

CURRENT CLINICAL SOLUTIONS

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Spotlight on Clocortolone Pivalate: Discussion and Case Reports

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In the 1930s, Edward Kendall first isolated six compounds from the adrenal glands at the Mayo Clinic (Rochester, MN). In 1948, his friend and colleague, Dr. Phillip Hench, and his team injected compound E into severe rheumatoid arthritis patients at St Marys Hospital and showed marked improvement in the symptoms of these patients. This was the first use of semi synthetically produced cortisone, of which a total of 9g could be produced. Kendall and Hench as well as Dr. Tadeus Reichstein of Switzerland won the Nobel Prize in 1950 for their work.

Since then, cortisone has been able to be synthesized in large scale and many subsequent steroidal molecules have been invented and used in varied delivery methods.

As dermatologists, we have access to a multitude of topical steroids that we choose from to treat our patients. These come in different molecules, concentrations, and vehicles that affect their efficacy and safety as well as the compliance of our patients.

In the following article, several questions will be posed to discuss the properties of topical glucocorticoids with an emphasis on clocortolone pivalate (Cloderm™ Cream 0.1%). The answers will examine some of the factors we consider when choosing a topical corticosteroid to treat steroid responsive dermatoses in our patients. The properties of the clocortolone pivalate molecule and Cloderm Cream will be discussed to gain an understanding of what they can offer our patients.

What do you consider when choosing a topical steroid to treat a patient's condition?

Topical glucocorticosteroids play a very important role in the treatment of steroid responsive dermatoses and are the most frequently used topical preparation in dermatology practices. They work by binding to intracellular glucocorticoid receptors leading to regulation of gene transcription, which in turns lead to upregulation of anti-inflammatory proteins and/or down regulation of pro-inflammatory proteins.¹ Steroids have anti-inflammatory as well as antiproliferative, immunosuppressive, and vasoconstrictive effects.^{2,3}

When choosing a topical steroid for the patient, there are many factors that I consider. One has to consider the patient (age, preference) as well as the type, severity, and location of disease. Many clinicians use these factors to decide the potency and vehicle of the topical steroid to use. However, we need to remember that not all topical steroids of same potency and similar vehicles are equivalent. We all understand that vehicles matter and make a difference but the molecular chemistry of each corticosteroid is also a significant factor that influences the efficacy and safety of the topical product.

So for each patient with a steroid responsive dermatoses, I choose a topical steroid based on key factors including the vehicle, the efficacy, and the potency of the product. Topical corticosteroids have an excellent safety profile and we need to reassure patients who are concerned about the use of steroids on their skin, or the skin of their children, and therefore may be less compliant than we would like.

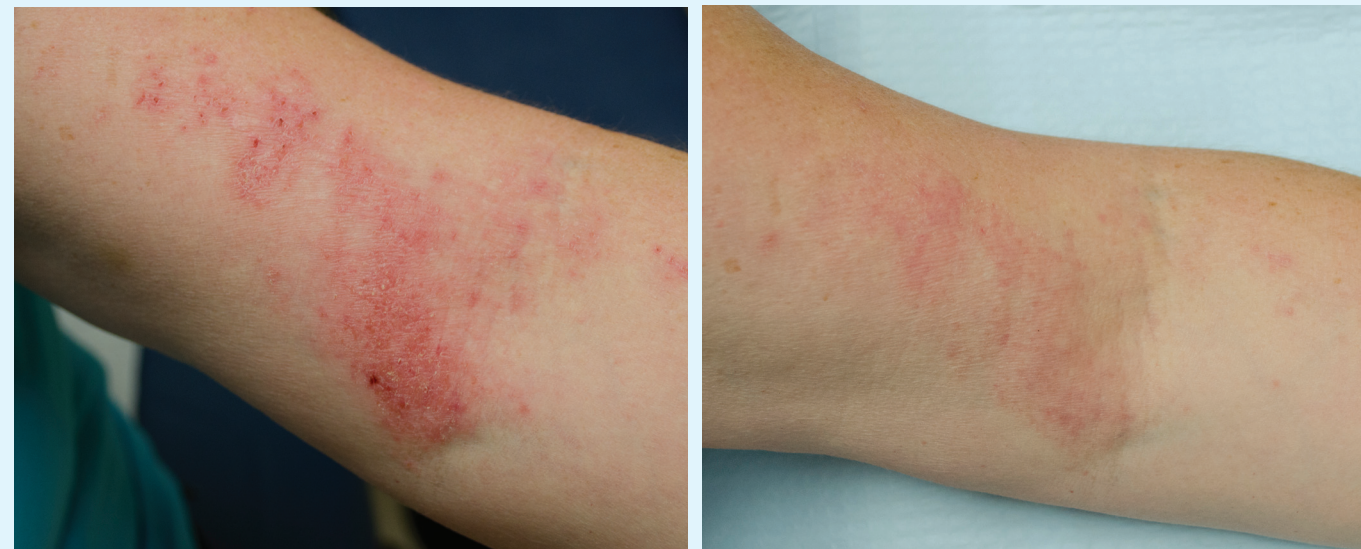
What is different about the clocortolone pivalate molecule?

All topical steroids we use are based on the original hydrocortisone molecule. Variation to this molecule leads to variation in the potency and safety profile of the resulting steroid.^{4,5}

Clocortolone pivalate is a class 4, mid potency steroid that is available in a 0.1% cream. It was designed with the goal of having the efficacy of a midpotent steroid by increasing the lipophilicity and potency of the molecule. Starting from a hydrocortisone molecule, the structure was modified by B-hydroxylation at C-11, methylation at C-16, double bond between C-1 and C-2, esterification at C-21, and halogenation at C-6 (fluorination) and C-9

CASE REPORT

Figure 1. Forty-four-year-old female with history of atopic dermatitis presents with flare of her eruptions on arms and thighs with complaint of severe itching. Diagnosis: Atopic dermatitis flare. Treatment: Cloderm Cream 0.1% bid.
Day 0; Pruritus 10/10
Day 2; Pruritus 2/10



(chlorination). These changes created a molecule that is more lipophilic (due to the esterification and methylation), with increased resistance to metabolic breakdown leading to increased duration of action (due to esterification) and higher potency (due to halogenation and methylation). Thus, we end up with a molecule that is more lipophilic than other commonly used mid-strength topical steroids, which may lead to enhanced absorption and penetration through the stratum corneum⁶ and higher concentration in the viable epidermis for greater efficacy.⁷ This leads to a rapid action and relief for my patients, which was shown in the Phase III trials.⁸

There is a common misconception that halogenation worsens the side effect profile of a topical steroid. This is supported by the high potency of certain halogenated topical steroids that have increased numbers of adverse events. However, the potency and the side effects of a topical steroid are influenced by the position of the halogens and not merely their presence.⁴ In the case of clocortolone pivalate, the halogen atoms help the molecule's affinity to the steroid receptors despite its large size (due to the pivalate group), therefore allowing it to achieve class 4 potency level.

Do you worry about adverse events of topical steroids and how does clocortolone pivalate stack up?

The adverse effects of topical steroids, although uncommon with proper use, are thought to increase with the increase in potency as well as duration of treatment.⁹

When thinking of potential adverse events of topical steroids, we need to consider skin versus systemic side effects. Most commonly, local effects can occur including atrophy, striae, telangiectasia, steroid induced acne, irritant, and allergic contact dermatitis.³ Although the latter is usually related to vehicle, real contact allergy to steroids can occur.

Systemic side effects usually occur when a high potency steroid is used for a long time on a large body surface area. This could lead to HPA axis suppression as well as growth retardation in children. The use of a steroid of any potency for an extended period of time around the eyelids can result in glaucoma.

Cloderm Cream received FDA approval in 1977 and has an excellent safety profile. According to the package insert the most common adverse events with Cloderm Cream include burning, itching, irritation, dryness, and folliculitis. In all clinical studies totaling 559 patients, the frequency of local and systemic adverse reactions was minimal. It has no age restriction on use but pediatric data are limited.^{8,10,11,12}

Furthermore, given the chronic nature of some steroid responsive dermatoses like atopic dermatitis and psoriasis, one has to consider the safety of long-term use of a topical steroid. In the case of Cloderm Cream, an analysis of 27 patients treated from 30 days up to 7 months showed a low rate of adverse events including, burning, itching, irritation, dryness or folliculitis^{5,8} with no evidence of striae, atrophy, or hypopigmentation.

Also, the potential of HPA axis suppression was studied with clocortolone pivalate in 10 healthy males who applied 30g of the 0.1% cream twice a day for 21 days while wearing a plastic sweat suit for 12 hours a day. Under these extreme conditions, effects on the HPA axis were studied by measuring plasma cortisol levels and urinary 17-ketosteroid levels. No evidence of adrenal suppression was found.

Finally, studies have shown no irritancy, phototoxicity, sensitization, or photoallergy to the 0.1% cream formulation.^{8,10}

The safety data and my clinical experience with Cloderm Cream in various dermatoses and different patients have allowed me to educate my patients about the low potential of any serious adverse events occurring with normal use.

How important does the vehicle play in your decision making process?

The vehicle of any topical product is extremely important, especially when treating dermatoses where the skin barrier is damaged. Our patients have a higher risk for allergy as well as irritation and burning sensation. A vehicle with high alcohol content may not be comfortable for a severe eczema patient to use.

The vehicle in Cloderm Cream is a simple cream containing only 9 ingredients including three emollients: white petrolatum, mineral oil, and stearyl alcohol. These emollients have been shown to help protect and improve the epidermal barrier function. Most of our patients, when needing steroids, have a certain level of barrier disruption. The emollients also help in the reduction of transepidermal water

CASE REPORT

Figure 2. Seventy-eight-year-old male with a two-year history of progressively worsening red, scaly, excoriated plaques on the trunk and extremities and complains of intense pruritus. Multiple OTC moisturizers used as well as occasional topical steroids. Diagnosis: Severe atopic dermatitis. Treatment: Cloderm Cream 0.1% bid.
Day 0; Pruritus 10/10
Day 7; Pruritus 2/10



loss. Furthermore, they are important in obtaining a cosmetically pleasing feel of Cloderm Cream. It is also free of lanolin or fragrance, which is important in my atopic dermatitis patients who are more prone to contact allergies.

How important is the allergy group C classification of a midpotent steroid?

The structure of a molecule affects its protein binding affinity and therefore its allergenicity. Clocortolone pivalate's structure, specifically its C-16 methylation, interferes with its protein binding. This results in a lower risk of contact allergy for group C steroids than in the case of steroids of other allergenicity groups although there is one report of allergy to clocortolone pivalate cream.¹³ Contact allergy to steroids from allergy groups A, B, and D2 are much more likely. We therefore need to consider this in our patients with chronic or refractory conditions, as allergic reactions to previously used corticosteroids can be hard to diagnose.

Disclosure

Dr. Hougeir is a consultant and speaker for Promius Pharma.

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Indication and Important Safety Information: Cloderm Cream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. 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. Please see full accompanying prescribing information. For more information see www.Cloderm.com.

RxOnly

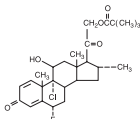
Cloderm[®] Cream, 0.1% (clocortolone pivalate)

**FOR TOPICAL DERMATOLOGIC USE ONLY—
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.
WARNING: KEEP OUT OF REACH OF CHILDREN**

DESCRIPTION: Cloderm Cream 0.1% contains the medium potency topical corticosteroid, clocortolone pivalate, in a specially formulated water-washable emollient cream base consisting of purified water, white petrolatum, mineral oil, stearyl alcohol, polyoxyl 40 stearate, carbomer 934P, edetate disodium, sodium hydroxide, with methylparaben and propylparaben as preservatives.

Chemically, clocortolone pivalate is
9-chloro-6 α -fluoro-11 β ,
21-dihydroxy-16 α methylpregna-1,
4-diene-3, 20-dione 21-pivalate.

Its structure is as follows:



CLINICAL PHARMACOLOGY:

Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.

(See **DOSAGE AND ADMINISTRATION**).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS: General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity.
(See **PRECAUTIONS—Pediatric Use**).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.

5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression:

- Urinary free cortisol test
- ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities *not* likely to have deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS:

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

Burning, Itching, Irritation, Dryness, Folliculitis, Hypertrichosis, Acneiform eruptions, Hypopigmentation, Perioral dermatitis, Allergic contact dermatitis, Maceration of the skin, Secondary infection, Skin atrophy, Striae, Miliaria.

OVERDOSAGE:

Typically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION:

Apply Cloderm (clocortolone pivalate) Cream 0.1% sparingly to the affected areas three times a day and rub in gently.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate anti-microbial therapy instituted.

HOW SUPPLIED:

Cloderm (clocortolone pivalate) Cream 0.1% is supplied in 30 gram and 75 gram pump bottles, 45 gram and 90 gram tubes.

30 gram pump bottle	NDC-67857-804-30
75 gram pump bottle	NDC-67857-804-51
45 gram tube	NDC-67857-804-45
90 gram tube	NDC-67857-804-90

STORAGE:

Store Cloderm Cream between 15° and 30° C (59° and 86° F).

Avoid freezing.

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