Topical corticosteroids are used in the management of a wide range of dermatologic conditions. Since they were introduced more than a half-century ago, they have grown to comprise the most widely prescribed topical drug class and continue to grow.

Primarily anti-inflammatory, they are thought to provide their effects via actions on mediator release and function, inflammatory cell function, and release of lysosomal enzymes.

Among topical corticosteroids currently on the market, clocortolone pivalate cream 0.1% (Cloderm® Cream, Promius Pharma, LLC) is an effective, upper mid-potency (class 4) steroid formulation with a wide range of potential clinical uses. The molecule, developed in the 1970s and introduced on the market in 1977, was specially designed to provide certain features that can optimize the patient experience.

The unique molecular structure of clocortolone pivalate enhances the potency and penetration of the drug, while also presenting a favorable safety profile. From a practical standpoint, the cosmetically elegant, moisturizing cream encourages patient satisfaction, and the versatile dosing options—a tube and pump—offer convenience.

Cloderm Cream’s broad indication includes the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Successful phase III clinical trials to support FDA approval of Cloderm Cream were undertaken in eczema and atopic dermatitis, psoriasis, contact dermatitis, and seborrheic dermatitis.

Clocortolone Pivalate Structure

Despite their widespread and efficacious use in dermatology, corticosteroids have historically been associated with certain adverse effects. The most frequent adverse effects associated with topical corticosteroids include atrophy, striae, acneiform eruption, and purpura, while hypertrichosis, pigmentation alterations, delayed wound healing, and exacerbation of skin infections occur less frequently. Another risk associated with topical corticosteroid use is steroid use/abuse/misuse dermatitis, previously often termed steroid rosacea or perioral dermatitis.

The rate of contact sensitization for corticosteroids has also garnered attention recently. Though the rate of sensitization is considerably higher than generally believed, sensitization is nonetheless uncommon.

The incidence of adverse effects is known to increase relative to the potency of the corticosteroid molecule and with prolonged use. There are corticosteroid formulations available on the market in seven potency categories from 1 (Superpotent) to 7 (Lowest potency). While clinicians invariably prescribe across these categories, depending on the severity of the condition being treated, a majority of patients will be treated with a corticosteroid in the mid-potency range. A class 4 upper mid-potency steroid, Cloderm Cream has no generic equivalent.

The topical corticosteroids now on the market have been chemically engineered from hydrocortisone, the prototype corticosteroid. All adrenal steroids share the same basic structure: three 6-carbon rings (A,B,C) and a single 5-carbon ring (D). (Fig. 1) All corticosteroids are 21-carbon compounds with a 2-carbon side chain at C17. Chemical modifications of the basic corticosteroid structure yield changes in steroid potency.

Clocortolone pivalate, the active ingredient in Cloderm Cream, incorporates many of the structural modifications associated with increased anti-inflammatory activity and percutaneous absorption. These include β-hydroxylation at C-11, methylation at C-16, double-bonds at C-1,2, esterification at C-21, and halogenation at C-6 and C-9 (Fig. 1). Because some older halogenated products were associated with significant adverse effects, many clinicians became wary of halogenated corticosteroids. However, evidence...
shows that the position and nature of the halogen atoms (in this case chlorine and fluorine), not simply their presence, determine both the potency and the incidence of adverse events.7 No other topical corticosteroid has Cloderm Cream’s unique C9 chlorination and C6 fluorination, associated with mid-strength potency.

In addition to its potency, the unique chemical structure of clocortolone pivalate contributes to its high lipohilicity, which aids rapid epidermal penetration. Formulating corticosteroids for topical delivery presents the challenge of penetrating the skin barrier. Lipid solubility is a major determinant of both drug absorption and drug penetration through the stratum corneum.8 It is generally accepted that topical corticosteroids that are lipid soluble possess greater anti-inflammatory potency than more polar molecules, owing to their higher concentrations in the viable epidermis.8 In studies of steroid percutaneous absorption, the most lipid soluble corticosteroids penetrated the stratum corneum at the fastest rates and were better delivered, with the highest epidermal concentrations.8

Furthermore, esterification at C-21 with substitution of the pivalate group increases duration of action, influences potency, and increases lipid solubility (Fig. 2). While substitution of a group as large as pivalate is likely to reduce glucocorticoid receptor affinity,9 the additional methyl group increases lipid solubility. Clocortolone pivalate has higher lipid solubility than other commonly used mid-strength topical corticosteroids (Fig. 2).10

**Patient Experience**

More rapid penetration and accumulation of active drug in the epidermis is expected to contribute to a rapid onset of therapeutic effect, and this has been seen with Cloderm Cream. In fact, in phase III clinical trials, treatment with Cloderm Cream provided a rapid onset of therapeutic effect among patients with eczema and atopic dermatitis.11 Statistically significant improvement relative to placebo was seen at Day 4. The frequency of adverse reactions was low. Despite its rapid penetration, no HPA-axis suppression (as determined by plasma cortisol levels) was observed in a 10-subject study where Cloderm Cream was applied under occlusion for 21 days.7,12

In the phase III atopic dermatitis study, treatment with Cloderm Cream provided statistically significantly greater effect than placebo, beginning at Day 4. The bi-lateral, split-body study measured objective criteria, such as erythema, edema, transudation, and, if present, bullae and vesicles, papules, plaques, scaling, crustings, fissures, and lichenification. Subjective measures included relief of pain, itching, or burning.

Cloderm Cream statistically significantly out-performed its vehicle base in both objective and subjective measures at all time points. It is interesting to note, however, that there was an appreciable level of patient satisfaction with the vehicle base at all time points, and a fair number of subjects achieved “satisfactory” therapeutic response to placebo early on. There were no adverse reactions observed throughout the trial period.12

In psoriasis trials, Cloderm Cream demonstrated superiority to placebo by Day 7 (continuing at Days 14, 21, and 28). The rate of reported adverse events was low and actually higher for placebo than for active treatment.12

**Important Safety Information.** The most common adverse events with Cloderm Cream include burning, itching, irritation, dryness, and folliculitis. Cloderm Cream is contraindicated in patients who are hypersensitive to any of the ingredients of this product. As with all topical corticosteroids, systemic absorption can produce reversible HPA-axis suppression. For more information and full prescribing information please visit www.cloderm.com or see accompanying PI.
In the trial designed to determine the influence of Cloderm Cream on HPA-axis suppression, healthy male subjects applied 30g of clocortolone pivalate cream 0.1% twice daily (for a total application of 60 grams) under occlusion. Occlusion was provided via plastic suits worn for 12 consecutive hours each day. No evidence of adrenal suppression (as determined by plasma cortisol) was seen over the 21-day trial period.11

Cloderm Cream can be used in combination with other therapies, including topical calcineurin inhibitors (TCIs). Combination therapy has been widely used in clinical practice and recently has been documented as effective in the literature. In one study, concomitant treatment with Cloderm Cream and tacrolimus ointment 0.1% produced significant improvement in dermatologic sum scores at days 14 and 21. Combination therapy was effective for measures of excoriation and induration at day 21 and erythema at day 14. The effectiveness of this combination treatment was seen early on, for excoriation at days 7 and 14, oozing or crusting at days 3 and 7, and lichenification at day 3.13

Clinical Applications
The moisturizing cream vehicle base of Cloderm Cream consists primarily of water and emollient ingredients, such as white petrolatum, mineral oil, and stearyl alcohol. This non-greasy cream vehicle is dispensed in either a tube or pump. There is no difference in the vehicle formulation in the tube or pump; the same cream is contained in either dispenser.

Either dispenser may provide unique benefits in specific settings. For example, when the prescriber is concerned that a patient may over- or under-apply a topical corticosteroid, the pump may be preferred. It dispenses a consistent “dose” of corticosteroid with each pump, and the prescriber may instruct the patient on the number of pumps to apply to any given anatomic site. (See Fig. 3 for information on dosing.) The pump may also be suitable for parents concerned about possibly over-applying corticosteroids on children, or when the prescriber worries about potential non-compliance. The pump simplifies the regimen, there is no mess, and no cap to replace. The flexible dosing of the tube may be preferred for other patients, including those with large surface areas of involvement. Providing enhanced therapeutic control and potential convenience, Cloderm Cream is available in four different sizes: the pump is available in the 30g and 75g size, while the tube is available in 45g and 90g.

Formulation advancements in recent years have led to new corticosteroid vehicles on the market, including foams, gels, and sprays, in addition to creams, lotions, solutions, and ointments. The selection of an appropriate vehicle depends on numerous factors, and novel vehicles may be particularly useful for certain applications, such as treatment of the scalp. Nonetheless an effective, moisturizing cream-based formulation remains an important option for a vast number of patient presentations. (See Case Report.)
Cream is contraindicated in patients who are hypersensitive to any of the ingredients of this product. As with all topical corticosteroids, systemic absorption can produce reversible HPA-axis suppression. For more information and full prescribing information please visit www.cloderm.com or see accompanying PI.

Clinical Applications

Low-to-mid potency steroids are prescribed when necessary for treatment of the face, axillae, or intertriginous areas, where thinner, more sensitive skin is associated with an increased susceptibility to common corticosteroid side effects. In my practice, I have prescribed Cloderm Cream for treatment of various sites. I have even prescribed the formulation for eyelid dermatitis. Data suggest topical corticosteroids can be used safely in the periorbital region, choice of a low- or mid-potency corticosteroid seems reasonable for such application.

Because, as noted, the risk for developing adverse events associated with topical corticosteroids increases as the potency of the drug or the duration of therapy increases, it is still widely acknowledged that topical corticosteroid use should be limited to short durations. However, many of the inflammatory dermatoses that respond to topical corticosteroids are chronic in nature, with relapsing remitting courses. As such, many patients require long-term maintenance therapy or “pulse therapy” aimed at periodic exacerbations of disease. For long-term and/or intermittent use, a low-to-mid potency corticosteroid, such as Cloderm Cream, is preferred over more potent steroids. In the case of the Cloderm Cream pump, the additional control over dosing provided by the pump dispenser helps to ensure that patients do not over-use or misuse the corticosteroid over the long term.

Conclusion

Topical corticosteroids remain a cornerstone of dermatologic care, with potential use for a wide range of inflammatory skin diseases. Though topical corticosteroids are historically associated with certain adverse effects that necessitate judicious use, the clinical reality is that within an appropriate regimen, they can be used to relieve inflammation and pruritus associated with acute and chronic dermatoses with an excellent safety profile.

The unique formulation of Cloderm (clocortolone pivalate) Cream 0.1% provides an important therapeutic option that may be suitable for many patients with steroid-responsive dermatoses. The specially engineered molecule balances needed potency and documented efficacy with a favorable safety profile. The lipophilic molecule absorbs quickly into the epidermis, contributing to a rapid onset of therapeutic effect.

The moisturizing cream base is elegant, providing emollient benefits that are desirable in many chronic dermatoses. The availability of two dispensing systems—a tube and a pump—allows clinicians to best match treatment to the needs of the patient and allows greater control of treatment.

Effective with an excellent safety profile for the treatment of atopic dermatitis, eczema, psoriasis, contact dermatitis, and other steroid-responsive dermatoses, Cloderm Cream is a versatile therapy in the dermatologist’s armamentarium.

Dr. Bikowski is a consultant for and has served on the Advisory Board and Speakers Bureau for Promius Pharma, LLC.

References

10. ChemSpider, Royal Society of Chemistry, 2011; chemspider.com
12. Data on file, Promius Pharma, LLC.

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