Topical Halcinonide and Betamethasone Valerate Effects on Plasma Cortisol

Acute and Subacute Usage Studies

Edward C. Gomez, MD, PhD; Lewis Kaminestein, MD; Phillip Frost, MD

The effect of topical application of halcinonide cream and betamethasone valerate cream on plasma cortisol was studied in an acute usage study as well as a subacute study, which more closely approximated common clinical usage. In the acute study, halcinonide cream caused a marked decrease in plasma cortisol, both with and without occlusion, in patients with extensive psoriasis, but only with occlusion in normal subjects. Betamethasone valerate cream decreased plasma cortisol levels in patients with extensive psoriasis when applied with occlusion and, to a lesser extent, without occlusion. In a double-blind subacute usage study without occlusion, two of 23 patients treated with halcinonide cream showed decreased plasma cortisol levels during the treatment period, while none of the 21 patients treated with betamethasone valerate cream showed such decreases. Three patients in the halcinonide group developed striae. Clinical response to halcinonide was superior to that with betamethasone valerate cream, but a similar number of patients were resistant to treatment with either medication. (Arch Dermatol 113:1195-1202, 1977)

The effects of topical application of potent fluorinated adrenal corticosteroid preparations, with or without occlusion, have been well documented. In the presence of an abnormal barrier to percutaneous absorption of a variety of corticosteroid preparations occurs to produce suppression of endogenous production of cortisol. Such studies have usually been acute usage experiments. The extrapolation from these studies to the common, usually longer term use of corticosteroid preparations in clinical practice is less clear.

In the course of evaluating adrenal effects of a new and potent topical corticosteroid preparation, halcinonide cream, we have compared the effects obtained with such an acute usage protocol to those obtained with subacute usage protocol, which more closely approximated the usual clinical situation. This article reports the adrenal effects of halcinonide cream, 0.1%, and betamethasone valerate cream, 0.1%, when applied for five days with and without occlusion to both normal and diseased skin, in comparison to the effects of the same preparations when used on an outpatient basis over a four- to six-week period without occlusion.

SUBJECTS AND METHODS

Patient Selection

All patients were volunteers who, after an explanation of the protocol to be followed, signed an informed consent form.

Table 1.—Relative Fluorescence of Cortisol, Halcinonide, and Betamethasone Valerate*

<table>
<thead>
<tr>
<th>Compound</th>
<th>nmoles</th>
<th>Fluorescence Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>4.9</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>9.8</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>19.6</td>
<td>75</td>
</tr>
<tr>
<td>Halcinonide</td>
<td>9.8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>19.6</td>
<td>0</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>9.8</td>
<td>0</td>
</tr>
<tr>
<td>Valerate</td>
<td>19.6</td>
<td>0</td>
</tr>
</tbody>
</table>

*Aliquots of 196 μM standard ethanolic solutions of the various corticosteroids were added to 4 ml of fluorescence reagent and incubated at room temperature for 30 to 60 minutes.

1. Fluorescence determined in fluorometrically, with use of excitation wavelength of 470 nm and emission wavelength of 520 nm.

Accepted for publication Nov 22, 1976.

From the Department of Dermatology, Mount Sinai Medical Center, Miami Beach. Dr Gomez is now with the Department of Dermatology, New York University Medical Center.

Reprint requests to Mount Sinai Medical Center, 4300 Alton Rd, Miami Beach, FL 33140 (Dr Frost).
Fig 1.—Application of halcinonide cream, 0.1%, to normal subjects 1 through 3. Points in rectangle indicate values of plasma cortisol on mornings after treatment days.

Fig 2.—Application of halcinonide cream, 0.1%, with occlusion, to normal subjects 4 through 6. Points in rectangle indicate values of plasma cortisol on mornings after treatment days.

that had been approved by the Research and Human Rights Committees of Mount Sinai Medical Center. One patient had atopic dermatitis; the other patients psoriasis.

Patients participating in the acute usage study had more than 30% of the total body surface involved and had not received systemically administered corticosteroids during the prior three months or topically administered corticosteroids during the previous month. Patients participating in the subacute usage study had at least 5% of the body surface involved and had not received systemically administered corticosteroids for the prior three months or topically administered corticosteroids for two weeks prior to beginning therapy. All patients in the acute usage study had normal pituitary-adrenal reserve as measured by a 24-hour oral metapirone test during the pretreatment period.

Experimental Design

Acute Usage Protocol.—The study was divided into a pretreatment period (days -4 to -1), a treatment period (days 1 to 5), and a post-treatment period (days 6 to 13). During the pretreatment period, a five-hour (100 gm) oral glucose tolerance test was done on day -4 and a metapirone test on day -3. Urine was collected daily to determine 17-hydroxysteroid and plasma cortisol levels. Specimens to determine blood glucose levels were taken two hours after breakfast on day -2.

During the treatment period, daily two-hour postprandial glucose determinations, plasma cortisol determinations, and 24-hour urine collections for urinalysis and 17-hydroxysteroid levels were performed.

During the post-treatment period, plasma cortisol determinations and 24-hour urine collections for urinalysis and 17-hydroxysteroid determinations were performed daily. Two-hour postprandial glucose determinations were done on days 6 and 11. The five-hour glucose tolerance test was repeated on day 10.

Fifteen grams of cream were applied to approximately 50% of the body twice daily at approximately 10 AM and 10 PM, by a nurse. When occlusion was indicated, the application of the cream was immediately followed by application of a plastic film held in place with tape and/or panty hose. The occlusive plastic film was left in place...
for ten hours after each application and then removed for two hours to allow the patient to bathe and dry prior to the next application.

Subacute Usage Protocol.—This was a double-blind study comparing halcinonide cream, 0.1%, and betamethasone valerate cream, 0.1%, applied three or four times a day, without occlusion. Patients were examined at weekly intervals for four to six weeks. On the initial visit blood was drawn for hematologic studies, chemical analyses of the blood, and duplicate plasma cortisol determinations. At the weekly visits these studies were repeated. Drugs were assigned according to a randomized schedule and were coded so that neither the investigator nor the patient was aware whether halcinonide cream or betamethasone valerate cream was used. To minimize the effect of diurnal variations of cortisol, patient visits were scheduled at the same time of day for each patient, but the time of day varied from patient to patient.

**Cortisol and Steroid Excretion Measurements**

Specimens for plasma cortisol determination were collected in tubes treated with heparin. Specimens were collected between 8 AM and 8:30 AM each day in the acute usage study. Twenty-four-hour urine specimens were collected from 8 AM each morning to 8 AM the following day and stored in a refrigerator until the analyses were to be done. Cortisol determinations were done by the method of Kitabchi and Kitchell. To ensure that the topical corticosteroids did not interfere with the fluorescence measurement of cortisol, the lack of reactivity of halcinonide and betamethasone valerate in this assay was confirmed (Table 1). The 17-hydroxycorticoid levels were determined by the method of Porter and Silber.

**RESULTS**

**Acute Usage Study**

Application of Halcinonide Cream to Normal Skin.—Three normal subjects had halcinonide cream, 0.1%, applied to 50% of the body surface area,
without occlusion, according to the acute usage protocol described above. Daily plasma cortisol determinations showed no evidence of adrenal suppression (Fig 1). Measurement of 17-hydroxysteroid excretion showed no evidence of adrenal suppression, except in subject 3, in whom 17-hydroxysteroid excretion was slightly lower on days 4, 5, and 6 than during the pretreatment days.

Three additional normal subjects had halecgonide cream, 0.1%, applied with occlusion, in a similar manner. Each of the subjects showed suppression of plasma cortisol during the treatment period (Fig 2). Subjects 4 and 5 showed progressive decrease in plasma cortisol until the morning after the final treatment. By the following morning, plasma cortisol levels in both of these patients had increased, indicating that the adrenal suppression was rapidly reversible. Subject 6 showed marked depression of plasma cortisol on only one of the treatment days. This value was definitely outside the normal range, but in view of the normal values found on the preceding and succeeding days, the possibility of a technical error must be considered.

**Application of Halecgonide Cream to Diseased Skin.**—Three subjects with widespread cutaneous involvement were treated with halecgonide cream, 0.1%, without occlusion. Two of the subjects had psoriasis and one had atopic dermatitis. The two subjects with psoriasis showed definite decreases of plasma cortisol on the mornings after treatment and a rapid increase to pretreatment values the days after the discontinuation of treatment (Fig 3). Subject 8 showed a marked decrease in plasma cortisol on the second morning after the initiation of treatment with a rise toward normal during the treatment period despite continued therapy. The rise in plasma cortisol during the treatment period was temporarily related to an extremely rapid improvement in the patient’s lesions. Subject 9, who had atopic dermatitis, showed no evidence of suppression of plasma cortisol during treatment.
Three additional subjects with widespread psoriasis were treated with halcinonide cream, 0.1%, with occlusion (Fig 4). All three showed a marked decrease in plasma cortisol values, which persisted throughout the treatment period despite the clinical improvement of the skin lesions. After the discontinuation of treatment, the plasma cortisol values rose rapidly to the pretreatment level.

Application of Betamethasone Valerate Cream to Diseased Skin.—Three subjects with widespread psoriasis were treated with betamethasone valerate cream, 0.1%, without occlusion (Fig 5). Subject 13 showed a mild decrease in plasma cortisol values only during the middle of the treatment period, while subject 14 showed a mild decrease in plasma cortisol values during the treatment period, which persisted for two days after discontinuation of treatment.

Subject 15 showed no evidence of suppression during the treatment period. Three patients were treated with betamethasone valerate cream, 0.1%, with occlusion. Figure 6 shows the plasma cortisol values obtained for two of these patients. Both show a decrease in plasma cortisol during the treatment period. Subject 16 showed a rise in plasma cortisol despite continued therapy with occlusion, while subject 17 showed a persistent decrease in plasma cortisol until the termination of therapy. The third patient (subject 18) treated with betamethasone valerate cream, 0.1%, with occlusion, showed no evidence of adrenal suppression (Fig 7). This same patient was also treated with halcinonide cream, 0.1%, with occlusion, and again failed to show a suppression of plasma cortisol or 17-hydroxysteroid excretion during the treatment. Plasma cortisol in this patient was in the high normal range with some values above the normal range.

Effects on Glucose Metabolism.—Four of the subjects tested had abnormal results to pretreatment glucose tolerance tests. Of these only one of the subjects demonstrated abnormal glucose metabolism in the course of the study, and these data have been reported separately.

Subacute Usage Protocol

Fifty-one outpatients between 9 and 76 years of age with psoriasis were treated with halcinonide cream, 0.1%, or betamethasone valerate cream, 0.1%, without occlusion, according to the double-blind subacute usage protocol described above. Of these patients, 44 patients completed four to six weeks of therapy. There were 31 male and 13 female patients. Involvement with psoriasis varied from approximately 5% (1/18) of the body surface to more than 50% (9/18) of the body surface. Of 44 patients completing the four to six weeks of therapy, nine had severe psoriasis, 25 moderate psoriasis, and nine mild psoriasis. Patients used between 225 and 500 gm of cream during the course of the study with an average usage of 472 gm.

A summary of the results of the study are shown in Table 2. Twenty-three of the patients completing the study were treated with halcinonide cream, 0.1%, and 21 were treated with betamethasone valerate cream, 0.1%. Of the patients treated with halcinonide cream, two showed mild, reversible adrenal suppression, and three developed striae. Of the patients treated with betamethasone valerate cream, none showed either adrenal suppression or striae formation.

Clinical response was graded at each visit and an overall clinical response assigned at the end of the study. Of the 29 patients treated with halcinonide cream, 18 had excellent responses. Only one of the 21 patients treated with betamethasone valerate cream had an excellent response. Both treatment groups had a similar number of patients who showed only fair or poor responses.

The plasma cortisol findings in the two patients showing adrenal suppression are shown in Fig 8. One patient was treated for four weeks with an excellent clinical response and showed a persisting decrease in plasma cortisol level as compared to the pretreatment and post-treatment values. Only 5% of the body surface was involved in this patient, much less than in many patients who showed no
evidence of adrenal suppression. The second patient evidencing adrenal suppression was treated for six weeks with an excellent response and a moderate decrease in plasma cortisol values compared to pretreatment and post-treatment values. This patient also had a smaller percentage (10%) of the body surface involved than did other patients who did not show adrenal suppression. Neither patient developed any notable side effects during the study period.

All three patients developing striae were in the group treated with halcinonide cream. Two of the patients developed the striae at sites of natural occlusion, one near the axillae and the second in the intergluteal fold. The third patient developed a band of striae around the waist, exactly matching the area under a wide leather belt that he customarily wore.

**COMMENT**

The suppression of adrenal function by topically applied corticosteroid preparations is amply demonstrated in the dermatologic literature. Most studies have used patients with widespread involvement with psoriasis or other dermatoses known to have an abnormal barrier to percutaneous penetration and in many cases have used occlusion to augment penetration of the corticosteroid preparation. Such studies are now performed to evaluate the safety of new corticosteroid preparations prior to marketing. Since the routine use of corticosteroid preparations in dermatologic practice is much different from the use of such preparations in the studies reporting adrenal suppression, it is of interest to monitor corticosteroid effects on the adrenal pituitary axis under conditions more closely resembling actual clinical usage.

The studies described here indicate that halcinonide cream, like other recently introduced corticosteroid preparations, has a suppressive effect on the adrenal-pituitary axis, as measured by a decrease in plasma cortisol levels after topical application to patients with widespread psoriasis, with or without occlusion. In addition, application to normal skin also causes a decrease in plasma cortisol levels, provided the area of application is occluded with a plastic film. No evidence of adrenal effects was noted when halcinonide cream was applied to 50% of the body surface of normal individuals without occlusion.

Betamethasone valerate cream also caused suppression of the plasma cortisol level in individuals with widespread psoriasis, both with and without occlusion. One individual with widespread psoriasis did not show adrenal suppression with either betamethasone valerate cream or halcinonide cream applied under occlusion. This individual had a relatively high cortisol level, including many values above the upper limit of normal, and
may have abnormal adrenal function. One patient developed a temporary alteration of glucose metabolism while under treatment with halcinonide and has been reported elsewhere. In contrast to the findings with the acute usage protocol, only two of 44 patients completing the subacute usage study showed evidence of adrenal suppression, both patients being in the halcinonide group. Three patients who developed striae were also in the halcinonide group. The finding of more side effects in the halcinonide treatment group than in the betamethasone valerate treatment group is not surprising since the clinical evaluations in this study, as well as reports of others, indicate that halcinonide cream is a more potent preparation than is the betamethasone valerate cream used for comparison.

The contrast between the acute usage study and the subacute usage study is striking. The data suggest that in routine clinical usage there is less adrenal suppression than would be expected from the acute usage studies. Assessment of pituitary-adrenal reserve might have revealed additional patients with effects from subacute usage, but the large number of patients involved precluded studies not easily performed on an outpatient basis.

The reliance solely on plasma cortisol values during the subacute usage study is not considered an important factor since the additional examination of 17-hydroxy cortisol excretion in the acute usage study yielded no additional information. Indeed, the difficulty of obtaining reliable 24-hour excretion values over a three-week period far exceeded the usefulness of these determinations. It is, of course, essential that the method used to determine plasma cortisol not measure the topical corticosteroids under study.

The potency of present-day preparations makes the performance of adrenal function tests of patients having widespread psoriasis during acute usage studies, with or without occlusion, of questionable value in the evaluation of new corticosteroid preparations. Most present-day steroids easily cause adrenal suppression in the majority of subjects so treated. More meaningful information can be obtained by studying subjects with an unaltered barrier, either with or without occlusion. Such studies would detect topical corticosteroid preparations having even greater potential for suppression of adrenal function, such as clobetasol propionate ointment, which was recently reported to cause profound decrease in plasma cortisol when applied to normal subjects without occlusion.

More recently, Carruthers et al have studied clobetasol propionate cream and ointment in normal subjects over a two-week period and found marked and persisting suppression of plasma cortisol during the treatment period, providing sufficient corticosteroid was applied (90 gm of preparation per week). Cortisol returned to normal on discontinuation of therapy. Patients under treatment for periods of ten weeks to 18 months with more than 50 gm per week also showed decreased plasma cortisol or reduced peak insulin stress test levels. Carruthers and associates also encountered a subject who showed no evidence of adrenal suppression at dosages causing suppression in other subjects (a situation similar to the patient in Fig 7). Their finding of diminished reserve on insulin stress is probably related to the prolonged periods of therapy and might have been overlooked in an acute usage study.

Long-term studies with patients having altered barriers are also logical in that they more closely approximate clinical usage and may provide some indication of additional side effects, such as striae formation, which would not be observed in short-term studies for the evaluation of acute effects or the determination of efficacy.

This investigation was supported in part by National Institutes of Health grant AM 10252.
E. E. Squibb and Sons provided the halcinonide cream (Halog) and betamethasone valerate cream (Valisone).

**Nonproprietary Names and Trademarks of Drugs**

**Betamethasone valerate—Valisone.**
**Halcinonide—Halog.**

---