

Clinical utility of clocortolone pivalate for the treatment of corticosteroid-responsive skin disorders: a systematic review

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Abstract: Clocortolone pivalate 0.1% cream is a class IV mid-strength topical glucocorticoid. After topical application the glucocorticoid achieves higher concentration in inflamed skin compared with normal skin. Furthermore, pharmacologic studies have shown that there is little systemic absorption of clocortolone pivalate and hence no adrenal suppression. Systematic review was performed to evaluate the efficacy and safety of the glucocorticoid. PubMed, the Cochrane Library, and individual websites of the top 20 dermatology journals were searched using a defined strategy. Following the selection criteria, eight clinical trials were selected, of which five were randomized controlled trials. The trials mainly included patients with atopic dermatitis and eczemas. Quality appraisal of randomized controlled trials was done using the Delphi list, which showed that the trials had weaknesses in several items. The results of the systematic review tend to show that clocortolone pivalate cream is generally effective with early onset of action and has a good safety profile in the treatment of these conditions. Further studies comparing this glucocorticoid with other glucocorticoids and treatments in steroid-responsive dermatoses are desirable.

Keywords: clocortolone pivalate, corticosteroid, glucocorticoid, systematic review

Introduction

Introduction of topical glucocorticoids for the treatment of skin diseases has led to marked improvement in outcomes in several conditions. Nowadays, topical glucocorticoids are the most frequently used topical preparations in dermatology. Their efficacy in skin diseases depends on their anti-inflammatory and antimetabolic actions and their capacity to decrease the synthesis of connective tissue molecules,¹ in addition to immunosuppressive actions. Use of these agents is common in eczematous dermatoses and also in many inflammatory dermatoses. Inherent responsiveness of skin diseases to topical glucocorticoids varies, and, consequently, diseases may be classified as highly responsive (flexural psoriasis, atopic dermatitis in children, seborrheic dermatitis), moderately responsive (psoriasis, atopic dermatitis in adults, nummular eczema, papular urticaria, lichen simplex), and minimally responsive (palmo-plantar psoriasis, nail psoriasis, dyshidrotic eczema, lupus erythematosus, lichen planus, insect bites).²

Glucocorticoids do not have direct antipruritic action but suppress the inflammatory component of the dermatoses, thereby indirectly alleviating itching such as in atopic dermatitis.³

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Pharmacology

Clocortolone pivalate is the international nonproprietary name of the compound that is chemically 9-chloro-6 α -fluoro-11 β , 21-dihydroxy-16 α methylpregna-1, 4-diene-3, 20-dione 21-pivalate (Figure 1).⁴ Clocortolone pivalate is available as a 0.1% cream for the treatment of skin diseases. The water-washable emollient cream base consists of purified water, white petrolatum, mineral oil, stearyl alcohol, polyoxyl 40 stearate, carbomer 934P, edetate disodium, and sodium hydroxide, with methylparaben and propylparaben as preservatives.⁴

Clocortolone pivalate has been classified as a class IV mid-strength subclass C (betamethasone type characterized by C16 methyl substitution)⁵ or as a low-potency glucocorticoid.⁶ The recommended frequency of application of clocortolone pivalate cream 0.1% is three times a day.⁴

A recent article has reported detection of three previously unknown impurities in a clocortolone pivalate bulk sample.⁷

Pharmacologic studies on clocortolone pivalate have shown the following characteristics: no evidence of contact sensitization by Draize sensitization studies, both in the absence and presence of ultraviolet light; no evidence of phototoxicity after application of clocortolone pivalate to both forearms after removal of the stratum corneum and irradiation with Wood's light; low potential to cause irritation after application to the skin for 21 days; 19 times greater concentration in inflamed skin than in normal skin in the in vivo studies, and 178 times greater in the in vitro studies; and absence of adrenal suppression after application

of 30 g twice daily under occlusion for 21 days to ten human volunteers.⁸ It was concluded that after topical application, clocortolone is readily bioavailable for local activity in the skin but has little potential to enter the systemic circulation.⁸ Studies in rats have shown that after topical application most of the clocortolone remains at the site of application, with only 2% reaching the deep layers of the stratum corneum.⁸ As the only corticosteroid in the market with a pivalate group at the 21 position,⁹ the pharmacologic profile of clocortolone pivalate makes it eminently suitable for human use.⁸ The presence of both fluorine and chlorine ions and the absence of the 17 hydroxyl group in clocortolone pivalate may be responsible for its relative lack of adverse effects.^{8,10}

Efficacy and safety of clocortolone pivalate in the treatment of skin diseases

We performed a systematic review of the efficacy and safety of clocortolone pivalate in the treatment of skin diseases. The published literature on the glucocorticoid was searched as follows.

Search strategy

The following databases were searched:

1. PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) was searched for “clocortolone” in all fields without activating any limits.

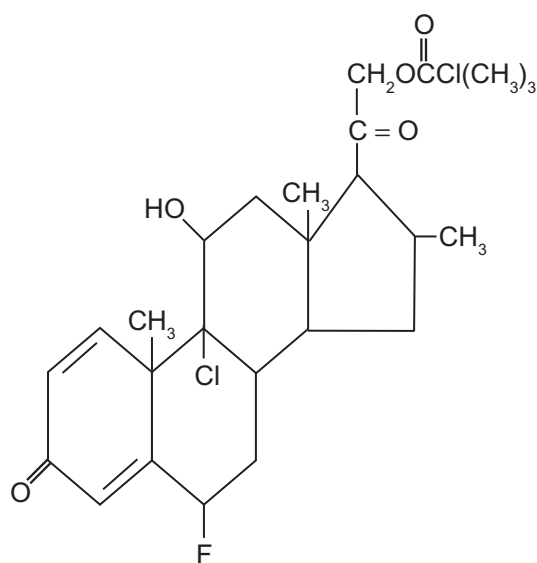


Figure 1 Clocortolone pivalate (chemical structure).⁴

Table 1 The Delphi list¹¹

Item number	Item	Assessment
1a	Treatment allocation: was randomization performed? (i) Correct randomization method described, (ii) inadequate randomization method described, (iii) randomization stated but method not described	i, ii, iii
1b	Was the treatment allocation concealed?	Yes/no/unclear
2	Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/no/unclear
3	Were the eligibility criteria specified?	Yes/no/unclear
4	Was the outcome assessor blinded?	Yes/no/unclear
5	Was the care provider blinded?	Yes/no/unclear
6	Was the patient blinded?	Yes/no/unclear
7	Were point estimates and measures of variability presented for the primary outcome measures?	Yes/no/unclear
8	Did the analysis include an intention-to-treat analysis?	Yes/no/unclear

Table 2 Summary and quality appraisal of the selected clinical trials of clcortolone pivalate 0.1% cream (CP) in skin disorders (quality appraisal of the randomized controlled trial [RCT] was done using the Delphi list)

Reference	Patients/centers/ country	Design/objectives	Interventions	Adverse effects	Efficacy	Conclusions	Quality appraisal of RCTs
Conde et al ¹²	Mild to moderate AD, mean age 7.9 years, BSA 5%–90%, n = 10, six completed study. Single center, US	Open trial; to determine both self-reported and actual adherence to CP in treatment of AD in a pediatric population	CP applied twice daily to affected areas, excluding face and groin; each application recorded; fitted with a MEMS device; 4 weeks' treatment; visits at baseline and weeks 1, 2, and 4; EASI, IGA, and target lesion score calculated; tubes weighed	None reported	CP generally effective with rapid improvement over first week. Overall change in EASI of 47.7% (P = 0.002), a 31.6% reduction in IGA (P = 0.026), and a 43.7% reduction in target lesion score (P = 0.009)	Overall actual adherence 18%–109%; overall self-reported adherence 71%–97%. Significant difference between self-reported vs actual adherence (P = 0.01). Poor adherence may explain nonresponse to topical corticosteroids	Not an RCT
Rosso ¹³	Mild to moderate AD. Single center, US	Randomized comparative open trial; to evaluate the benefit of a ceramide-based skin care regimen used in combination with CP and impact of topical corticosteroid therapy on epidermal barrier integrity	Subjects (n = 61) randomized to twice-daily use of synthetic detergent bar cleanser+CP (group 1), ceramide-containing MVE gentle cleanser+CP (group 2), or ceramide-containing MVE gentle cleanser + CP + ceramide-containing MVE lotion (group 3). Target areas evaluated at baseline and weeks 1, 2, and 4 by using skin hydration and TEWL. Signs and symptoms of dermatitis were evaluated using a four-point scale	None reported	Minimal differences between group 1 and group 2 for all study parameters; subjects in group 3 exhibited marked improvement in signs and symptoms, skin hydration, and TEWL vs other two groups	CP does not adversely affect skin hydration or epidermal barrier integrity and may be more effective when combined with ceramide-based MVE cleanser and ceramide-based MVE lotion	Ia: iii Ib: N 2: U 3: N 4: N 5: NA 6: N 7: N 8: U
Draelos et al ⁹	Patients with irritant contact dermatitis of hands. Authors from two centers in US	Open trial; to assess efficacy of CP in combination with a barrier cream for irritant contact hand dermatitis	53 patients with an MSS of 22.9 out of a possible 35. CP + a barrier cream used for up to 28 days	Not reported	After 28 days of treatment, 77% of the patients showed at least an 83% drop in their MSS	CP + barrier cream effective in treatment of irritant contact dermatitis of hands	Not an RCT
Cargill and Pillai ¹⁴	Studies 1 and 2: eczema/AD. Study 3: Contact dermatitis. Single center, US	Controlled; to examine the effects of CP in eczema/AD and contact dermatitis	CP applied thrice daily for 14 days (study 1 [n = 209] and 2 [n not mentioned]) and 21 days (study 3 [n = 44]). Studies 1 and 3 parallel group, number of patients receiving CP and vehicle not mentioned. Study 2 paired comparison	< 12% of patients reported adverse events, < 5% discontinued treatment	Study 1: more CP-treated patients had satisfactory response vs vehicle (69% vs 51%) with faster onset of action. Study 2: CP more effective 71% vs 36% (P < 0.001). Study 3: more CP-treated patients had good to excellent response (87% vs 50%, P < 0.025)	CP effective in eczema/AD and contact dermatitis with good safety profile	Ia: iii Ib: N 2: U 3: N 4: N 5: NA 6: N 7: N 8: U

(Continued)

Table 2 (Continued)

Reference	Patients/centers/ country	Design/objectives	Interventions	Adverse effects	Efficacy	Conclusions	Quality appraisal of RCTs
^a Torok and Slayton ¹⁵ and Torok et al ¹⁶	Adolescent and adults with AD. Authors from three centers, US	Randomized, investigator-blinded, controlled, parallel-group trial; to evaluate the safety and efficacy of concomitant therapy with CP and TO vs either alone	57 patients divided into three groups of 19 each. Group A: CP + TO, each twice daily, additional CP applications for skin irritation not relieved by cleanser or moisturizer. Group B: CP twice daily. Group C: TO twice daily. All patients used a cleanser and moisturizers. Age range 16–65 years, equivalent numbers in each 10-year age cohort. BSA 5%–20%. Duration 21 days. Evaluations on days 0, 3, 7, 14, and 21	No significant differences for transient pruritus and burning or stinging, although these adverse effects were less in Group A	Group A superior to group C in percentage change for dermatologic sum score at days 14 ($P = 0.024$) and 21 ($P = 0.033$), excoriation at day 21 ($P = 0.028$), induration at day 21 ($P = 0.033$), and erythema at day 14 ($P = 0.048$). Group A also superior to group B in excoriation at days 7 ($P = 0.045$) and 14 ($P = 0.037$), oozing or crusting at days 3 ($P = 0.034$) and 7 ($P = 0.012$), and lichenification at day 3 ($P = 0.031$)	Combination of CP and TO superior to either used alone in AD	Ia: iii Ib: N 2: U 3: Y 4: Y 5: N 6: N 7: Y 8: Y
Rosenthal ¹⁷	Eczema/AD. Single center, US	Double-blind, randomized, paired comparison; to assess the efficacy and safety of CP vs placebo in eczema/AD	CP and placebo applied thrice daily. Patients evaluated at baseline ($n = 100$), and days 4 ($n = 99$, mean age 35 years, range 4–73 years), 7 ($n = 97$), and 14 ($n = 96$)	None	CP superior vs placebo ($P < 0.01$) in all objective and subjective rating parameters	CP effective in eczema/AD with rapid early response, good safety, and patient acceptance	Ia: iii Ib: N 2: Y 3: Y 4: Y 5: NA 6: Y 7: N 8: N
Binder ¹⁸	Eczema/AD, 20 females, nine males, mean age 30 years, (no data of five dropouts). Single center, US	Double-blind, placebo-controlled randomized, parallel trial; to determine efficacy and safety of CP in eczema/AD	17 patients applied CP and 12 patients vehicle thrice daily for 14 days. Patients evaluated on days 0, 4, 7, and 14 to calculate index of clinical symptomatology (four-point scale) and a physician's rating of improvement (five-point scale). Four patients using CP who had maximal improvement at day 4 were excluded from further evaluation. Similarly, patients using placebo who had maximal improvement	Irritation and dryness, clinically significant in one patient in each group, did not necessitate discontinuation	Decrease in index of clinical symptomatology greater at each evaluation with CP vs placebo but not significant. Physician's ratings of satisfactory response (good and excellent ratings combined): CP vs placebo, day 4, 47% vs 8% ($P = 0.0286$); day 7, 69% vs 30% ($P = 0.0214$); day 14, 77% vs 50% ($P = 0.0324$). Overall satisfactory improvement CP vs	CP may be effective in the treatment of eczema/AD with low incidence of adverse effects	Ia: iii Ib: N 2: Y 3: Y 4: Y 5: NA 6: Y 7: Y 8: N

<p>Mackey⁹</p> <p>(two at day 4 and two at day 7) were excluded from further evaluation. But these were included in overall evaluations at the end</p>	<p>placebo, 82% vs 66%</p>	<p>CP applied twice daily for 1–4 weeks according to individual requirements for maximal response. Occlusive dressings were used in nine eczema, seven psoriasis, and in one lichen planus patient; occlusion to some areas in two eczema and four psoriasis patients</p>	<p>CP generally well tolerated with no systemic effects. Local side effects: blisters on leg (one patient), secondary infection (two), irritation or stinging (seven, severe in one necessitating discontinuation)</p>	<p>Eczema: very effective or effective in 69%. Improvement in erythema, scaling, pruritus, lichenification ($P < 0.001$), and weeping ($P < 0.05$). 19 patients in physician opinion (20 in patients' opinion) considered to have responded better to CP than previous medication. Psoriasis: very effective or effective in 40%. Marked improvement ($P = 0.0001$) in erythema, scaling, and pruritus. Seven cases in both physician and patients' opinion responded better to CP than previous treatment. No response in keloid, lichen planus. Only pruritus relieved in acne rosacea.</p>	<p>Not an RCT</p>
<p>Eczema (contact dermatitis, varicose eczema, photodermatitis, chronic dermatitis of hands, lichen chronicus simplex, pruritus vulvae, AD), average age 39.3 years, $n = 52$; psoriasis, average age 32.1 years, $n = 27$; others (acne rosacea, keloid, lichen planus), average age 45 years, $n = 3$. Total number of cases 85, data of 82 who completed study. Single center, Ireland</p>	<p>Open trial; to assess efficacy of CP in eczema, psoriasis, keloid, acne rosacea, and lichen planus</p>	<p>CP applied twice daily for 1–4 weeks according to individual requirements for maximal response. Occlusive dressings were used in nine eczema, seven psoriasis, and in one lichen planus patient; occlusion to some areas in two eczema and four psoriasis patients</p>	<p>CP generally well tolerated with no systemic effects. Local side effects: blisters on leg (one patient), secondary infection (two), irritation or stinging (seven, severe in one necessitating discontinuation)</p>	<p>Eczema: very effective or effective in 69%. Improvement in erythema, scaling, pruritus, lichenification ($P < 0.001$), and weeping ($P < 0.05$). 19 patients in physician opinion (20 in patients' opinion) considered to have responded better to CP than previous medication. Psoriasis: very effective or effective in 40%. Marked improvement ($P = 0.0001$) in erythema, scaling, and pruritus. Seven cases in both physician and patients' opinion responded better to CP than previous treatment. No response in keloid, lichen planus. Only pruritus relieved in acne rosacea.</p>	<p>Not an RCT</p>

Note: References 15 (poster abstract) and 16 (full article) refer to the same trial.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; EASI, eczema area and severity index; IGA, investigator global assessment; MEMS, medication event monitoring system; MSS, mean sum score; MVE, multivesicular emulsion; N, no; NA, not applicable; TEWL, Transepidermal water loss; TO, tacrolimus 0.1% ointment; U, unclear; Y, yes.

- The Cochrane Library (<http://www.thecochranelibrary.com/view/0/index.html>) was searched for “clocortolone” in “search all text.”
- The top 20 dermatology journals were identified according to the current impact factors as available on <http://impactfactor.weebly.com/dermatology.html>. The websites of these journals were searched individually for “clocortolone.”

The search was conducted on February 26, 2012. The full texts of all articles identified by this search were obtained, and then these were filtered through the following selection criteria for the purpose of evaluating the efficacy and adverse effects of clocortolone pivalate. The search was repeated on April 11, 2012, and the same results were obtained.

Selection criteria

Inclusion criteria were (1) clinical trial, (2) English language article, and (3) articles in other languages with English abstracts that contained sufficient information about methods and results. Exclusion criteria were (1) articles that referred to salts of clocortolone other than pivalate, and (2) review article.

Data extraction

After reading the full texts of the selected articles, the following variables were noted separately for each article: details of the patients, number of centers participating in the study, name of the country where the study was performed, trial design, objectives of the trial, interventions, adverse effects detected in the trial, efficacy, and conclusions.

Quality appraisal

Quality appraisal of the randomized controlled trials (RCTs) was done using the Delphi list (Table 1).¹¹ The Delphi list was expanded in respect of item number 1a to give three options: (1) correct randomization method described, (2) inadequate randomization method described, and (3) randomization stated but method not described. These subcategories provided clarity about the way the randomization was performed in the trials. Treatment allocation concealment, which is considered to be the most important indicator of quality of a trial, was understood to have taken place only when there was a clear statement about it or when there was a statement that meant that treatment to be allocated was not known before the patient was entered into the study.

All articles that passed the selection criteria^{9,12–19} and those excluded by the selection criteria^{5,7,8,10,20–38} are mentioned in the list of references. Reasons for exclusion of the articles

(nonfulfilment of inclusion criteria [IC] and/or fulfilment of exclusion criteria [EC]) are mentioned in parenthesis. The results of the systematic review are shown in Table 2.

A systematic search of the literature as explained previously identified one review article.¹⁰ This review article was excluded from the systematic review following the selection criteria. But this review article included results of nine studies; hence, it is being described here. Of the nine studies, two studies^{17,18} have been included in the systematic review; the remaining seven studies are unpublished. Results of the eight double-blind studies have been reviewed together in the article.¹⁰ In these studies, 297 patients were included (atopic dermatitis, 209; contact dermatitis, 44; seborrheic dermatitis, 44). The patients used clocortolone pivalate cream three times a day for 3 weeks and were evaluated weekly. The results showed the glucocorticoid to be significantly better than the vehicle. Several patients used the cream for up to 90 days. No adverse effects were noted, suggesting a good safety profile of the cream. The ninth unpublished study was a chronic use open study of 110 patients (psoriasis, 35; eczema/atopic dermatitis, 66; other steroid responsive dermatitis, nine). The cream was applied for 3 weeks with an option of continuing for 210 days. The efficacy of clocortolone pivalate

Table 3 Conclusions with levels of evidence^a derived from the systematic review of clinical trials of clocortolone pivalate (CP)

Serial number	Conclusion	Level of evidence
1	CP effective in eczema/AD and contact dermatitis compared with vehicle with good safety profile ^{14,17,18}	2
2	CP may be more effective when combined with ceramide-based MVE cleanser and ceramide-based MVE lotion ¹³	2
3	Combination of CP and tacrolimus ointment is superior to either used alone in AD. No significant differences among the groups for transient pruritus and burning or stinging ^{15,16}	2
4	Actual adherence to treatment with CP is significantly less compared with self-reported adherence ¹²	4
5	CP along with barrier cream effective and safe in treatment of irritant contact dermatitis of hands ⁹	4
6	CP effective for eczema. Also effective in psoriasis but less so. Outstanding antipruritic effects, especially in lichen chronicus simplex and AD. No systemic effects and mild local adverse effects ¹⁹	4

Note: ^aOCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>.

Abbreviations: AD, atopic dermatitis; MVE, multivesicular emulsion.

was rated as good to superb, and a few patients noted mild dryness, which was attributed to the cream vehicle. This study suggested that the cream may be applied for long periods of time without development of significant delayed or cumulative local or systemic side effects.¹⁰

Conclusion

Clocortolone pivalate is a mid-potency topical glucocorticoid available as a 0.1% cream. Pharmacologic studies have shown that after topical application this glucocorticoid achieves higher concentration in inflamed skin than in normal skin, and that it has little potential to enter the systemic circulation and cause adrenal suppression. In the systematic review of its efficacy and safety for the treatment of skin diseases, eight clinical trials were selected, of which five were RCTs. The trials have mainly included patients with atopic dermatitis and eczemas. The main conclusions of the present systematic review along with the levels of evidence are mentioned in Table 3. Although the quality appraisal of RCTs showed weaknesses in several items, the results tend to show that clocortolone pivalate cream is generally effective and safe for the treatment of these conditions. Inadequate attention has been paid to detect the occurrence of systemic adverse effects in the clinical studies. Further studies comparing this glucocorticoid with other glucocorticoids and treatments in steroid-responsive dermatoses are desirable.

Acknowledgment

We thank Dr Akhil Maheshwari, Associate Professor of Pediatrics and Pharmacology, Chief, Division of Neonatology, University of Illinois at Chicago for help in obtaining the full texts of three articles.

Disclosure

The authors report no conflicts of interest in this work.

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