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Evaluation of Adrenal Suppression of a Lipid Enhanced, Topical Emollient Cream Formulation of Hydrocortisone Butyrate 0.1% in Treating Children with Atopic Dermatitis

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Abstract: Corticosteroids are currently the first line of treatment for patients with atopic dermatitis. In the pediatric population however, the potential impact of adrenal suppression is always an important safety concern. Twenty boys and girls, 5–12 years of age, with normal adrenal function and a history of atopic dermatitis were maximally treated three times daily with a lipid-rich, moisturizing formulation of hydrocortisone butyrate 0.1% for up to 4 weeks. At the conclusion of the 4-week treatment period, cosyntropin injection stimulation testing showed no evidence of adrenal suppression. In addition, the therapy was noted to be highly efficacious, with a clinical success rate of 80% (Physician Global Score of (0) clear or (1) almost clear). No local side effects associated with prolonged use of topical corticosteroids were reported. In summary, this study supports the contention that this lipid-rich, moisturizing formulation of hydrocortisone butyrate 0.1% was a well-tolerated and beneficial treatment for atopic dermatitis, demonstrating no adrenal suppression in the pediatric population aged 5–12 years. The relevance of these findings for children below 5 years of age, because of difference in body mass/surface area ratios, remains to be determined.

Effective management of chronic, recurrent inflammatory diseases of the skin in children can reduce the severity and duration of intermittent flare-ups, and contribute to a quality of life comparable with that of individuals unaffected by disease. Estimates of the prevalence of atopic dermatitis (AD) vary from 10% to 17% (1,2), with 87% of children with the disease exhibiting signs and symptoms by 5 years of age (3). In many cases

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the first-line therapy for the management of AD exacerbations is topical corticosteroids (4). In fact, as per the American Academy of Dermatology Guidelines for the treatment of AD, topical steroids are the class of therapy by which other therapies are measured for the treatment of this disease (5). Class IV and/or V mid-potency topical steroids are efficacious in the treatment of AD in pediatric populations; however, the potential impact on adrenal suppression has not been well characterized.

Topical hydrocortisone butyrate 0.1% (HB 0.1%) has been found to be well tolerated and beneficial for the treatment of AD in adults, and has been available in a variety of dosage formulations (6). However, the potential for adverse systemic effects is greater in children compared with adults because of the larger ratio of surface area to body mass.

The lipid-rich vehicle formulation used in this product has been shown to repair the skin barrier function as evidenced by improvement in transepidermal water loss after a standardized insult with sodium lauryl sulfate (7). A vehicle, in addition to having general skin care effects, can also affect the amount of drug delivered to the cutaneous target and the amount of drug available for systemic absorption. To assess the potential for systemic safety concerns, the adrenal effects of this topical formulation of 0.1% hydrocortisone butyrate in a lipid-rich, moisturizing vehicle warranted evaluation.

OBJECTIVES

The objective of this study was to evaluate the potential for HPA axis suppression in a pediatric population that received HB 0.1% in a lipid-rich, moisturizing cream formulation for the treatment of moderate to severe AD. Measurements of effectiveness were recorded to characterize the clinical response.

MATERIALS AND METHODS

This was an open-label, multicenter study to evaluate the potential adrenal suppressive effects of topically applied hydrocortisone butyrate 0.1% in a lipid-enriched cream (Locoid Lipocream; Ferndale Laboratories, Inc., Ferndale, MI). Conditions that assured a significant exposure to the topical preparation included three daily applications over a minimum body surface area of 25%. The duration of treatment was for a maximum of 4 weeks. The open label nature of this design as well as the three times daily use (package insert provides for 2 to 3×/day) over a 4-week period are typical FDA requirements for a study of this type to assure maximal adrenal challenge to the therapy. In those subjects noted to be clear at 3 weeks, treatment was discontinued early. Healthy boys and girls with stable AD, 5–12 years of age were eligible for enrollment in the study. Prior to enrollment, parents or guardians provided written informed consents, and subjects 7–12 years of age provided written informed assent.

The use of systemic corticosteroids, immunomodulators, PUVA therapy, or antimetabolites within 4 weeks prior to entry into the study was prohibited. Likewise, use of topical AD therapies (including corticosteroids), exclusive of emollients, within 2 weeks of entry was prohibited. Stable maintenance therapy with oral antihistamines or asthma medications was permitted. A medical history and physician examination were performed to assure compliance with the entry criteria. Preentry urine pregnancy tests were conducted for girls 11 years of age or older, to exclude pregnant subjects from the study. Vital signs and standard laboratory tests including chemistry, hematology, and urology were performed at baseline (day 1) and end-of-treatment (day 22 or 29, as appropriate).

Subjects who met the entry criteria at day 1 were scheduled for follow-up weekly evaluations at days 8, 15, 22, and 29. A seven-point Physician's Global Assessment (PGA) of overall disease severity (0 = clear; 1 = just perceptible/almost cleared; 2 = mild; 3 = moderate; 4 = marked; 5 = severe; 6 = extreme) was used to determine the criteria for entry into the study, i.e., a minimum entry score equal to or more than 3, and to assess clinical improvement at each of the subsequent visits. A four-point scoring system (0 = none; 1 = mild; 2 = moderate; 3 = severe) of the severity of individual signs was recorded at each visit for erythema, infiltration/papulation, excoriation, lichenification, oozing/crusting, and scaling. Pruritus severity also utilized a four-point system. Descriptions of interference with activities of daily life were used to define pruritus scores. The percentage of body surface area (%BSA) involvement was recorded at each visit. All adverse events reported during the course of the study were recorded and evaluated.

Cortrosyn® (cosyntropin for injection), a synthetic analog of adrenal corticotrophic hormone, was used to challenge the responsiveness of the adrenal gland. The cosyntropin stimulation test (CST) with a 30 minute post-injection assessment was first performed on day 1 before the initiation of treatment, and then again at the end-of-treatment. A normal adrenal response was defined as a post-stimulation cortisol level greater than 18 μg/dL (8).

All statistical processing was performed using SAS® software (SAS Institute Inc., Cary, NC). Descriptive statistics, i.e., means, standard deviations, ranges, were used for data presentation. No formal hypothesis testing was performed for this open-label study.

RESULTS

Twenty-one subjects were enrolled into the study, with one lost to follow-up after the day 1 baseline visit. The remaining 20 subjects completed the study. Baseline demographic and disease severity information is presented in Table 1.

Two subjects whose condition cleared and remained cleared at the day 22 visit satisfied the protocol conditions for successful outcome, and after their end-of-treatment CST, ended their participation in the study. The remaining subjects (18/20) completed a full 4 weeks (28 days) of treatment. None of the 20 subjects tested with cosyntropin stimulation was found to be suppressed at the end-of-treatment with hydrocortisone butyrate 0.1% (Table 2).

Physician Global Assessment scores and sign and symptom scores improved (Fig. 1). The final scores (PGA = 0) of the two subjects who completed the study after 3 weeks were carried forward and included in the day 29 results. The figure shows a progression of improvement over the 3- to 4-week treatment period with 48% of the subjects cleared or almost cleared at week 2, and 80% at week 4.

The changes in %BSA involvement and signs and symptoms of AD are dramatic and consistent with the improvement seen in the PGA as shown in Fig. 1 and Table 3.

The treatment was well tolerated. No changes in vital signs or in chemistry, hematology, or urology laboratory tests were observed. Adverse events that were judged to be related to the use of drug were reported in two subjects: one with a mild, transient burning at the application site during the first day of use, and the second with a tinea corporis infection.

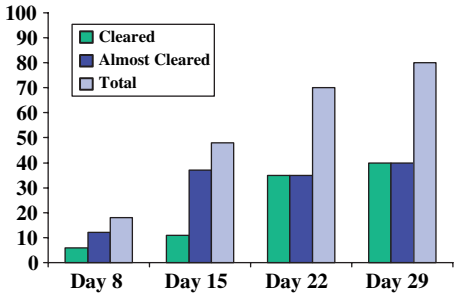

Figure 1. Physician's Global Assessment: percentage of subjects cleared and almost cleared.

TABLE 1. *Demographics and Disease Severity*

Age (years)	
Mean (±SD)	9 (2.5)
Range	5–12
Gender	
Male	10 (50%)
Female	10 (50%)
Race	
White	13 (65%)
Black/African American	4 (20%)
Asian	2 (10%)
Hawaiian or Pacific Islander	1 (5%)
Weight (kg)	
Mean (±SD)	32 (9.8)
Range	18–54
Height (cm)	
Mean (±SD)	132 (13.8)
Range	105–151
%BSA involvement	
Mean (±SD)	50 (17.2)
Range	25–80
Physician's Global Assessment	
Moderate	9 (45%)
Marked	9 (45%)
Severe	2 (10%)

TABLE 2. *Cosyntropin Stimulation Tests*

	Mean cortisol concentration (μg/dL, ±SD)	
	Pre-stimulation	Post-stimulation
Baseline	15.8 (7.0)	28.3 (5.5)
End-of-treatment	13.0 (4.6)	27.8 (4.5)

TABLE 3. *Lesion Severity Scores and Area of Involvement**

	Baseline (day 1)	End-of-treatment (day 29)
%BSA involvement	50 (17)	13 (20)
Pruritus	2.4 (0.6)	0.5 (0.7)
Erythema	1.8 (0.8)	0.5 (0.6)
Infiltration/papulation	2.1 (0.5)	0.8 (0.9)
Lichenification	2.0 (0.7)	0.6 (0.8)
Excoriation	2.0 (0.7)	0.3 (0.6)
Scaling	1.7 (0.6)	0.4 (0.7)
Oozing/crusting	0.9 (0.7)	0.1 (0.3)

*Standard deviations noted in parentheses.

DISCUSSION

An evaluation of the potential for systemic effects of topically applied corticosteroids is an important consideration in the selection of the therapeutic agent to be used in treating pediatric populations. Vasoconstrictor testing (VC assay) is typically performed to characterize the relative potency of these therapies, but the degree of vasoconstriction is a pharmacodynamic indicator of the local cutaneous activity that may or may not correlate with the potential for systemic effects. Direct measures of systemic activity such as HPA-axis suppression studies are necessary to assess the potential for systemic toxicity.

The systemic potency of a topical corticosteroid is dependent not only on the amount, kinetics, and inherent potency of the molecular entity that enters the systemic circulation, but also on the topical vehicle. The vehicle can play a major role in determining the transcutaneous absorption of the active agent. The lipid-rich, emollient cream vehicle used in this formulation of hydrocortisone butyrate 0.1% was engineered to optimize both its moisturizing potential and the delivery of the active moiety into the skin, while maintaining the cosmetic attributes that make creams popular. A double-blind study of this formulation compared with other commonly used midpotency agents in the treatment of atopic and hand dermatitis demonstrated a patient preference for the lipid-enriched formulation (9).

The primary objective of this study was to assess the risk of adrenal suppression with this 0.01% hydrocortisone butyrate formulation. Twenty AD subjects, aged 5–12, with a mean BSA of 50% were treated for up to 4 weeks. None of the subjects demonstrated adrenal suppression, based upon Cortrosyn® stimulation testing, at the end of the treatment period. No local side effects such as thinning, striae, or telangectasia that are associated with prolonged use of topical corticosteroids were reported and the subjects also demonstrated significant clinical improvement. The relevance of these findings for children below 5 years of age, because of difference in body mass/surface area ratios, remains to be determined.

CONCLUSIONS

Hydrocortisone butyrate 0.1% formulated in a lipid-enriched, emollient vehicle base, appears to be safe, both systemically and locally, for continuous daily administration over a 4-week duration of therapy in a population as young as 5 years of age. In particular, in this study, under maximal use conditions over a 4-week period there was no evidence of clinical or laboratory adrenal suppression or local topical steroid side effects identified in any subject. All subjects in this study retained normal adrenal function as demonstrated by CST testing.

ACKNOWLEDGMENT

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REFERENCES

1. Schultz-Larsen F, Holm K, Henningsen K. Atopic dermatitis: a genetic-epidemiological study in a population-based twin sample. J Am Acad Dermatol 1986;15:487–494.
2. Laughter D, Istvan JA, Tofte SJ et al. The prevalence of atopic dermatitis in Oregon schoolchildren. J Am Acad Dermatol 2000;43:649–655.
3. Rajka G. Atopic dermatitis. In: Rook A, ed. Major problems in dermatology. London: W.B. Saunders, 1975:2.
4. Eichenfield LF, Hanifin JM, Luger TA et al. Consensus conference on pediatric atopic dermatitis. J Am Acad Dermatol 2003;49:1088–1095.
5. Guidelines for the Care of Atopic Dermatitis, American Academy of Dermatology. Approved July 26, 2003, Available at: http://www.aadassociation.org/Guidelines/atopic.html. Accessed February 28, 2005.
6. Product Information for Locoid (Hydrocortisone butyrate 0.1%), Lipocream®, Ointment, Cream and Solution, Ferndale Laboratories, Inc.
7. Data on file at Ferndale Laboratories, Inc.
8. Product Information for Cortrosyn® (cosyntropin for injection), Organon, Inc.
9. Fowler J Jr., Fransway A, Jackson JM et al. Hydrocortisone butyrate 0.1% cream in the treatment of chronic dermatitis. Cutis 2005;75:125–131.