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case report

ANAPHYLACTOID REACTION TO CORTICOSTEROID: CASE REPORT AND REVIEW OF THE LITERATURE

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It has been suggested that corticosteroids can cause allergic reactions including anaphylaxis. Thirty-five patients have been reported to have anaphylaxis-like reactions following exposure to hydrocortisone in topical and parenteral preparations. We describe a further case of a nonatopic woman who developed urticaria during intravenous infusion of hydrocortisone. A review of the literature reveals that IgE-mediated immediate hypersensitivity has not been definitely proven in any case. We conclude that the clinical manifestations occasionally experienced after receiving hydrocortisone are most likely pseudoallergic reactions.

Introduction

ADVERSE reactions to corticosteroids are relatively uncommon. Since they are commonly employed to treat adverse drug reactions, it is ironic to discover they themselves are capable of precipitating an allergic-like reaction. Our knowledge about the mechanisms of drug reactions is quite limited, and this is especially true with the small number of reactions reported with corticosteroids. It is possible that some of the previously reported reactions were due to traces of impurities or additives in the preparation or to formation of a unique metabolite. The reaction may be immunologic or non-immunologic in nature. Unfortunately, the clinical signs, ie, hives, anaphylaxis, delayed rash, etc. may be seen with both types of reaction.

Hydrocortisone is manufactured in several derivative forms and these are found in topical, ophthalmic, oral, and injectible preparations. These preparations are widely used in the treatment of numerous common medical problems and especially acute exacerbations of severe bronchial asthma. In spite of the relative infrequency of adverse reactions to corticosteroids, the combination of frequent widespread usage, the diversity of disease processes treated, and the low index of suspicion for an untoward reaction decreases the likelihood that

such a reaction is correctly recognized. Although several reports of suspected allergic reactions to corticosteroids had already appeared, Mendelson et al¹ reported the first instance of immediate anaphylaxis ascribed to Solu-Medrol[®] and Solu-Cortef[®] in 1974. There have also been reports of adverse reactions to prednisolone, porcine ACTH,³ dexamethasone,⁴ betamethasone,⁵ a pancuronium (an anti-depolarizing muscle relaxant with a steroid structure).⁶ Signs and symptoms reported with the use of various hydrocortisone preparations include bronchospasm,^{1,7-11} shock,¹² urticaria,^{1,7,9,13} and angioedema.^{12,14} We report an adverse reaction to hydrocortisone (Abbott A Hydrocort[®]) and review the literature on this subject. An attempt is made to categorize the past literature on the mechanism involved.

Case Presentation

A 59-year-old white woman with endstage renal disease secondary to chronic glomerulonephritis was admitted to the Oregon Health Sciences University for transplantation evaluation. During this evaluation, she received 100 mg of IV hydrocortisone (Abbott A Hydrocort[®]) to measure steroid responsiveness. The test involves treating leukopenic ($<6000/\text{mm}^3$ WBC) pretransplant patients with 100 mg hydrocortisone intravenously (IV). A positive response results in an increase in the WBC to greater than $6000/\text{mm}^3$ within four hours later. Patients who do not respond adequately are considered for splenectomy prior to transplantation. While the hydrocortisone was being administered by slow IV push, the patient began experi-

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ing and developed nasal congestion with clear rhinorrhea. Within minutes, hives appeared over the face associated with periorbital angioedema, generalized pruritis and "a thick tongue." There was no change in blood pressure and bronchospasm was not heard. The urticaria and angioedema responded to hydroxyzine treatment within five hours.

The medical history was negative for atopic disease. There was no prior exposure to hydrocortisone or other corticosteroids and no previous adverse reaction to any medication. There was a history of urticaria following ingestion of clams, pineapples, prunes, raisins, currants, carrots, and grapefruits. These episodes were successfully controlled by eliminating these foods from her diet.

Laboratory evaluation revealed a total serum IgE of 62 U/mL. Screening intradermal skin tests to a variety of northwest allergens applied at a concentration of 10^{-4} and 10^{-3} (weight by volume) showed mildly positive reactions to house dust, housedust mite, English walnut, and western weeds. The results of intradermal skin testing to methylprednisolone (SoluMedrol^R) and hydrocortisone (Abbott A Hydrocort^R) from dilutions of 1:100,000 to 1:1 were negative. There was also no response to hydrocortisone diluent (Abbott A Hydrocort^R) or stock diluent. The diluent contained Na_2HPO_4 , NaH_2PO_4 , and benzyl alcohol. A histamine control was positive. Rechallenge with IV hydrocortisone or diluent was not performed. To date no transplant has been done on this patient.

Discussion and Literature Review

Reactions to IV Hydrocortisone. There have been several case reports of allergic type reactions to different hydrocortisone preparations. Efcortel^R is the 21-disodium phosphate ester of hydrocortisone. In 1969, Borltrop and Diba¹⁵ reported four asthmatic children who developed perineal pain after intravenous administration of Efcortel^R. One of these patients was re-challenged and complained of generalized pruritis. A second patient received hydrocortisone hemisuccinate and prednisolone without adverse reaction. Mendelson et al¹ reported a 17-year-old asthmatic who developed a pruritic urticarial rash, angioedema, and increased bronchospasm shortly after receiving either methylprednisolone sodium succinate (Solu-Medrol^R) or hydrocortisone sodium succinate (Solu-Cortef^R) IV. This patient had a total IgE level greater than 1000 U/mL and screening intradermal skin tests were positive to pollens and house dust. Intradermal skin tests to 1:100 Solu-Medrol^R and 1:100 Solu-Cortef^R were negative; however, direct skin testing with pure methylprednisolone or hydrocortisone resulted in an immediate wheal and flare reaction. Challenge with intravenous Solu-Medrol^R led to recurrence of bronchospasm, angioedema, and urticaria. No reaction was observed with IV Solu-Medrol^R diluent. Methylprednisolone sodium suc-

dema, and bronchospasm. Hayhurst et al⁸ described two additional asthmatics who developed worsening bronchospasm after receiving hydrocortisone sodium succinate (Solu-Cortef^R). The first patient was challenged with 50 mg of intravenous hydrocortisone sodium succinate without effect. An additional 150-mg dose was immediately followed by intense bronchospasm. Prick tests were positive (5-mm wheal) with Solu-Cortef^R, but negative to methylprednisolone and dexamethasone. The second patient was not skin tested or re-challenged. Six additional cases^{9-11,16} of reactions including two cases of respiratory arrest and two cases of cardiac arrest have been reported. Two of these cases⁹ occurred in patients with longstanding asthma and aspirin intolerance (idiosyncrasy).

Reactions to Intramuscular Hydrocortisone. There have been two case reports^{12,14} of reactions to intramuscular hydrocortisone. The first¹⁴ is a 31-year-old drug addict with a 15-year history of asthma. During an acute flare of asthma, he was treated with 200 mg of hydrocortisone sodium succinate (Efcortelan^R) intramuscularly (IM). Within ten minutes he developed facial angioedema and urticaria. There was no change in the clinical degree of bronchospasm. The urticaria and angioedema resolved within one hour. Further studies were not carried out. The second case¹² involved a 29-year-old female with no atopic history. She was hospitalized for cataract excision and lens repair following a traumatic injury to her eye. Preoperatively the patient was given 100 mg hydrocortisone sodium succinate by IM injection. Within minutes she experienced circulatory collapse, general erythema, facial edema, and unconsciousness. The total serum IgE was 170 U/mL. Intradermal skin tests showed a significant immediate reaction to hydrocortisone sodium succinate. There were no reactions to sodium phosphate buffer from the succinate solution, the diluent or hydrocortisone acetate. These results implicate the corticosteroid as the moiety causing the reaction in this patient and specifically display sensitivity to the succinate but not the acetate ester of hydrocortisone. There is a history of previous exposure to oral prednisolone but no history

Table 1. Criteria for Drug Allergy as Opposed to Pseudoallergic Reactions (modified from Ref 21)

1. No reaction to earlier treatment
2. Reaction usually appearing only after several days of treatment
3. Risk of reaction existing at doses below therapeutic range
4. Clinical manifestations which differ from general pharmacologic effect of the drug
5. Reaction observed totally unpredictable from animal testing
6. Reaction observed only reported in a small proportion of the population
7. Clinical syndrome generally accepted as allergic in nature
8. Blood and/or tissue eosinophilia
9. Antibodies or T lymphocytes that react specifically with the drug or a metabolite

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Table 2. Summary of Hydrocortisone Reactions in the Literature

Author	No. of Patients	Sex	Drug/Contaminant	Clinical Sign	Duration	Skin Test
Sams W, et al	1	F	Sodium laurylsulfate, topical	Vesicular dermatitis	Weeks	+P.T.**
Kooij R	1	M	1% hydrocortisone, topical	Dermatitis	Weeks	+P.T.
Church R	5	1M, 4F	21 diol acetate, topical	Dermatitis		+P.T.
Kendall P	9	not available	Hydrocortisone, SQ	8 urticaria 1 bronchospasm	<36 hours	not done
King R	1	F	Hydrocortisyl ^R , SQ	Urticaria, emesis unconsciousness	3 days	+ID†
O'Garra J	3	2M, 1F	Hydrocortisone acetate, SQ	Throat constriction jt. pain, petechial rash, vomiting, chest tightness	3-4 days + ID	1 pt. with
Ashford R	1	M	Hydrocortisone sodium succinate, IM (Efcortelan ^R)	Urticaria	1 hour	not done
Rodger R	1	F	Hydrocortisone sodium succinate, IM	Circulatory collapse gen. erythema, facial edema and unconsciousness	Minutes	+ID
Barltrop D, et al	4	3M, 1F	21-disodium phosphate ester of hydrocortisone (Efcortelan ^R), IV	Perineal pain pruritis	Minutes	not done
Mendelson L, et al	1	M	Hydrocortisone (Solu-Cortef ^R), IV	Rash, bronchospasm, urticaria	Not available	-ID
Hayhurst M	2	1M, 1F	Hydrocortisone (Solu-Cortef ^R), IV	Bronchospasm	Hours	1 pt. with +ID
Kounis N	2	2M	Hydrocortisone sodium succinate, IV	Loin pain, tremor unconsciousness cardiac arrest	Minutes	-I.D.
Partridge M, et al	2	2F	Hydrocortisone sodium succinate Hydrocortisone sodium phosphate, IV	Bronchospasm urticaria, respiratory arrest	<1 day	not done
Chapman S, et al	1	M	Hydrocortisone succinate (Solu-Cortef ^R), IV	Bronchospasm Unconsciousness	Not available	+I.D.
Ward K, et al	1	F	Hydrocortisone sodium succinate (Efcortelan ^R), IV	Bronchospasm cardio-pulmonary arrest	Not available	-P.T.

** Patch Test.

† Intra-dermal.

regarding potential previous exposure to hydrocortisone.

Reactions to Intra-Articular and Soft Tissue Injections of Hydrocortisone. Steroid injections into joints and periarticular soft tissues to treat rheumatologic complaints gained wider usage in the early 1950s. Kendall⁷ reported the incidence of side effects following 6,700 hydrocortisone injections in 2,256 consecutive cases. The specific hydrocortisone preparations used were not stated. Probable allergic reactions included 8 cases of urticaria and one case of bronchospasm. In three of the eight cases with urticaria, the injection included 2% procaine and 1,000 U of hyaluronidase. Urticarial reactions appeared between 30 minutes and eight hours following injection. The one instance of bronchospasm occurred in a 48-year-old man who had a significant past history of asthma and atopy. He developed bronchospasm and urticaria within 45 minutes of the injection. The injection also contained a combination of hydrocortisone with 2% procaine and 1000 U hyaluronidase. Other non-allergic reactions included hemorrhages, nausea, vomiting, local urticaria, local weakness, and local sepsis. Eleven patients developed short-lived urticaria around the injection site. The overall incidence of all types of reactions to local injection of hydrocortisone was 1.09% in this study. In 1960, King¹³ described the case of a 50-year-old woman who received 5 mL of Hydrocortisyl^R injected into the rotator cuff because of pericapsulitis.

Four hours after the injection she developed urticaria followed by unconsciousness and shock. This was associated with abdominal pain, nausea, vomiting, hematemesis, melena, and petechiae. All of this resolved within five days. Intradermal skin tests with a control solution, penicillin and a 0.01 mL of Hydrocortisyl^R resulted in a 0.75-cm erythematous plaque forming in 24 hours at the site of corticosteroid injection. Three reactions to soft tissue injections of hydrocortisone acetate suspensions were reported by O'Garra¹⁷ in 1962. These patients experienced throat constriction, joint pain, edema of the face, a petechial rash, vomiting, and chest tightness several hours following injection. Intradermal skin tests to hydrocortisone acetate were negative in two of these patients. The third patient had a positive patch test using hydrocortisone acetate suspension. Intradermal skin tests with pure hydrocortisone acetate resulted in a 1-cm wheal while there was no reactivity to injection of the steroid vehicle.

Reactions to Topical Hydrocortisone. In 1957, Sams and Smith¹⁸ reported a case of contact dermatitis caused by hydrocortisone ointment. Patch testing revealed a delayed response to the ointment base which consisted of a self-emulsifying wax (Ieramol) and sodium lauryl sulfate. In this case the ointment base appeared to be the cause. One year later, Kooij¹⁹ described a further case of contact dermatitis following treatment of eczema with 1% hydrocortisone ointment. Patch tests to a variety of hydrocortisone ointments were positive

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as were patch tests to neomycin 3% and chloromycetin 6%. A positive patch test resulted with a solution of 6% hydrocortisone succinate in water. The same hydrocortisone succinate solution produced no reaction in patch tests in control subjects. The cross reactivity with a variety of hydrocortisone products and the positive patch test to pure hydrocortisone succinate solution in a concentration not leading to reactions in controls suggests that the corticosteroid was the cause of contact dermatitis. Church²⁰ in 1960 reported five additional cases of contact dermatitis following treatment with hydrocortisone acetate ointment. Three of these patients were patch tested to purified hydrocortisone acetate as well as to breakdown products of hydrocortisone produced during the manufacturing process. None of these subjects reacted to the purified corticosteroid; however, they all reacted to the original ointment to which they had been exposed. All three patients reacted to 0.25%, 0.5%, and 1% 21-diol-acetate. The 21-diol acetate is the chemical precursor of hydrocortisone acetate. The commercially available hydrocortisone acetate ointment contains about 1% of 21-diol acetate because the catalysis is not complete. The results of this report suggest that impurities during manufacturing such as contaminants or as in this case precursor substances may be the cause of an adverse reaction.

Summary

Allergic reactions to hydrocortisone have been reported since the late 1950s. A variety of topical and parenteral preparations have all been implicated. In the literature reviewed, the corticosteroid itself, a precursor of the corticosteroid, or a companion compound present in the commercial product have all been implicated as the cause of these reactions. The mechanism involved in most of these reactions appears to be non-immune in nature, ie, pseudoallergic drug reaction. Van Arsdel²¹ has published criteria that we considered in determining whether an adverse reaction was allergic (Table 1). A summary of the cases of allergic type reactions to hydrocortisone as they appear in the literature is presented in Table 2. Applying Van Arsdel's criteria to these reported cases and requiring that six of ten criteria be met in order for a case to be considered allergic, all of the cases were considered to be non-allergic and one appeared to be modulated by a contaminant or unwanted metabolite. Excipients such as parabens or metabisulfite appear in these products and have been associated with allergic reactions. There was

no unifying patient characteristic that could be used in predicting these reactions save the fact that in most instances of severe anaphylactoid reactions, a large amount of drug was infused or injected rapidly.

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