

A case of hydrocortisone desensitization in a patient with radiocontrast-induced anaphylactoid reaction and corticosteroid allergy

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ABSTRACT

Allergic reactions and systemic desensitization to corticosteroids have been documented rarely in English language literature. These reactions appear more often when the agent is applied topically and may lead to dangerous complications in patients if administered i.v. Therefore, the safety and efficacy of using an i.v. corticosteroid for desensitization in a patient who has a history of allergy to corticosteroid must be weighed carefully, especially when the aim of its use is to prevent an allergic reaction from a second drug. We report a case of successful systemic hydrocortisone desensitization in a patient with radiocontrast-induced anaphylactoid reaction and corticosteroid allergy. Sensitization to corticosteroids was determined through skin testing. The patient was desensitized to hydrocortisone and premedicated with hydrocortisone and diphenhydramine and subsequently underwent cardiac catheterization with radiocontrast without adverse reaction.

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CASE REPORT

A 62-year-old black woman presented for preoperative evaluation for a cholecystectomy. The patient was to undergo a cardiac catheterization with contrast material because of unstable angina and positive cardiac stress test. However, she had a reported allergy to both radiocontrast material and to corticosteroids. Several months before presentation, the patient underwent a computed tomography scan with contrast. Within 3 minutes of administration of the contrast material, she developed nausea, flushing, and pruritus. One year before presentation, within minutes after an intraarticular glucocorticoid injection to the right elbow, the patient developed pruritus, urticaria, and edema at the site, which spread to the upper arms and then to the entire body. She did not receive any other new medications and did not ingest any new foods. The symptoms quickly resolved with diphenhydramine. Her medical history was significant for end-stage renal disease, coronary artery disease, hypertension, and chronic cholecystitis. Her medications included aspirin, metoprolol, sevelamer, calcium acetate, and vitamins. Cardiac catheterization with i.v. contrast was considered absolutely necessary in this case because

of the severe cardiac disease. Therefore, premedication was essential, which necessitated corticosteroid desensitization before the procedure.

Skin-prick testing was performed to different corticosteroids on the patient and control. The control revealed no positive skin reactions to any of the tested corticosteroids. On the other hand, the patient developed positive reactions to all tested corticosteroids, with the least reactive skin test revealing a 3+ positive immediate reaction to hydrocortisone. The respective half-lives for the tested corticosteroids are hydrocortisone, 80–118 minutes; methylprednisolone, 78–188 minutes; and dexamethasone, 110–210 minutes. A protocol introducing escalating doses of hydrocortisone with short intervals was developed because the half-life of hydrocortisone is the shortest among the tested corticosteroids (Table 1). Each dose of hydrocortisone was diluted in minute volumes of fluid yielding a total of 75 mL to avoid fluid overload because the patient had end-stage renal disease. During the process of desensitization, the patient developed slight pruritus and erythema between the third and fourth dose, which resolved immediately with 50 mg of diphenhydramine. After a successful desensitization procedure, the patient continued to be on hydrocortisone, 200 mg i.v., every 4 hours. The patient was premedicated with hydrocortisone, 200 mg, and diphenhydramine, 50 mg, i.v. 1 hour before the cardiac catheterization. The patient received i.v. radiocontrast material during the cardiac catheterization without any adverse reactions.

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Table 1 Hydrocortisone desensitization protocol

Time (min)	Strength (doubling)	Dose (mg)	Concentration (mg/mL)	Total (mL)	Cumulative Dose (mg)	Cumulative Dose (mL)
$t = 0$	0.000001	0.001	0.001	1	0.001	1
$t = 15$	0.000002	0.002	0.001	2	0.003	3
$t = 30$	0.000004	0.004	0.001	4	0.007	7
$t = 45$	0.000008	0.008	0.001	8	0.015	15
$t = 60$	0.00002	0.02	0.01	2	0.035	17
$t = 75$	0.00003	0.03	0.01	3	0.065	20
$t = 90$	0.00006	0.06	0.01	6	0.125	26
$t = 105$	0.0001	0.1	0.1	1	0.225	27
$t = 120$	0.0003	0.3	0.1	3	0.525	30
$t = 135$	0.0006	0.6	0.1	6	1.125	36
$t = 150$	0.001	1	1	1	2.125	37
$t = 165$	0.002	2	1	2	4.125	39
$t = 180$	0.004	4	1	4	8.125	43
$t = 195$	0.008	8	1	8	16.125	51
$t = 210$	0.02	20	10	2	36.125	53
$t = 225$	0.03	30	10	3	66.125	56
$t = 240$	0.06	60	10	6	126.125	62
$t = 255$	0.13	130	10	13	256.125	75

Dosing schedule: Given every 15 min and administered over ~ 5 min. On completion of the protocol ($t \sim 4.5$ hr), a full dose of 200 mg (1.6 mL) of i.v. hydrocortisone was given every 4 hr.

The i.v. rate of administration (micromedex-hydrocortisone): For administration as an i.v. bolus, hydrocortisone solution should be diluted to 50 mg/mL and administered over 3–5 min (Taketomo et al., 1998). For administration as an intermittent infusion, hydrocortisone solution should be diluted also.

RADIOCONTRAST MEDIA ALLERGY

Radiocontrast media (RCM), colloids, and opioids account for $<10\%$ of anaphylaxis during surgical and interventional procedures.¹ In accordance to the studies performed by Lang *et al.*, greater risk for anaphylactoid reaction exists in female patients,² patients receiving β -adrenergic blockers, and for asthmatic patients.³

Contrast media reactions may be classified as anaphylactoid, vasomotor, severe (life-threatening), and fatal. Anaphylactoid reactions mimic IgE-mediated hypersensitivity with urticaria, angioedema, wheezing, dyspnea, hypotension, or shock. These reactions occur in 2–8% of all patients. Vasomotor reactions occur in 5–8% of the patient population and consist of nausea, vomiting, flushing, and warmth. Severe reactions occur in 0.1% of the patients, and fatal reaction incidence is minute: 0.01–0.001%. The latter occur mostly in patients undergoing i.v. cholangiography or in patients undergoing i.v. urography.⁴

The pathogenesis is considered to be idiopathic and multifactorial. It is attributed to mast cell degranulation and histamine release,⁵ activation of mast cells and basophils, activation of the complement system, activation of the contact system, and the conversion of L-arginine into nitric oxide. On the other hand, there is a supplementing theory of RCM being pseudoanti-

gens. They can combine with antibodies but can not produce antibodies themselves. This property appears to be dependent on aggregation in high concentrations and varies with different media. It is nonspecific in relation to antibodies and suggests binding to the Fc portion of immunoglobulins. It appears that the least toxic of current media show the best binding and in sufficient concentration can inhibit contrast-induced mast cell activation and/or noncontrast antigen-induced mast cell activation, which in its turn is postulated to be associated with pseudoantigens excess. RCM in lesser concentrations and/or lesser binding can trigger mast cell activation.⁶

Pseudoallergic reactions also involve modulation of enzymes and proteolytic cascades in plasma.⁷ These reactions are caused by liposomal formulations of i.v. drugs and imaging agents, infusion liquids containing micelle-forming amphiphilic lipids or synthetic block-copolymer emulsifiers, and iodinated RCM with limited solubility in water. Common features of the latter includes their capacity of activation of the complement system and often cause symptoms of typical manifestations of excessive anaphylatoxin generation in blood; therefore, these reactions are called "C activation-related pseudoallergy" (CARPA). To fit CARPA within the classic scheme of hypersensitivity reactions (HSRs),

a subdivision of type I allergy is proposed based on the mechanism of activation of mast cells and basophils. The new scheme distinguishes direct and receptor-mediated HSRs, with the latter subdivided into true IgE-mediated allergy, anaphylatoxin-mediated CARPA, and IgE plus anaphylatoxin double-triggered reactions.⁸

IgE is a homocytotropic antibody binding to the surface of the mast cell. Antigen with affinity for IgE triggers conformational change at the cell surface, resulting in the release of chemical mediators from the mast cell granules. The mediators histamine, slow reacting substance of anaphylaxis, and eosinophilic chemotactic factor cause smooth muscle contraction, increased capillary permeability, eosinophil attraction, and increased glandular secretions. The release of mediators from the mast cell granules is controlled by intracellular levels of cyclic nucleotides. In particular, elevated cAMP inhibits mediator release. Adrenergic, cholinergic, and prostaglandin receptors all influence mediator release. Histamine is mediated *via* H₁- and H₂-receptors, individually and in combination. H₁-receptors mediate coronary artery vasoconstriction, wheezing, cutaneous vascular permeability, and a possible increase in heart rate. H₂-receptors stimulate ventricular and atrial inotropy, arterial chronotropy, coronary vasodilation, and rises in basophilic cAMP (neither H₁- nor H₂-receptors mediate increases of cAMP in mast cells). The characteristic immunopathology of immediate hypersensitivity reactions is a result of local or systemic mediator release. Routine investigation of patients should include eosinophil counts and IgE in blood and secretions and immediate hypersensitivity skin tests. Therapeutic principles include restoration of inhibitory levels of cyclic nucleotides, antagonism of mediator effects, and immunologic manipulation of the IgE-mediated allergic reaction.^{9,10}

Genovese *et al.*, performed a comparison of three contrast media agents (ioxaglate, ioxithalamate, and ioversol). They found that all three RCM agents induce the release of preformed mediators (histamine and tryptase) from human lung but not from skin mast cells. However, the induction of *de novo* synthesis of leukotriene C₁ or prostaglandin D₂ from basophils or any other type of mast cells was not observed. The authors concluded that the role of RCM agents as incomplete secretagogues on human basophils and mast cells cause an increased release of already preformed mediators, such as histamine and tryptase.¹¹

Skin testing to radiocontrast is not considered helpful because of the complex pathophysiological mechanism of pseudoallergic reactions mentioned previously. Patients with suspected reactions to radiocontrast therefore are premedicated generally with corticosteroids and antihistamines to decrease the risk and severity of a reaction.^{1,4,6,12-15} In fact, Greenberger *et al.* recommended i.v.

hydrocortisone and diphenhydramine for pretreatment.¹⁶

CORTICOSTEROID ALLERGY

The incidence of corticosteroid allergies varies between 2.9 and 5.1%.¹⁷ These reactions are usually a delayed contact reaction and occur when corticosteroids are applied topically and are seen in up to 6% of patients undergoing patch testing.^{18,19} Less commonly, an immediate type I reaction can occur and both immediate and delayed reactions have been reported.²⁰ Cross-reaction with corticosteroids within a group often occurs but also has been reported between groups.²¹ Cross-reactivity occurs less frequently in triamcinolone, amcinonine, halcinonine, flucinonide, and desonide.²² The studies from England suggested that predominant use of nonfluorinated corticosteroids (hydrocortisone, hydrocortisone-17-butyrate, and budesonide) results in a higher prevalence of corticosteroid contact allergy and the C17 side chain of hydrocortisone has been suggested to be involved in protein binding and therefore is the antigenic site on the carbon rings.^{19,23}

CASE SUMMARY

Because of the temporal relation of this patient's reaction to corticosteroids and the positive skin test, the corticosteroid allergy in our patient is believed to be IgE mediated and corticosteroid desensitization for this patient was contemplated. The patient was desensitized successfully to a corticosteroid and was premedicated with hydrocortisone and diphenhydramine before being administered radiocontrast. This case illustrates that i.v. desensitization may be a suitable approach to therapy in patients allergic to corticosteroids who require systemic corticosteroid administration.

Simple strategies could be used to reduce risk of anaphylaxis and anaphylactoid reactions: consideration of the route of drug administration, identification of patients with known cause(s) of reactions, and the knowledge of cross-reaction of medications with possible induction of anaphylaxis or CARPA. Desensitization procedures, as well as gradual-dose escalation protocols could be implemented based on patient history and diagnostic testing. Classic management of anaphylaxis is based on control of airways, breathing, and circulation.²⁴

CONCLUSION

Clinicians should be aware that allergic reactions to corticosteroids can occur. Skin testing may be considered to identify corticosteroid allergy. This case illustrates that i.v. desensitization may be a suitable approach to therapy in corticosteroid allergic patients who required systemic corticosteroid administration.

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