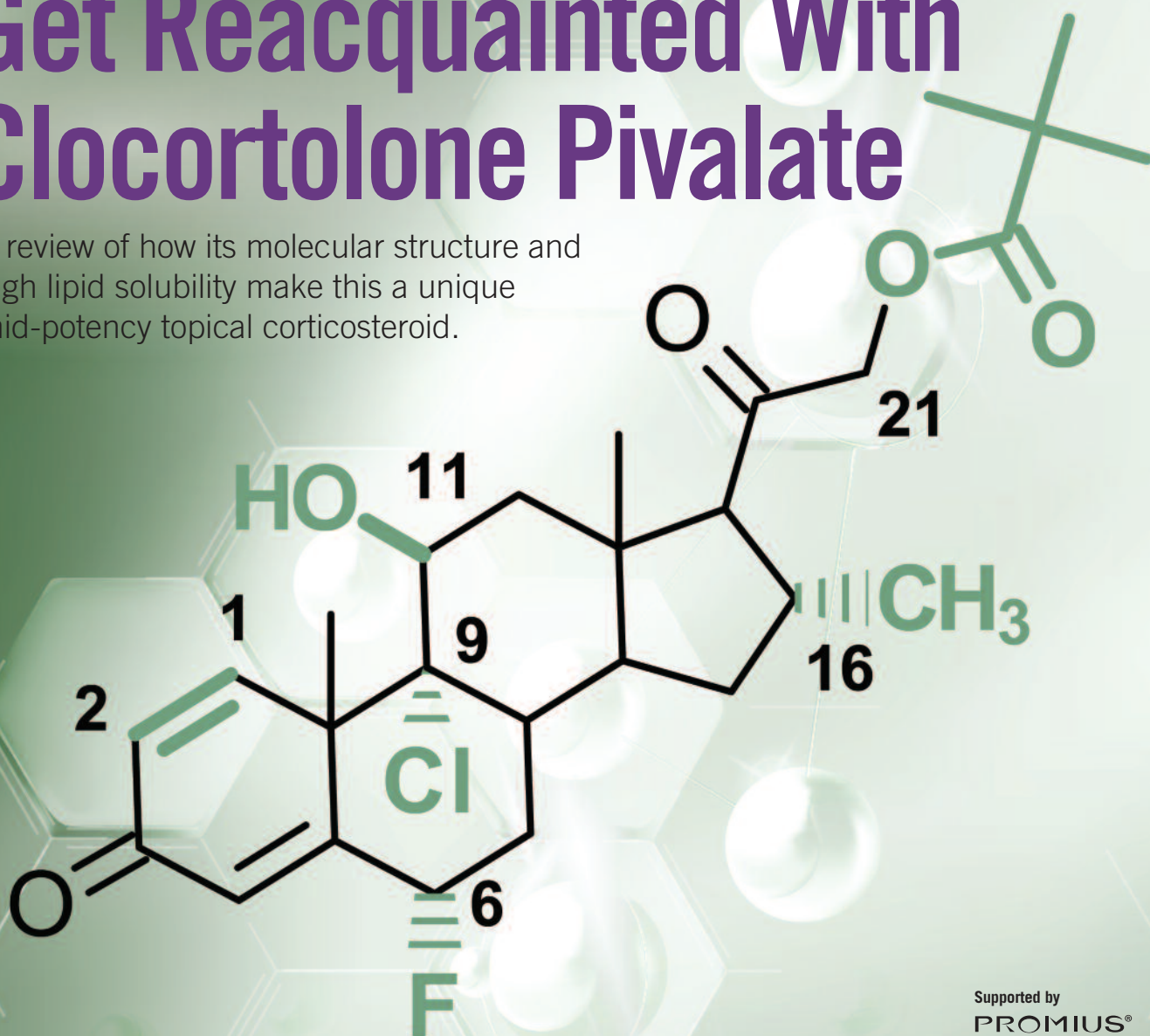


Get Reacquainted With Clocortolone Pivalate

A review of how its molecular structure and high lipid solubility make this a unique mid-potency topical corticosteroid.



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Leon Kircik, MD

Although topical corticosteroids are effectively used to manage common dermatologic conditions, many of us are concerned about their adverse events. In fact, 80.7% of respondents to one survey said they had fears about using topical corticosteroids, and 36% acknowledged they had not adhered with topical corticosteroid therapy due to safety concerns.¹ This despite the excellent safety profile of topical corticosteroids when used properly.

Patients may think corticosteroids are virtually interchangeable, but there are many formulations, potencies and safety profiles. While all members of the corticosteroid class have common characteristics — because all are chemically engineered from hydrocortisone — the reality is that each topical corticosteroid formulation has unique features based on its exclusive molecular structure and essential features of its vehicle base.

To enhance patient confidence in therapy and potentially encourage therapeutic adherence, physicians must understand key concepts regarding corticosteroid safety and efficacy in order to select the appropriate corticosteroid for their patients. They must also be prepared to educate patients about these features.

The mid-potency topical corticosteroid clocortolone pivalate 0.1% cream (Cloderm[®] Cream) (Promius Pharma, LLC) provides a useful example for addressing the influence of molecular structure, vehicle formulation, potency and safety on the patient experience.

Engineering the Molecule

Topical corticosteroids are primarily anti-inflammatory, acting on mediator release and function, inflammatory cell function and release of lysosomal enzymes.² Corticosteroids are 21-carbon compounds with a 2-carbon side chain at C-17.^{2,3,4} All adrenal steroids share the same basic structure: three 6-carbon rings (A, B, C) and a single 5-carbon ring (D). Although modifying the molecular structure may yield a variety of changes in topical corticosteroid characteristics, molecular modification is usually done to influence potency and efficacy.⁴

As a class, topical corticosteroids are associated with certain well-known potential adverse effects⁵ that increase in incidence and severity proportionate to agent potency and duration of use. The most frequent adverse effects associated with topical corticosteroids include burning, itching, irritation, dryness, folliculitis, atrophy, striae, acneiform eruptions

and purpura. Other, less common adverse effects include hypertrichosis, pigmentation alterations, delayed wound healing and exacerbation of skin infections.^{5,6} Topical corticosteroids may also be associated with sensitization, which is relatively rare.²

Topical steroid potency is a source of potential confusion for patients and some clinicians. Topical corticosteroids are available across a range of potencies from 1 (superpotent) to 7 (lowest potency). Although the highest and lowest potency topical corticosteroids are important in managing dermatologic diseases, the clinical reality is that most patients are treated with mid-potency topical corticosteroids. Generally, mid-potency topical corticosteroids are thought to provide a favorable balance of safety and efficacy for both short-term application and for longer-term and intermittent use.

Clocortolone pivalate 0.1% was introduced to the market in 1977 in a moisturizing cream vehicle base. It is an effective, upper-mid-potency (class 4) steroid formulation with a wide range of potential clinical uses.

Among the structural modifications used to engineer clocortolone pivalate are β -hydroxylation at C-11, methylation at C-16, double bonds at C-12, esterification at C-21, and halogenation at C-6 and C-9. These structural features of clocortolone pivalate have increased the molecule's anti-inflammatory potency and lipophilicity and, subsequently, its penetration.

The medical community has misunderstood, to some degree, the effects of halogenation on a corticosteroid molecule. Certain halogenated high-potency corticosteroids have been associated with increased rates of significant adverse effects, leading clinicians to associate halogenation with reduced safety. However, the chemistry behind corticosteroids shows that this is a misperception.⁵

Halogen atoms in themselves don't increase the incidence of adverse events associated with topical corticosteroids. Rather, the position and nature of the halogen atoms mediate the potency of the molecule and the incidence of adverse events.⁵ The halogen atoms in clocortolone pivalate are chlorine at C-9 and fluorine at C-6 — a unique feature of the molecule not found in any other corticosteroid. These modifications produce a corticosteroid in the upper mid-potency range, but with a safety profile associated with a much lower-potency molecule, as discussed below.

Important Safety Information. The most common adverse events with Cloderm Cream include burning, itching, 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.

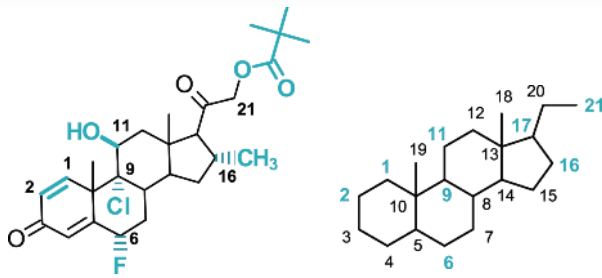


Figure 1. Structural modifications associated with improved anti-inflammatory activity and improved percutaneous penetration (left) compared to steroid nomenclature (right).

Source: Promius Pharma, LLC

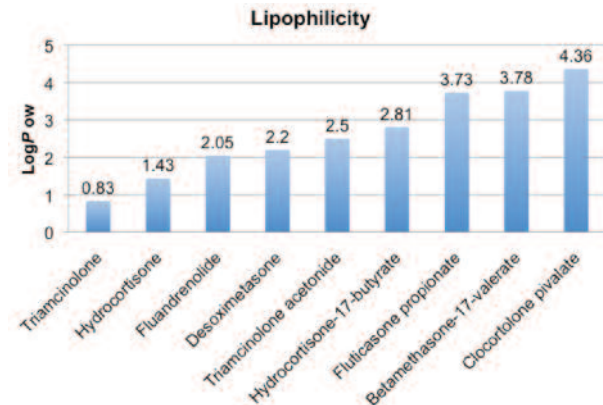


Figure 2. Partition ratios of commonly used mid-strength topical corticosteroids. The partition ratio represents the concentration of drug in each phase of an immiscible mixture of octanol and water at equilibrium ($\log P_{ow}$). Higher values indicate greater lipid solubility.

Source: Advanced Chemistry Development, Inc., chemical database.

The clocortolone pivalate molecule's unique features make it highly lipophilic, which is an important characteristic of topical steroids. Esterification at C-21 with substitution of the pivalate group is linked directly to increased lipid solubility, duration of action and potency. Additionally, adding methyl groups helps increase lipid solubility. In fact, clocortolone pivalate has the highest lipid solubility of many commonly used mid-strength topical corticosteroids (See Figure 1).⁷

High lipid solubility is associated with increased absorption and penetration of drugs through the stratum corneum.² This may explain why highly lipophilic topical corticosteroids are shown to achieve higher concentrations in the viable epidermis, thus exhibiting greater anti-inflammatory potency.^{8,9} Percutaneous absorption studies confirm that, compared with less lipophilic molecules, the most lipid-soluble corticosteroids were better delivered, penetrated the stratum corneum at the fastest rates and exhibited the highest epidermal concentrations.^{8,9} (See Figure 2.)

The large size of the pivalate group would be expected to somewhat reduce glucocorticoid receptor affinity,¹⁰

however halogenation at C-6 or C-9 is shown to enhance receptor affinity and may counter reduced binding due to the molecules' size.¹¹

Safety

Cloderm Cream was uniquely designed to provide upper-mid-level potency with an excellent safety profile in order to present a favorable treatment option for a wide range of patients. Per the prescribing information, the use of clocortolone pivalate 0.1% cream has no age restrictions.

As suggested above, a lipophilic molecule such as clocortolone pivalate is expected to absorb rapidly and accumulate in the viable epidermis. A study of HPA-axis suppression involved healthy male patients who applied 30 g of clocortolone pivalate 0.1% cream twice daily (total application of 60 g) under occlusive 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.¹²

Many of the most common steroid-responsive dermatoses that may be treated with a mid-potency topical corticosteroid — such as atopic dermatitis (AD), eczema and psoriasis — are relapsing in nature. One common concern is the safety of long-term topical corticosteroid use.

In an analysis of patients treated with clocortolone pivalate 0.1% cream for more than 30 days — some patients used the drug for up to 7 months — no systemic, cumulative or delayed adverse events were related to Cloderm Cream treatment. The overall frequency and severity of adverse events was low.¹² Among patients who used Cloderm Cream long-term, or for an average of 16 weeks, only one patient reported a treatment-related adverse event. This was a case of dryness that required no additional treatment.¹² Across various Phase III trials, the rate of adverse events associated with clocortolone pivalate therapy was low. The most common adverse events with Cloderm Cream include burning, itching, irritation, dryness and folliculitis. No patients developed striae or skin atrophy over the treatment period.¹²

As noted, corticosteroid allergy has been identified as an emerging but infrequent phenomenon. Clocortolone pivalate is in allergy group C, betamethasone-type steroid, and should not be prescribed to patients with a history of group C allergies. It's also worth noting that group C topical steroid group is the smallest group and the least likely to be associated with topical corticosteroid allergy.¹³

Formulating the Vehicle

Engineering the molecule is, of course, just one aspect of drug development. Vehicle formulation should optimize potency by maximizing delivery at the target site and encourage good patient adherence. The vehicle of Cloderm Cream is moisturizing, yet non-greasy, and con-

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tains the emollient ingredients, white petrolatum, mineral oil and stearyl alcohol.

Emollient creams such as Cloderm Cream help improve epidermal barrier function. This is an important consideration in managing steroid-responsive dermatoses such as eczematous diseases and psoriasis.¹⁴ Occlusive emollients moisturize the skin by replacing lipids in the stratum corneum and providing a physical barrier that prevents evaporative epidermal water loss. Additionally, the non-greasy emollient cream improves the skin feel and may rapidly improve the feel of dry, eczematous skin.

The cream vehicle formulation is dispensed in either a tube or pump. Dispensing product from a pump may be associated with more control than other dispensers. More importantly, the pump provides a consistent dose of medication, providing prescriber and patient more treatment control. The prescriber instructs the patient on the number of pumps of medication to apply to any given anatomic site.

Clinical Applications and Evidence

As a class IV mid-potency topical corticosteroid, clocortolone pivalate may be used for a range of steroid-responsive dermatoses. The hydrating cream vehicle may be especially useful for treating eczema, atopic dermatitis and psoriasis — all of which were investigated in successful Phase III trials.

As expected of a highly lipophilic corticosteroid with enhanced potency, Cloderm Cream was shown in Phase III clinical trials to provide a rapid onset of therapeutic effect.¹² Patients with eczema and AD saw a statistically significant improvement relative to placebo at day 4. The AD trial measured objective criteria, such as erythema, edema and transudation; bullae and vesicles, papules, plaques, scaling, crusting, fissures and lichenification, if present; and subjective measures, such as relief of pain, itching or burning. The frequency of adverse reactions was low.¹²

In psoriasis trials, active treatment with Cloderm Cream was superior to placebo by day 7. Active therapy was shown to be superior to placebo at days 14, 21 and 28. As in the AD study, the rate of reported adverse events was low, and none were significant. In fact, the incidence of reported adverse events was actually higher for placebo than for active treatment.¹²

Conclusion: Clinical Realities

As a class, topical corticosteroids are associated with certain adverse events that vary in severity and incidence. The risk for developing adverse events increases as the drug potency or therapy duration increases. Prescribers can reduce the risk of adverse events by selecting formulations that effectively balance efficacy and safety. Educating patients about properly using topical corticosteroids and describing characteristics of the specific therapeutic agent selected may help allay patient fears and improve therapeutic adherence.

Characteristics of a topical corticosteroid formulation that influence its potency and safety are molecular structure, the presence and location of halogen atoms, lipophilicity, molecule size and vehicle–base characteristics. The unique formulation of clocortolone pivalate 0.1% cream (Cloderm Cream) provides a therapeutic option with a long-documented history of efficacy and safety.

The selectively engineered molecule, which has no generic equivalent, has a high lipid solubility, so it absorbs quickly into the epidermis and confers a rapid onset of therapeutic effect, as demonstrated in clinical trials.¹² The moisturizing, cosmetically elegant cream base delivers emollient benefits. As a class IV mid-potency steroid, Cloderm Cream is very versatile and not associated with a high risk for HPA-axis suppression or other adverse effects.



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