

Letter to the Editor

Hypersensitivity to systemic corticosteroids: An infrequent but potentially life-threatening condition

To the Editor:

Corticosteroids have been prescribed extensively for their immunosuppressive, antiproliferative, antiallergic, and anti-inflammatory effects. Paradoxically, they have been reported to trigger immediate allergic responses, including life-threatening ones.¹⁻⁴ Hypersensitivity to corticosteroids can often go undiagnosed because symptoms can mimic some of the emergency conditions for which they are given, such as shock, status asthmaticus, or anaphylaxis. Patients are therefore at risk of receiving the same offending corticosteroid more than once, which might be life-threatening.

Systemic steroid hypersensitivity is overall uncommon. Several patients reportedly had allergic reactions to more than 1 corticosteroid.^{5,6} However, the degree of cross-reactivity between different corticosteroids remains unknown. Some patients have had allergy skin prick tests (SPTs) and intradermal tests (IDTs)^{4,6}; however, these have not been standardized, and their sensitivity and specificity have not been clearly determined. Drug challenge with an alternative steroid under medical supervision is an important clinical tool when steroid therapy is considered necessary.

We report on 15 patients who were evaluated in our allergy program between 1998 and 2010 for symptoms suggestive of steroid allergy. All but 1 of these patients underwent SPTs/IDTs (within days to around a year of the reaction). Ninety percent of patients who were challenged with an alternative corticosteroid tolerated the medication. To date, this is the largest series of systemic corticosteroid allergy reported in the medical literature in which SPTs/IDTs were done with the same method.

A retrospective chart review was performed. SPTs were done by applying a drop of the test solution at full concentration. Only SPTs were done for prednisone and prednisolone because these are only available for oral use. IDTs were performed for the other steroids at 1:1000, 1:100, 1:10, and full-strength concentrations. Results of the SPTs/IDTs were considered positive when the wheal reaction was at least 3 mm larger than that elicited by the saline control. Benzyl alcohol 0.9% testing was performed for some patients when they reacted to a steroid formulation containing this preservative. When medically necessary, challenges were performed with a steroid that demonstrated a negative SPT result, IDT result, or both.

Patients' clinical presentations, SPT and IDT results, and outcomes of the steroid challenge are summarized in Table I. Test results were negative for 3 healthy control subjects (except for betamethasone and triamcinolone, which were not done). Three subjects had clinical reactions to more than 1 steroid before their presentation to our program. Of a total of 19 reactions, 7 (36%) were consistent with anaphylaxis, whereas the others were limited to mucocutaneous symptoms. Five were secondary to prednisone, 5 to prednisolone, 4 to methylprednisolone succinate, 3 to dexamethasone, 1 to triamcinolone acetonide, and 1 to hydrocortisone succinate. SPTs and IDTs were performed in 14 patients (1 was lost to follow-up). None of the patients who reacted to prednisone or prednisolone had a positive SPT result. Further evaluation for

these 2 medications by means of IDTs could not be done because the only formulation available is for oral use.

However, all but 1 of these patients (subject 7) had positive IDT results to at least 1 other steroid.

Ten of 15 patients underwent steroid challenge, and 9 (90%) tolerated the drug with no reaction. Only patient 9 had a negative IDT result to dexamethasone; however, this patient reacted during the challenge with urticaria.

All patients who had a history of reaction to 1 or more steroids with a formulation compatible for IDTs had a positive reaction to that specific steroid or steroids on SPTs or IDTs, except for one who was lost for follow-up and could not be tested. Therefore the sensitivity of the IDT appears to be significant: of 7 reactions to these steroids (including the dexamethasone reaction for patient 9), 6 (86%) corresponding IDT results were positive. However, the rate of false-positive results is difficult to estimate because we did not proceed with challenging patients with a positive test result to a particular steroid and yet no known prior exposure to that medication.

The exact prevalence of corticosteroid-induced hypersensitivity reactions remains unknown. In one prospective study approximately 0.1% of 10,000 doses of steroids administered to 202 children were thought to have a possible allergic reaction.⁷ Symptoms included pruritus, hives, and anaphylaxis-like reactions. These symptoms, when combined with positive SPT results, IDT results, or both, suggest type I hypersensitivity reactions. *In vitro* allergen-specific IgE testing to corticosteroids is very difficult to perform and has only been reported in a few articles.^{2,8} It is yet unclear whether the triggering molecule is the steroid itself or whether the corticosteroid or its metabolite acts like a hapten bound to a protein, making the complex allergenic. Immediate reactions to corticosteroids have been reported to different corticosteroids,^{6,9} as well as to specific conjugated esters.⁸ Although some articles have suggested that cross-reactivity is higher between hydrocortisone and methylprednisolone than with halogenated steroids, such as dexamethasone and betamethasone,^{4,5} others reported concomitant allergy between these.⁹ In our study no increased cross-reactivity could be identified based on clinical presentation, IDT test results, or both. In addition, although some articles concluded that the incidence of hydrocortisone and methylprednisolone allergy seems higher than with other steroids,^{5,6} this was not observed in our series in which 52% of the reactions were secondary to oral prednisone or prednisolone, which are commonly used for outpatient therapy. This was likely secondary to the increased use of these steroids compared with others.

In an excellent review of the literature from 1966 to 1997 on allergic reactions to systemic corticosteroids, IDT results were found to be positive in 19 (76%) of 25 cases.⁶ In addition, in many cases a negative IDT result correlated with a systemic tolerability to the drug tested. In our series the sensitivity of the IDT was 86%.

Patient 1 had an interesting presentation. After anaphylaxis to methylprednisolone, she tolerated 2 dexamethasone infusions and then had anaphylaxis to the third pulse. It is therefore advisable to prescribe injectable epinephrine for emergency use to outpatients with steroid allergy receiving an alternate well-tolerated steroid medication because they might be at risk for sensitization with time.

TABLE I. Characteristics of patients with corticosteroid allergy

Subject no.	Sex	Age (y) at time of reaction	Underlying condition(s)	Reaction to steroids
1	Female	10	Juvenile rheumatoid arthritis*	Methylprednisolone succinate (containing benzyl alcohol) infusion: chest tightness, tachycardia, generalized swelling, urticaria; dexamethasone sodium phosphate infusion: chest tightness, tachycardia, generalized swelling, urticaria
2	Male	5	Asthma,* eczema, food and environmental allergies	Prednisolone: unilateral periorbital swelling and urticaria on 2 occasions
3	Male	8	Allergic reaction to squaric acid (consisting of facial swelling and erythema),* asthma,* food and environmental allergies	Prednisolone (given on 2 occasions): difficulty in breathing, agitation
4	Male	4	Juvenile dermatomyositis*	Methylprednisolone succinate infusion: urticaria, vomiting, pallor, abdominal pain and a decrease in oxygen saturation down to 92%
5	Male	3	Juvenile dermatomyositis*	Methylprednisolone succinate infusion: pruritic rash on the face and body
6	Female	24	L4-L5 disk herniation*	Prednisone: pruritus, urticaria within 1 hour of ingestion
7	Male	9	Asthma,* aspirin and acetaminophen allergy	Prednisolone: gagging, throat tightness, flushing Prednisone: gagging, throat tightness, flushing, hives
8	Male	20	Poison ivy,* asthma, allergic rhinitis	Triamcinolone acetonide (containing benzyl alcohol) injection: immediate rhinorrhea, sneezing, difficulty breathing, diffuse urticaria treated successfully with methylprednisolone intravenous and subcutaneous epinephrine
9	Male	10	Poison ivy,* asthma	Prednisone: itchy rash of the trunk, ears, and neck
10	Male	10	Poison ivy,* asthma (received prednisone on 3 different occasions before his reaction)	Prednisone: urticaria persisted until prednisone was stopped
11	Female	2	Asthma,* environmental allergies, multiple antibiotic allergies	Prednisolone: facial swelling and erythema Received again at an outside allergist's office and had urticaria on the back Dexamethasone: generalized urticaria Hydrocortisone oral (at an outside allergist's office) oral: urticaria
12	Female	3	Asthma,* environmental allergies	Prednisolone: severe lip and tongue swelling
13	Male	11	Dermatomyositis*	Methylprednisolone succinate infusion: urticaria
14	Female	15	Bursitis and tendinitis	Dexamethasone liquid given by means of iontophoresis: rash and erythema at site of patch within 1 hour of iontophoresis
15	Male	10	Asthma,* allergic rhinitis, multiple drug allergies (antibiotics, acetaminophen, NSAIDs)	Prednisone: rash and eye swelling on 2 occasions before presentation Challenged in clinic for confirmation before testing: developed a pruritic erythematous rash after ingestion of 5 mg

An empty cell indicates that the test for that particular steroid was not done. Wheals and flares were measured in millimeters.

NSAIDs, Nonsteroidal anti-inflammatory drugs.

*Condition for which the steroid was given at the time of the reaction.

†Methylprednisolone succinate (10 mg/mL, preservative free).

‡Dexamethasone sodium phosphate (4 mg/mL, containing benzyl alcohol).

§Hydrocortisone sodium succinate (10 mg/mL, preservative free).

||Prednisone and prednisolone sodium phosphate (15 mg/5 mL) SPT results were negative (data not included in the table).

¶Benzyl alcohol: SPTs were performed at full concentration, and IDTs were performed at 1:1,000, 1:100, and 1:10 dilutions.

*Betamethasone (6 mg/mL, containing a mixture of betamethasone sodium phosphate and betamethasone acetate, with edentate disodium and benzalkonium chloride).

**Triamcinolone acetonide (10 mg/mL, containing benzyl alcohol).

††Most challenges were performed within days to weeks of testing.

TABLE I. (Continued)

Methylprednisolone†	Dexamethasone‡	Hydrocortisone§	Other(s)	Challenge††
Positive IDT result at 10 mg/mL, wheal 8, flare 11	Positive IDT result at 4 mg/mL, wheal 5, flare 8	Negative	Benzyl alcohol¶: negative	Hydrocortisone infusion: tolerated Prednisone: tolerated
Negative	Positive IDT result at 4 mg/mL, wheal 7, flare 18	Negative		Not done
Positive IDT result at 10 mg/mL, wheal 5, flare 10	Positive IDT result at 4 mg/mL, wheal 15, flare 0	Negative		Prednisone: tolerated
Positive IDT result at 0.01 mg/mL, wheal 4, flare 10	Positive IDT result at 0.04 mg/mL, wheal 5, flare 12	Positive IDT result at 0.1 mg/mL, wheal 4, flare 10		Prednisolone pulses: tolerated
Positive IDT result at 10 mg/mL, wheal 9, flare 9	Negative	HC: positive IDT result at 10 mg/mL, wheal 7, flare 7		Dexamethasone infusion: tolerated Continued on oral prednisolone
Positive IDT result at 10 mg/mL, wheal 8, flare 30	Positive IDT result at 4 mg/mL, wheal 10, flare 30	Negative	Betamethasone#: positive IDT result at 6 mg/mL, wheal 8, flare 40	Declined
Negative	Negative	Negative		Methylprednisolone oral: tolerated
Negative	Negative	Negative	Triamcinolone**: positive IDT result at 0.01 mg/mL, wheal 6, flare 35 Benzyl alcohol: negative	Not done after testing but has tolerated methylprednisolone
Positive IDT result at 10 mg/mL, wheal 7, flare 0	Negative	Positive IDT result at 1 mg/mL, wheal 7, flare 10		Dexamethasone oral: pruritus and urticaria over trunk, base of neck, behind the ears, and on left flank treated with diphenhydramine (Benadryl)
Positive IDT result at 10 mg/mL, wheal 10, flare 20	Negative	Positive IDT result at 0.01 mg/mL, wheal 8, flare 20		Dexamethasone oral: tolerated
Not done (patient lost to follow-up)	Not done (patient lost to follow-up)	Not done (patient lost to follow-up)		Not done
	Negative	Positive IDT result at 1 mg/mL, wheal 9, flare 10		Not done
Positive IDT result at 0.01 mg/mL, wheal 5, flare 18	Positive IDT result at 0.004 mg/mL, wheal 5, flare 17	Positive IDT result at 0.01 mg/mL, wheal 5, flare 15		Prednisolone oral: tolerated
Positive IDT result at 0.01 mg/mL, wheal 7, flare 10	Positive IDT result at 0.004 mg/mL, wheal 9, flare 9	Positive IDT result at 0.01 mg/mL, wheal 6, flare 8	Betamethasone: positive IDT result at 0.006 mg/mL, wheal 10, flare 15	Not done
Positive IDT result at 0.01 mg/mL, wheal 5, flare 10	Negative	Negative		Dexamethasone oral: tolerated

Larger studies are required to determine prevalence, the degree of cross-reactivity between different corticosteroids, and the sensitivity and specificity of SPTs and IDTs.

We thank Vicki Hamel, RN; Pamela Hamilton, RN; Janet Weaver Holleran, RN; and Barbara Grant, RN, for performing skin and intradermal testing on

patients and Stacey Glynn, PharmD, for providing information related to steroid formulations.

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Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

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doi:10.1016/j.jaci.2010.09.030