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Cutaneous Reactions to Injectable Corticosteroids

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Abstract and Introduction

Abstract

Corticosteroids are used to treat a variety of medical conditions. While topical preparations are known to commonly cause allergic contact dermatits, systemic use of these drugs rarely causes cutaneous reactions. (This paper presents) Two cases of (systemic) injectable corticosteroid use resulting in delayed hypersensitivity reactions are presented.

Introduction

Glucocorticosteroids are commonly used in dermatology and other medical specialties for their immunosuppressive and antiinflammatory effects. These medications can be administered topically and systemically through various routes.[1] Topical corticosteroids are commonly recognized causes of allergic contact dermatitis.[2,3] Systemically administered preparations, however, are an infrequent cause of cutaneous reactions, few cases of which are reported in the literature.[4] We present two cases of cutaneous delayed-type hypersensitivity reactions to different classes of injectable corticosteroids used for treatment of articular disease.

Case Report 1

A 71-year-old woman complained of itching and redness for 1 month in the left gluteal area at the site of an epidural injection (Fig 1). The patient had received an injection of bupivacaine (Marcaine, Abbott Laboratories, North Chicago, IL) and methylprednisolone acetate 40 mg/mL (Depo-Medrol, Pharmacia and Upjohn, Kalamazoo, MI) in the area 1 day prior to the development of symptoms. She had been receiving these epidural injections for treatment of her lumbar disk disease for 3 years. The patient received a total of six injections over this period but developed a cutaneous reaction only after the last injection.

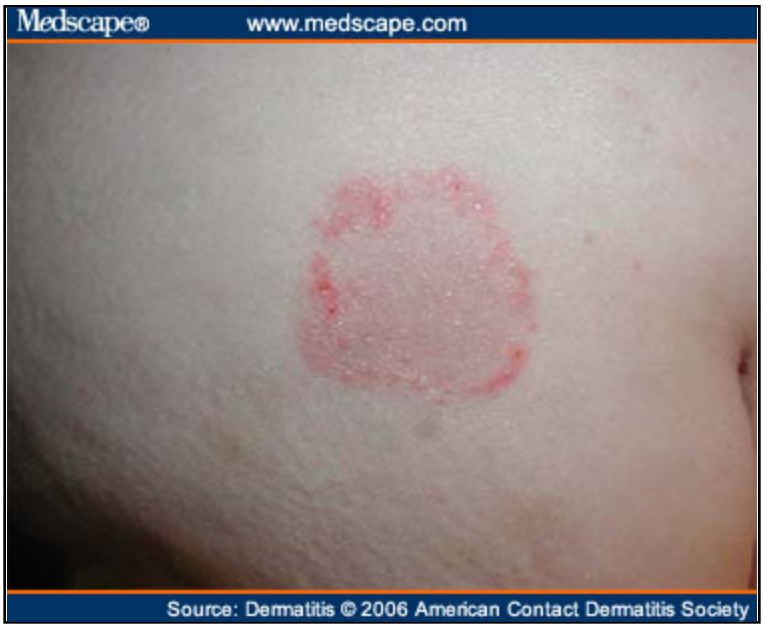

Figure 1. A 4.0 cm annular erythematous indurated plaque in the left gluteal area at the injection site.

Depo-Medrol is a corticosteroid suspension consisting of methylprednisolone acetate as the active ingredient and benzyl alcohol as a preservative. Polyethylene glycol, polysorbate 80, monobasic sodium phosphate, dibasic sodium phosphate, and sodium chloride are other constituents of the preparation.[5]

The patient's medical history was significant for osteoarthritis, spinal stenosis, and lumbar degenerative disk disease. She denied previously having skin disease or using topical corticosteroids.

On physical examination, a 4.0 cm annular erythematous indurated plaque was noted in the left gluteal area. Potassium hydroxide testing was performed to rule out a dermatophyte and had a negative result.

An allergic reaction to the injection material was considered. Patch testing was performed with our screening series of 93 allergens and selected corticosteroids, according to the guidelines of the North American Contact Dermatitis Group. The corticosteroids tested included tixocortol 1% in petrolatum, triamcinolone acetonide 1% in petrolatum, betamethasone-17-valerate 1% in petrolatum, alclomethasone-17,21-dipropionate 1% in petrolatum, dexamethasone-21-phosphate disodium salt 1% in petrolatum, and clobetasol-17-propionate 1% in petrolatum. Positive ++ and +++ reactions to the corticosteroid marker tixocortol-21-pivalate 1% in petrolatum were seen at 48 hours and 72 hours, respectively. A ++ positive reaction to the preservative p-chloro-m-cresol 1% in petrolatum was noted at 72 hours and was not considered to be relevant. Results of the remainder of the screening, corticosteroid, and cosmetic series were negative.

Intradermal testing on the forearms with 0.1 cc of solution was subsequently performed with 40 mg/mL of Depo-Medrol (as is), 125 mg/2 cc of preservative-free methylprednisolone sodium succinate, preservative-free sodium chloride 0.9%, benzyl alcohol 0.9%, lidocaine 1%, and bupivacaine 0.25%. A positive reaction to Depo-Medrol (a 2 cm area of indurated erythema) was seen at 48 hours and 96 hours and persisted for 2 weeks. Preservative-free methylprednisolone sodium succinate also caused a positive reaction at 48 hours (a 3 cm area of erythema and induration at the test site). There was no reaction to the preservative-free sodium chloride, benzyl alcohol, or the anesthetics. Intradermal testing with 0.1 cc of Kenalog-40 (Bristol-Myers Squibb Company, Princeton, NJ) containing triamcinolone acetonide 40 mg/mL was also performed, and the result was negative.

This patient exhibited a delayed-type hypersensitivity reaction to methylprednisolone. The results were discussed

with the patient's pain management physician, and therapy was successfully changed to triamcinolone acetonide epidurals for treatment of the patient's lumbar disk disease.

Case Report 2

A 75-year-old woman presented with a history of warmth and redness in her right knee after receiving intra-articular injections of Kenalog-40 containing triamcinolone acetonide 40 mg/mL for osteoarthritis. She had received two injections over a 4-month period. Approximately 2 days after the last injection, the patient noticed a cutaneous eruption on her right knee; this eruption eventually generalized. Oral prednisone was used successfully to clear the eruption prior to the patient's visit.

The patient's medical history was significant for osteoarthritis and osteoporosis. The patient had no known drug allergies or history of skin disease. She denied having used topical corticosteroids in the past.

Given the patient's history, an allergic reaction to the injection material was considered. Patch testing was performed with the North American Contact Dermatitis Group standard allergen series and with the New York University Skin and Cancer Unit's steroid allergen series and anesthetic series (Table 1). At both 48 hours and 96 hours, ++ reactions were noted to balsam of Peru, fragrance mix, hydrocortisone valerate, desonide, betamethasone dipropionate, mometasone furoate, betamethasone valerate, diflorasone diacetate, triamcinolone acetonide, amcinonide, hydrocortisone butyrate, budesonide, alclometasone dipropionate, clobetasol propionate, and dexamethasone. The patient did not react to tixocortol-21-pivalate (Fig 2), a screening agent for allergy to group A corticosteroids, which include prednisone, methylprednisolone, and hydrocortisone (Table 2). The patient's clinical improvement following therapy with oral prednisone can be explained on this basis.

Table 1. New York University Skin and Cancer Unit Steroid Allergen Series and Anesthetic Series

Steroid Allergen Series
1. Hydrocortisone valerate 1% pet 2. Desonide 0.5% pet 3. Hydrocortisone 1% pet 4. Betamethasone diisopropionate 1% alc 5. Mometasone furoate 1% pet 6. Betamethasone valerate 1% alc 7. Diflorasone diacetate 1% pet 8. Triamcinolone acetonide 1% pet 9. Amcinonide 1% alc 10. Hydrocortisone-17-butyrate 1% alc

11. Pivalone 1% pet 12. Budesonide 0.1% pet 13. Alclomethasone-17,21-dipropionate 1% pet 14. Clobetasol-17-propionate 1% pet 15. Dexamethasone-21-phosphate disodium salt 1% pet
Anesthetic Series
1. Tetracaine (amethocaine) hydrochloride 1% pet 2. Lidocaine hydrochloride 15% pet 3. Benzocaine 5% pet 4. Procaine hydrochloride 1% pet 5. Prilocaine hydrochloride 5% pet 6. Menthol 2% pet 7. Dibucaine hydrochloride 5% pet

alc = alcohol; pet = petrolatum

Table 2. Classes of Corticosteroids

Group A	
Cloprednol	Prednisolone
Hydrocortisone	Prednisolone acetate
Hydrocortisone acetate	Prednisolone caproate
Methylprednisolone	Fludrocortisone acetate
Prednisone	Tixocortol pivalate
Group B	
Budesonide	Triamcinolone
Desonide	Triamcinolone diacetate
Flunisolide	Triamcinolone acetonide

Fluocinonide	Amcinonide
Procinonide	Flucloronide
Halcinonide	Fluocinolone acetonide
Group C	
Betamethasone	Fluprednidene acetate
Dexamethasone	Desoximetasone
Clocortolone	Halometasone
Fluocortolone	
Group D1	
Beclomethasone dipropionate	Alclometasone-17,21-dipropionate
Betamethasone dipropionate	Betamethasone-17-valerate
Clobetasone butyrate	Clobetasol propionate
Diflorasone diacetate	Clobetasone propionate
Fluticasone propionate	Mometasone furoate
Diflucortolone valerate	
Group D2	
Hydrocortisone-17-butyrate	Methylprednisolone aceponate
Hydrocortisone-17-aceponate	Prednicarbate
Hydrocortisone-17-buteprate	Hydrocortisone valerate

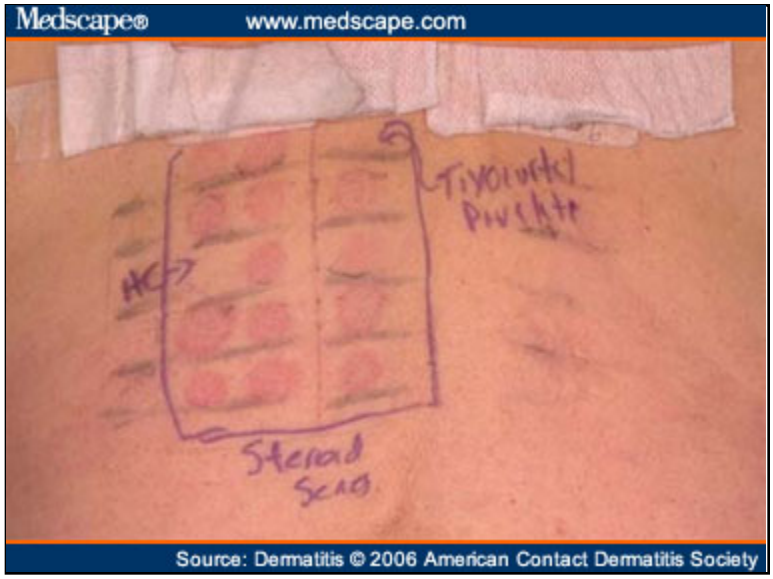

Figure 2. Patch-test reactions to corticosteroids. All tested corticosteroids except tixocortol-21-pivalate and

hydrocortisone caused positive reactions.

This patient exhibited a delayed hypersensitivity reaction to triamcinolone acetonide as well as to a number of corticosteroids in groups B, D1, and D2. Discontinuation of intra-articular corticosteroid injections of Kenalog-40 resulted in no further cutaneous eruptions.

Discussion

Topical corticosteroids are frequently recognized causes of allergic contact dermatitis.[2,3] The results of a North American Contact Dermatitis Group study indicate contact allergy incidences of 3.0% for tixocortol-21-pivalate, 1.1% for budesonide, and 0.5% for hydrocortisone-17-butyrate.[6] Patients may also be sensitized when corticosteroids are administered through intravenous, intramuscular, intra-articular, or intralesional routes, causing either local or widespread rashes.[7] However, these systemically administered preparations are an infrequent cause of both immediate and delayed reactions.[4] The clinical manifestations of parenteral corticosteroid allergy are variable and include immediate reactions such as anaphylaxis[7] and urticaria.[8] Delayed hypersensitivity reactions may present as eczematous eruptions, generalized exanthems,[8] and panniculitis.[9] The onset of an allergic reaction may occur after acute or chronic exposure.[4]

Patch testing is a commonly used method for the detection of type IV allergic reactions to corticosteroids.[10] Several studies have established tixocortol pivalate as a sensitive and specific marker for hydrocortisone allergy. Patch testing with both tixocortol pivalate and budesonide can detect up to 90% of patients with corticosteroid hypersensitivity.[10,11] Although the most advantageous vehicle and concentration for corticosteroid patch testing have not been well established,[12] studies recommend testing tixocortol pivalate and budesonide in a petrolatum or ethanol base,[13] with a concentration of 1.0% for optimal results.[14,15] Intradermal testing is also used for detecting allergic reactions to corticosteroids and is important, especially when the results of epicutaneous testing are negative.[16]

On the basis of stereochemistry, corticosteroids are classified into five groups: A, B, C, D1, and D2[17] (see Table 2).[16] Substances from the same group are thought to cross-react[18,19] although this is not universally accepted.[20] In particular, corticosteroids in group B have been shown to cross-react not only with members of their own group but also with the corticosteroids in group D2.[16]

Table 2. Classes of Corticosteroids

Group A	
Cloprednol	Prednisolone
Hydrocortisone	Prednisolone acetate
Hydrocortisone acetate	Prednisolone caproate
Methylprednisolone	Fludrocortisone acetate
Prednisone	Tixocortol pivalate
Group B	
Budesonide	Triamcinolone
Desonide	Triamcinolone diacetate
Flunisolide	Triamcinolone acetonide

Fluocinonide	Amcinonide
Procinonide	Flucloronide
Halcinonide	Fluocinolone acetonide
Group C	
Betamethasone	Fluprednidene acetate
Dexamethasone	Desoximetasone
Clocortolone	Halometasone
Fluocortolone	
Group D1	
Beclomethasone dipropionate	Alclometasone-17,21-dipropionate
Betamethasone dipropionate	Betamethasone-17-valerate
Clobetasone butyrate	Clobetasol propionate
Diflorasone diacetate	Clobetasone propionate
Fluticasone propionate	Mometasone furoate
Diflucortolone valerate	
Group D2	
Hydrocortisone-17-butyrate	Methylprednisolone aceponate
Hydrocortisone-17-aceponate	Prednicarbate
Hydrocortisone-17-buteprate	Hydrocortisone valerate

Reported allergic reactions to parenteral methylprednisolone are rare and include two cases of conjunctival inflammation after retrobulbar injection for iridocyclitis,[21] generalized nonpruritic rash after intra-articular injection,[22] and widespread urticaria after injections into the spine for cervical spondylosis.[23] Reactions to parenteral triamcinolone acetonide are also infrequent but are well documented in the literature. Reported cases include a generalized eruption after intramuscular injection[24] and a fixed drug eruption after intra-articular administration.[25]

Although reported cases in the literature are uncommon, contact allergy to systemic or intralesional corticosteroids should not be disregarded as a possible cause of hypersensitivity reactions. Patch testing and intradermal testing are necessary for diagnosis if an allergic reaction is suspected. An awareness of this type of reaction is important for all clinicians who use parenteral corticosteroids as therapy.

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