Decreased mineralocorticoid activity as in dexamethasone, betamethasone and triamcinolone is accomplished by the addition of a 16-α methyl, 16-β methyl, or 16-α hydroxyl group.

Finally, epidermal enzymes cause the de-esterification of topical corticosteroids into inactive metabolites. Increased potency can be accomplished by inhibiting de-esterification through halogenation at the 21 position.

Vehicle

The vehicle of a topical corticosteroid can influence percutaneous absorption and therapeutic efficacy. Corticosteroids in an ointment vehicle may be more potent than the same molecule in a cream, lotion or other preparation because occlusive vehicles enhance percutaneous absorption through increased hydration of the stratum corneum.

When choosing a topical steroid, one must first decide on the desired potency based on the severity and the location of the skin disease. Then, one must decide on the vehicle based on the type of lesion to be treated, need for hydration or drying effect, location and potential for irritation

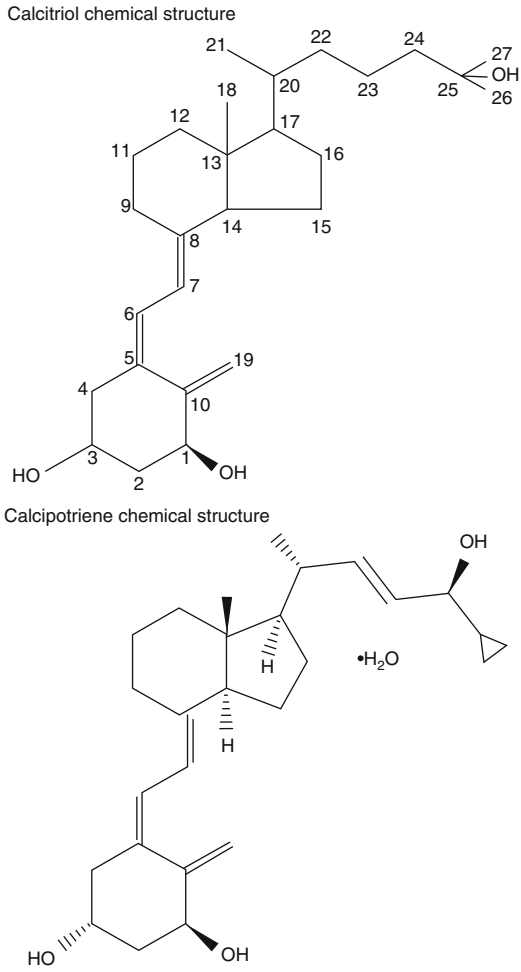

Fig. 6.2 Diagram of steroid molecule. (*Top*) Calcitriol chemical structure, (*Bottom*) Calcipotriene chemical structure

by components of the vehicle. Lotions tend to be elegant for the face, ointments work well for dry lesions and gels are more useful in hairy areas or for a drying effect for a wet lesion. Potent and superpotent topical steroids should be avoided on the face and intertriginous areas due to the risk of atrophy.

The vehicle may alter the pharmacokinetics of a topical steroid molecule thereby affecting its potency. Propylene glycol and alcohol, common solvents, can affect percutaneous absorption by altering the topical corticosteroid molecule's solubility in the vehicle. Propylene glycol enhances potency through increasing penetration through the stratum corneum. Very occlusive agents, such as ointments, also increase the absorption of topical corticosteroids through increased hydration of the stratum corneum [3].

For some agents brand-name preparations are not always equivalent to generics and may have higher or lower potency. For example, Valisone 0.1 % cream (Schering) and Kenalog 0.1 % cream (Westwood-Squibb) have both demonstrated increased vasoconstriction over generics [2]. In addition, Synalar 0.025 % cream is also more potent than generic fluocinolone acetonide 0.025 % cream (Fougera and Company) [2]. However, Aristocort 0.025 % cream and Aristocort 0.05 % cream (Lederle Laboratories) are significantly less potent than generic triamcinolone 0.025 and 0.05 % cream (Fougera and Company) [2]. In general, generic vs. brand-name ointments tend to be closer in vasoconstrictive assays than creams. Additionally there are differences between different generic preparations as well as different brand-name preparations of the same topical corticosteroids [4].

Bioavailability and penetration of the topical corticosteroid increase with inflamed or diseased skin as well as with increased hydration of the stratum corneum. The thickness of the stratum corneum is inversely proportional to the degree of penetration of the topical corticosteroid [5].

Immunologic Mechanisms

Topical corticosteroids are closely involved with all aspects of inflammation in the body. They affect both the adaptive and innate immunity. TCS have been shown to decrease the number and function of Langerhans' cells which are antigen presenting cells found in the skin important in initiating immune responses. Neutrophils are decreased, less adherent to vascular endothelium and have decreased phagocytic function [6–8]. Similarly, leukocytes show decreased antibody-dependent cellular toxicity and natural killer cell function [9, 10]. In addition, the production of many cytokines is decreased including interleukin (IL)-1, IL-2, interferon (IFN)-γ, tumor necrosis factor and granulocyte-monocyte-stimulating factor [2].

Topical steroids decrease the mitotic rate of the epidermis thereby causing thinning of the stratum corneum and granulosum and flattening of the basal layer [11]. TCS also cause atrophy of the dermis through inhibition of fibroblast proliferation, migration, chemotaxis and protein synthesis. They have also been shown to cause inhibition of fibroblast synthesis of both glycosaminoglycans and collagen [12–14].

Use in Psoriasis

The antiproliferative and atrophogenic characteristics of TCS are useful in treating psoriasis. Topical corticosteroids are the mainstay of treatment and often first-line for the management of mild to moderate psoriasis as well as for intertrigous areas and genitalia as these areas can become irritated with the use of other topical agents. In general, for the treatment of localized plaque-type psoriasis high potency or superpotent TCS are prescribed twice daily. Optimal improvement with high potency TCS is often achieved after 2 weeks. Katz and colleagues in several studies indicated the efficacy of clobetasol ointment or betamethasone dipropionate ointment in clearing plaque type psoriasis and found that remission could be maintained by applying 3.5 g three times a week: on Sat am, Sat pm and Sun am [15, 16].

In a placebo-controlled trial, Katz et al. demonstrated that with maintenance therapy consisting of 12 weeks of weekend-only use of betamethasone dipropionate ointment, 74 % of patients remained in remission as compared to 21 % of the patients receiving placebo [17].

Occlusion can greatly increase penetration and efficacy of TCS. Studies have demonstrated that triamcinolone acetonide 0.1 % ointment under occlusion is more effective than clobetasol propionate 0.05 % cream twice daily or triamcinolone acetonide 0.1 % ointment alone [18, 19]. Flurandrenolide (Cordran) tape is frequently prescribed due to its occlusive nature and has been shown to be superior to twice-daily diflorasone diacetate ointment in a randomized bilateral comparison study of plaque-type psoriasis [20]. Clobetasol propionate lotion applied under occlusion with a hydrocolloid dressing (Duoderm ET) once weekly also showed faster remission of psoriasis than unoccluded clobetasol propionate ointment applied twice daily [21, 22]. Foams have been found to have increased efficacy over lotions of the same class of TCS when treating the scalp [23, 24].

In the case of more severe psoriasis, vitamin D analogues are frequently added at the onset as there is a synergistic effect with TCS.

Combination with Other Therapies

Topical corticosteroids work synergistically with light therapy as well as many systemic agents. Psoriasis clears faster when using psoralen plus ultraviolet A (PUVA) with TCS versus PUVA alone. The addition of topical corticosteroids to cyclosporine therapy also leads to more rapid clearance of psoriasis [25]. Topical steroids may also be combined with salicylic acid, anthralin or tazarotene and which provide increased efficacy due to increased penetration. Lower dose etretinate can be prescribed when using a combination of triamcinolone 0.1 % cream compounded with 5 % salicylic acid [25].

Adverse Effects

Systemic adverse effects from topical corticosteroids are uncommon and are increased with young age, liver disease, renal disease, the potency of the drug, amount of skin surface involvement, the use of occlusion, frequency of application and the duration of treatment [2]. The liver metabolizes corticosteroids and the kidneys excrete metabolized and unmetabolized corticosteroid [26]. A higher skin surface-to-body ratio is present in infants and young children as they are not able to rapidly metabolize corticosteroids [27]. Catch-up growth is expected when topical corticosteroids are discontinued in this population. However, caution should be exercised when

prescribing long-term topical corticosteroids near puberty as this may cause premature fusion of the epiphyseal plates and ultimate growth suppression [28]. Cushing's syndrome and hypothalamic-pituitary-adrenal (HPA) axis suppression has been noted in patients applying high quantities of topical corticosteroids for prolonged periods of time [29–31]. Screening for HPA axis suppression is done using the 8 AM plasma cortisol level and definitive diagnosis requires the cosyntropin test.

Local adverse effects are also rare but occur more frequently than systemic adverse effects. Cutaneous atrophy is the most commonly observed side effect and is characterized by telangiectasias, striae, hypopigmented, wrinkled or shiny skin [32]. Striae are typically seen after many weeks to months of topical steroid use; risk factors include the potency of corticosteroid, the location of application, the use of occlusion and the use in infancy/childhood. A 2011 pediatric study by Hong et al. demonstrated that appropriate long-term use of topical corticosteroids in children with dermatitis does not cause skin atrophy [33]. Their findings counter the commonly held "corticosteroid phobia" which describes an exaggerated and often irrational fear of using topical steroids. The primary concern often being that they will "thin the skin".

Another potential side effect is perioral dermatitis that may sometimes occur on the face after the use of topical corticosteroids. It is characterized by erythematous papules in a periorificial distribution. Perioral dermatitis is treated with oral tetracycline in addition to a long taper with a non-fluorinated topical corticosteroid such as hydrocortisone acetate cream.

Prolonged use of topical glucocorticoids on the eyelids can lead to glaucoma and cataracts and thus is not recommended [34]. Glaucoma has also been reported in a patient who used 0.1 % betamethasone-17-valerate cream at bedtime for hand eczema for seven consecutive years. Eye contact occurred inadvertently at night [35].

Allergic contact dermatitis to topical steroids may occur and can be suspected when a patient fails to respond to topical steroid therapy or flares with topical steroid therapy [36, 37]. The allergy may be to the vehicle or the actual corticosteroid molecule, this can be confirmed with patch testing. A delayed check at 96 h is required as topical corticosteroids often have a delayed reaction and persist for at least 96 h [38]. Loss of clinical effect or tolerance may occur with repeated application of topical corticosteroids and is known as tachyphylaxis. This occurs more commonly with higher strength topical corticosteroids. Recovery from tachyphylaxis usually occurs after a rest period of a few days. There is no established regimen to prevent tachyphylaxis. A commonly recommended regimen is twice daily application of TCS for 2 weeks followed by a 1 week rest period or weekend-only application [39]. Inadequate response to topical corticosteroids in the treatment of psoriasis can be mistaken for tachyphylaxis [40].

Vitamin D Analogues

Structure, Biosynthesis and Mechanism of Action

Vitamin D as a treatment for psoriasis was first discovered after a patient receiving oral vitamin D for osteoporosis was cured of psoriasis [41]. Calcitriol which is the active form of vitamin D_3 was found to inhibit the proliferation and modulate the differentiation of keratinocytes [42]. However, the therapeutic doses of oral vitamin D_3 produce hypercalcemia and hypercalciuria thus limiting its dermatologic usage. As a result, vitamin D analogues were developed which have a lower risk of hypercalcemia but maintain the other beneficial cellular effects. There are currently four vitamin D_3 analogues out in the market which include: calcipotriene, calcitriol, tacalcitol and maxacalcitol.

The skin is both a synthesizer of vitamin D (where 7-dehydrocholesterol is converted to vitamin D3 in the presence of ultraviolet (UV) radiation) and a target organ for vitamin D activity. Vitamin D receptors transduce the effects of 1,

25-dihydroxyvitamin D_3 and have been identified in keratinocytes, Langerhans' cells, melanocytes, fibroblasts and endothelial cells [43]. The vitamin D receptor (VDR) is activated by binding to its ligand (1,25-dihydroxyvitamin D_3) or a synthetic analogue such as calcipotriene or calcitriol. This vitamin D receptor complex in association with the retinoid X receptor-α (RXR-α) then binds to specific DNA binding sites called vitamin D response elements resulting in induction or repression of the gene that contains these vitamin D response elements. In addition to inhibiting the proliferation of keratinocytes and promoting epidermal differentiation, vitamin D promotes the formation of the cornified envelope by increasing gene expression and thereby increasing levels of involucrin and transglutaminase [44].

Vitamin D also possesses anti-inflammatory benefits. It has been shown to increase levels of interleukin (IL)-10 (which is an anti-inflammatory cytokine) and decrease levels of IL-8, a pro-inflammatory chemokine, in psoriatic plaques [45]. In addition, it has been shown to inhibit the production IL-2 and IL-6 by T cells, blocks transcription of interferon (IFN)-γ and inhibits cytotoxic T cell and natural killer cell activity [46].

Calcitriol

Calcitriol is the natural active form of vitamin D3. Calcium metabolism is affected by calcitriol through release of calcium from bone, decreasing parathyroid hormone, increasing tubular resorption of calcium in the kidney and stimulating calcium transport in the intestines. Thus, if applied excessively, it may result in hypercalcemia and hypercalciuria. It is available in an ointment form as Vectical (USA) and Silkis (Europe).

Calcipotriene (Calcipotriol)

Calcipotriene is a synthetic form of calcitriol. It was the only vitamin D analogue that was available in the U.S. for many years. Its molecular structure differs slightly from calcitriol. Calcipotriene contains a double bond and ring structure in its side chain enabling it to be metabolized much more rapidly and, as a result, is less likely to cause hypercalcemia. It is available under ointment, cream and solution forms under the trade names Dovonex (USA), Daivonex (Europe, Asia), Psorcutan (Europe) and Dermocal (South America).

Tacalcitol

Tacalcitol's (1,24(OH) $_2D_3$) structure is slightly different from calcitriol but it has a similar affinity for vitamin D receptors and therapeutic effects. It contains a hydroxyl group at the 24-position rather than at the 25-position. It is less selective than calcipotriene in its effect on calcium metabolism and has been shown to induce hypercalcemia at equivalent doses to calcitriol. It is available in an ointment, cream, lotion and solution form in Japan and as an ointment form only in Europe as Curatoderm.

Maxacalcitol

Maxacalcitol (1α,25-dihydroxy-22-oxacalcitriol) is available as Oxarol in Japan and has been shown to be ten times more potent than calcitriol and tacalcitol in inhibiting keratinocyte proliferation and 60 times less calcemic than calcipotriene [47]. It has shown benefit in the treatment of psoriasis and has not posed a significant risk of hypercalcemia.

Taclonex ®

Taclonex is a two-compound ointment or solution containing calcipotriol 50 μg/g plus betamethasone dipropionate 0.5 mg/g which combines a vitamin D analog and a corticosteroid. This formulation is used bid and preserves the activity and bioavailability of the two components. It is convenient for patients, well tolerated and has been shown to aid with compliance [48].

Indication for Psoriasis

Vitamin D analogues perform as well as midpotency steroids but less well than superpotent steroids in the treatment of psoriasis [49, 50]. Calcipotriene applied twice daily has been shown to be more effective than applied once daily, though once-daily application was more effective than placebo [51]. Ashcroft et al. found calcipotriene to be equivalent to potent topical steroids at 8 weeks of treatment [52]. Calcipotriene was associated with slightly more skin irritation than topical steroids but rarely led to withdrawal of therapy. Twice daily usage as compared to daily usage has not been associated with increased irritation [53].

In a study of 114 patients by Bruce and Colleagues, they found that calcipotriene ointment was superior to fluocinonide ointment in the treatment of plaque psoriasis and that this superior efficacy continued through week 6 [54]. A study by Camarasa et al. in 2003 randomized 258 psoriasis patients to be treated with either calcitriol or betamethasone dipropionate 0.05 % ointment and found that though betamethasone was associated with slightly higher global improvement, a statistically significantly higher proportion of patients remained in remission following calcitriol therapy (48 %) than betamethasone therapy (25 %) [55].

Calcipotriene may be used for intertriginous psoriasis though burning and irritation are commonly encountered [53]. Once daily application in these areas may be less irritating. Calcipotriene is an effective and well-tolerated modality for treating scalp psoriasis and in combination with other topical agents may lead to improved response to treatment. In long-term studies, calcipotriene has been shown to be a safe and effective therapy for the chronic management of psoriasis. Sustained disease improvement has been documented with its use twice daily for 1 year with no elevation in serum calcium levels [56].

The use of vitamin D analogues has been studied in children with psoriasis and has been found to be effective. In an uncontrolled pilot study, with long-term follow-up of 106 weeks, patients showed significant improvement in PASI scores compared with the baseline level. No serious side effects or hypercalcemia were detected. However, the mean plasma values of 1,25-dihydroxyvitamin D3 were decreased and half of the patients had levels below the normal range. Thus if using long-term calcipotriol monitoring vitamin D levels is suggested [57].

Use with Other Treatment Modalities

Topical steroids are commonly used in conjunction with vitamin D analogues. They have a synergistic effect when used in combination. It has been clearly demonstrated that the combination improves the clinical response rate and minimizes the side effects of both treatments [53, 58]. Topical steroids reduce or eliminate the irritation associated with calcipotriene use. Additionally, a study by Lebwohl demonstrated that patients using superpotent topical steroids on weekends and calcipotriene during the week maintained a longer remission than if using superpotent topical steroids alone [59].

Formulations of a combination of calcipotriene and betamethasone valerate ointment have demonstrated greater efficacy and a more rapid onset of action compared to either medication alone [60]. The combination, which is now available in gel form, is highly effective for scalp psoriasis and is associated with significantly fewer side effects than with calcipotriol alone [61].

Combining vitamin D analogues and phototherapy has been documented in numerous studies to cause lesions to clear more rapidly than either entity alone and produces a greater reduction in Psoriasis Area and Severity Index (PASI) [62, 63]. Studies combining PUVA with calcipotriene have also demonstrated increased efficacy than when using PUVA alone [64]. Total cumulative UVA exposure required for clearance of psoriasis is reduced thus decreasing the risk of developing skin cancer.

It is recommended that vitamin D analogues be applied following phototherapy as the application of vitamin D analogues prior to UV radiation

has been shown to lead to degradation of vitamin D analogues and can alter the transmission of UV light. Lebwohl and colleagues showed that greater than 90 % of calcitriol ointment is degraded upon exposure to UVA, broadband UVB or narrowband UVB [65].

Vitamin D analogues have been combined with many systemic therapies to enhance efficacy and decrease toxicity. The combination of acitretin and calcipotriene has been shown to enhance the response of acitretin in psoriatic patients and has allowed for a reduction in dosing, leading to fewer dose-dependent side effects [66]. Similarly, the combination of calcipotriol with cyclosporine has shown increased efficacy when compared to cyclosporine and placebo and allows for lower cyclosporine dosing and less toxicity [67, 68]. Calcipotriene paired with methotrexate has also allowed for decreased dosing of methotrexate and increased time to relapse following the discontinuation of methotrexate [69]. Vitamin D analogues are now also being studied with biologics. A recent study by Kircik demonstrated that the combination topical agent of betamethasone dipropionate 0.064 % with calcipotriene 0.005 % maintains the efficacy of etanercept after a step down dose to 50 mg weekly from 50 mg twice weekly [70]. Campione et al. demonstrated the effectiveness of calcipotriol in a group of etanercept low-responders [71].

Adverse Effects

The main side effects of vitamin D analogues are application-site burning and irritation. These symptoms are more common on the face and in intertriginous areas, with irritation developing in about 20 % of patients treating those areas [72]. Irritation is self-limited and resolves quickly once the drug is discontinued. The current recommendation is that weekly amounts of topical calcipotriene be kept under 100 g [73]. Serum parathyroid hormone levels should be checked if weekly amounts exceed 100 g. Patients with renal disease may be at higher risk of developing hypercalcemia even when applying less than 100 g per week.

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