Multiple Corticosteroid Orally Elicited Allergic Contact Dermatitis in a Patient With Multiple Topical Corticosteroid Allergic Contact Dermatitis

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Corticoid allergic contact dermatitis (ACD) may be topically or systemically elicited. Allergic contact dermatitis to topical corticosteroids is relatively common, whereas reports of orally elicited ACD to corticosteroids are rarer. Patients allergic to one corticosteroid often exhibit cross-reactivity to other corticoids. We have previously reported a 46-year-old woman with contact allergy documented by patch and provocative use testing to multiple topical corticosteroids. On further testing, she was thought to have multiple corticoid orally elicited ACD to triamcinolone, methyl prednisolone, dexamethasone, and prednisone. Oral provocation tests were performed in a single-blind fashion following the method of Alanko and Kauppinen [Diagnosis of drug eruptions: clinical evaluation and drug challenges. In, Skin Reactions to Drugs (Kauppinen K, Alanko K, Hannuksela M, Maibach HI, eds). Boca Raton, FL, CRC Press, 1998.]. The five oral corticosteroids tested were triamcinolone, methyl prednisolone, dexamethasone, prednisone, and hydrocortisone. Four of the five challenged corticosteroids (i.e., triamcinolone, methyl prednisolone, dexamethasone, and prednisone) produced a generalized maculopapular eruption in a delayed manner. The fifth challenged corticoid, hydrocortisone, had no adverse effect on this patient. This patient was unusual in that she exhibited polysensitivity to a spectrum of oral and topical corticosteroids. Hydrocortisone was identified as a corticosteroid for future clinical use. This is an important finding since corticosteroids are important emergency drugs.

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Allergic contact dermatitis (ACD) to topical corticosteroids is relatively common, having been reported in frequencies of 2.3 to 4.9% in recent studies involving many patch-tested patients. [1-5] Patients allergic to one topical corticosteroid often exhibit cross-reactivity to other topical corticoids. Corticosteroids may also sensitize subjects when used orally, parenterally, or intralesionally, although these modes of sensitization are presumed less common. Reactions to ingested, parenteral, or intralesional corticoids usually occur in patients previously sensitized by percutaneous absorption of a topically applied corticoid. Lauerma *et al*[6] documented this phenomenon: four patients who had known ACD to topical group A corticosteroids all experienced cutaneous reactions following administration of oral hydrocortisone.

We have previously reported a case of a 46-year-old woman with contact allergy to multiple topical corticosteroids, as evidenced by extensive patch tests and provocative use tests (PUT/ROAT).[7] The results from this previous study are summarized in Table I. Because this woman initially presented with chronic dermatitis, which flared up after taking oral prednisone, further testing was performed using oral challenges. She was subsequently thought to also have multiple corticoid orally elicited ACD to triamcinolone, methyl prednisolone, dexamethasone, and prednisone.

Materials and Methods

Oral provocation tests were performed in a single-blind fashion under strict medical supervision. Patch testing and PUT/ROAT had been performed (see above) more than one year previously. The patient was deemed free of active dermatitis at times of entry to each oral challenge. The five oral corticosteroids tested were triamcinolone, methyl prednisolone, dexamethasone, prednisone, and hydrocortisone. Each

Table I

Patch Tests and PUT/ROAT in Corticoid ACD Patient*

Corticosteroid	Class	Concentration (%)	Patch Test† 96 hrs	PUT/ROAT
Alclomethasone dipropionate	D	0.05, 1.0	+	+
Amcinonide	B	0.1	+	+
Betamethasone benzoate	C	0.05	+	+
Betamethasone valerate	D	0.1, 1.0	+	+
Budesonide	B	0.1	+	NT
Clobetasol propionate	D	0.05, 1.0	+	+
Clocortolone pivalate		0.1	0	+
Desonide	B	0.05	+	NT
Desoximetasone	C	0.25, 0.05	+	+
Dexamethasone phosphate disodium	C	1.0	+	+
Diflorasone diacetate		0.05	+	NT
Fluocinolone acetonide	B	0.025, 0.01	+	NT
Fluocinonide	B	0.05	+	+
Flurandrenolide (tape)		-	NT	+
Fluticasone propionate		0.05	+	+
Halcinonide	B	0.1	NT	+
Halobetasol propionate		0.05	+	NT
Hydrocortisone	A	1.0, 2.5	0	NT
Hydrocortisone acetate	A	1.0, 2.5	NT	-
Hydrocortisone valerate	D	0.2	+	NT
Hydrocortisone butyrate	D	0.1, 1.0	+	+
Hydrocortisone buteprate		0.1	NT	+
Mometasone furoate	D	0.1	+	+
Prednicarbate	D	0.1	NT	-
Tixocortol pivalate, Pivolone“	A	1.0	0‡	NT
Triamcinolone acetonide	B	0.1, 1.0	+	+

*Data are modified from Chang et al.[7] †0 = no reaction; + = positive reaction; NT = not tested. ‡Patch test was positive at 120 hours.

drug was tested at separate times. For each drug, a test dose was administered orally in the morning (day 1). The patient was allowed to eat normally, but was not given any other medications. Clinical symptoms and signs were recorded after 1 hour, then at hourly intervals for 10 hours, then at 24 hours.[8] The state of the skin, body temperature, pulse rate, and blood pressure were routinely recorded. If at 24 hours (day 2), the drug produced no reaction, then a further dose of the same drug was given. This subsequent dose was usually higher than the previous one, if the previous dose was deemed too low. If no eruption appeared,

Table II

Oral Provocation Tests in Corticoid ACD Patient

Drug	Class	Dose	Equivalent Unit Dose	Response
Triamcinolone	B	Day 1: 8 mg (4 mg bid*) Day 2: 12 mg (4 mg tid) Day 3: 8 mg (4 mg bid)	4 mg	Day 3: generalized maculopapular eruption
Methyl prednisolone	A	Day 1: 2 mg (2 mg od) Day 2: 6 mg (2 mg tid) Day 3: 4 mg (2 mg bid)	4 mg	Day 3: generalized maculopapular eruption
Dexamethasone	C	Day 1: 0.25 mg (0.25 mg od) Day 2: 0.75 mg (0.25 mg tid) Day 3: 0.50 mg (0.25 mg bid)	0.75 mg	Day 3: generalized maculopapular eruption
Prednisone	A	Day 1: 20 mg (20 mg od) Day 2: 20 mg (20 mg od)	5 mg	Day 2: generalized maculopapular eruption
Hydrocortisone	A	Day 1: 20 mg bid Day 2: 40 mg bid Day 3: 60 mg bid Day 4: 80 mg bid	20 mg	No reaction

*bid, twice per day; tid, three times per day; od, once per day

then yet another dose of the same drug was administered on day 3. Details of the oral provocation tests of this patient are shown in Table II.

Results

In the previous study involving patch testing and PUT/ROAT, the patient was found to be allergic to 23 corticosteroids, but seemed to tolerate hydrocortisone, tixocortol-21-pivalate, and prednicarbate, as documented by negative patch tests, with or without PUT/ROAT. Hydrocortisone and tixocortol are both class A corticoids, so it was postulated that she might tolerate other class A drugs such as prednisone and methyl prednisolone. As can be seen from the results of the oral challenges, this was not the case.

In the oral provocation tests, four of the five orally challenged glucocorticoids, i.e., triamcinolone, methyl prednisolone, dexamethasone, and prednisone, produced similar results—a generalized maculopapular eruption in a delayed manner (see Table II). No systemic reactions were observed. Each eruption gradually subsided upon withdrawal of each drug and inert therapy such as emollients. The fifth challenged corticoid, hydrocortisone, had no adverse effect on this patient.

Discussion

Allergic contact dermatitis is usually produced by external exposure of the skin to an allergen. In sensitized individuals, such as this patient, a systemically administered allergen may occasionally reach the skin through the circulatory system and produce a dermatitis clinically resembling a maculopapular drug reaction.[9] Although systemic administration, including oral, parenteral, and intralesional routes, may produce this condition, the first sensitizing exposure to the allergen was probably topical.[9] Ingestion of an allergen by such a person may result in various morphologic responses, for example, a generalized eczematous response or maculopapular-like drug eruptions, such as in our case, or more focal flares at sites of previous dermatitis, and may sometimes be accompanied by more systemic effects, like nausea and general malaise.[10]

Reports of orally elicited ACD to corticosteroids are rare in comparison to topical ACD. Prednisolone is by far the most commonly implicated.[11-15] Reports of other orally elicited corticoids exist, but are scarce, as are reports of oral challenges to verify these sensitivities.

From the results of our prior study and of this study, it would seem that this unusual patient is not only sensitized to a spectrum of topical corticoids, but also has multiple corticoid orally elicited ACD. The management of any patient with ACD, be it systemically induced or topically induced, is elimination or minimization of the involved medications. This obviously poses a clinical problem for this patient, who is allergic to such a range of corticoids and yet may require medication for her long-standing dermatitis. In-

Table III

Test Method—Oral Challenge (Oral Provocation Test) 8

WHO?	Patients with a suspected drug eruption, as per clinical history and examination.
WHY?	To induce a mild form of the eruption, so the causative drug can be identified.
WHEN?	1-2 months after original eruption clears, except: in severe reactions, i.e., urticaria, wait 6-12 months.
WHERE?	Test under controlled conditions, such as in a hospital.
WHAT?	Test components of drug, when practical. Test only one substance per day.
HOW?	A test dose of the suspected drug is given orally in the morning. The patient is allowed to eat normally, but ideally not given any other medication. Flare-up of the eruption and other clinical signs/symptoms are recorded at hourly intervals for 10 hours, then at 24 hours. If no reaction observed at 24 hours, then test is repeated with a larger dose of the same drug.
HOW MUCH?	Start with a low dose, usually less than therapeutic dose, e.g. 1/10 of therapeutic dose.

deed, corticosteroids have long been established as a major therapeutic option for ACD. Moreover, corticoids are an important emergency drug, thus it is crucial that one be identified for future use.

Coopman *et al*.[16] have suggested four major classes of corticosteroid allergens, grouped according to substitutions at the C17 and C21 positions (i.e., in the D-ring), based on the frequency of cross-reactivity. These four classes are class A (hydrocortisone type—no methyl substitution on C16, no side chain on C17, possibly short side chain on C21), class B (triamcinolone acetonide type—*cis* diol or ketal function on C16 and C17, possibly a side chain on C21), class C (betamethasone type— methyl substitution on C16, no side chain on C17, possibly a side chain on C21), and class D (hydrocortisone-17-butyrate type—side chain ester on C17). However, many exceptions occur with these groups and further refinement is being performed. For instance, based on computer analysis of extensive patch test results, Mihaly[17] has suggested further subclassification of group D into D1 (methyl substitution on C16 and halogenation on the base structure, side chain ester on C17, and possibly on C21) and D2 (no methyl substitution on C16 and no halogenation of the four ring structure, side chain ester on C17, possibly on C21). In our patient, cross-reactivity is a likely mechanism, since she had not previously been exposed to several of the tested corticoids, although concomitant sensitivities cannot be ruled out. On testing, sensitivities did not seem to fall into the Coopman-defined categories. Methyl prednisolone, prednisone, and hydrocortisone belong to class A, triamcinolone to class B, and dexamethasone to class C. (Oral class D corticoids are uncommon, therefore, oral challenge was not performed with a class D corticoid.) In fact, the accumulative results of her patch tests, PUT/ROAT, and oral challenges demonstrate that her corticoid allergies span the entire selection of corticoid categories.

More recent studies by Wilkinson *et al*.[18,19] on corticosteroid cross-reactions have demonstrated that the major determinant of cross-reactions is substitution at the C6 and C9 positions of the corticosteroid, i.e., in the B-ring. The D-ring substitutions (i.e., C16 and C17) were found to be important, but to a lesser extent, while substitutions at C21 had no significance at all. In these studies, they found that in hydrocortisone and budesonide allergy, the antigenic determinant was located in the B-ring. They demonstrated that patients sensitized to hydrocortisone and budesonide were most likely to react to other non-C6 and non-C9 substituted corticosteroids. Further work is necessary to determine whether these results apply to other corticosteroids.

Coopman *et al*.[16] also suggested the use of marker corticoids for corticosteroid allergies, for example, tixocortol pivalate as a screening agent for group A corticoids. Studies have validated this. For example, Burden and Beck[5] found 90.8% sensitivity to tixocortol pivalate among 131 cases of corticosteroid sensitivity. Our patient, however, showed no reaction to tixocortol or hydrocortisone, and yet reacted strongly to methyl prednisolone and prednisone, also group A corticoids. One explanation for this may be poor absorption of the topical corticosteroid into the skin during patch testing. For example, in one study, 1 mg hydrocortisone in petrolatum caused a reaction in only 2 of 24 patients suspected of hydrocortisone allergy, whereas 1 mg hydrocortisone administered intradermally caused reactions in all 24 patients.[20] Commercial preparations of corticosteroids are sometimes used in patch testing for this reason, since they contain excipients that enhance skin penetration, thereby increasing bioavailability.[21] Another explanation may be the anti-inflammatory nature of cor-

ticosteroids,[22,23] which may result in false negatives. Because of this effect, delayed readings are sometimes helpful. For instance, although 1% tixocortol pivalate showed no reaction at 96 hours, a positive patch test reaction was observed at 120 hours.

Provocative use tests (PUT/ROAT) have similar limitations to patch testing, such as poor percutaneous penetration. Intradermal testing avoids this penetration barrier, and has yet to be tested on this patient.

Conclusion

Corticoid ACD may be topically or systemically elicited. Patch tests or PUT/ROAT are useful in determining ACD to topical medications, and the oral provocation test is a safe and effective method of detecting orally elicited ACD. Alanko and Kauppinen[8] provide details and principles of drug challenges derived from vast clinical experience. This information has been summarized in Table III.

Our case report typifies the usual patient with ACD to corticosteroids, who presents with a chronic dermatitis and is either unresponsive or deteriorates with corticosteroid therapy. However, our case is unusual in that she exhibited polysensitivity to a spectrum of oral as well as topical corticosteroids. This polysensitivity imposes severe clinical limitations for treatment of her dermatitis. We have, however, finally identified an oral glucocorticoid that she can tolerate—hydrocortisone—and additional oral corticoid challenges are contemplated.

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