

M J Aust 1991;
154:210-214

CASE REPORTS

Anaphylactoid reaction to intravenous hydrocortisone sodium succinate: a case report and literature review

David A Fulcher and Constance H Katelaris

ABSTRACT Reports of corticosteroid sensitivity reactions are rare in the medical literature. We report an anaphylactoid reaction to hydrocortisone sodium succinate given intravenously which occurred on two occasions during treatment of a patient for asthma. Intradermal testing with a wide range of steroid preparations gave positive results with hydrocortisone sodium succinate, methylprednisolone sodium succinate and methylprednisolone acetate. No reactions occurred to dexamethasone sodium phosphate administered intravenously, prednisolone given orally or beclomethasone dipropionate by inhalation. Results of a radioallergosorbent test (RAST) were negative for hydrocortisone sodium succinate. (Med J Aust 1991; 154: 210-214)

Asthma is a common condition in medical practice and often requires the use of corticosteroids in inhaled as well as systemic formulations. Steroids given intravenously have become standard practice in the management of acute severe exacerbations of asthma; hence it is of interest that on rare occasions steroids themselves can induce anaphylactoid reactions. The case presented demonstrates such a reaction.

Clinical record

A 43-year-old man was referred for investigation of anaphylactoid reactions to hydrocortisone given intravenously. He had had childhood asthma which largely resolved by the age of 10 years. One year before presentation (1988) his asthma had recurred and was controlled with inhalations of beclomethasone dipropionate and salbutamol sulphate. There was no evidence of aspirin sensitivity. Three weeks before presentation, worsening asthma prompted his admission to a local hospital. He was treated with nebulised salbutamol sulphate and given intravenously (250 mg bolus then

bolus of hydrocortisone sodium succinate (200 mg, Solu-Cortef, Upjohn). The preservative content of the Solu-Cortef is unknown since both preservative-added and preservative-free preparations were in common use in the institution at that time. Vomiting occurred almost immediately, followed by severe bronchospasm and cyanosis, which responded to adrenaline (0.8 mg) administered intravenously.

Four hours later another bolus of hydrocortisone sodium succinate (200 mg) was given more slowly. Again within minutes severe bronchospasm occurred with cyanosis and virtually no audible air entry. This attack was more easily reversed with nebulised salbutamol sulphate. Hydrocortisone sodium succinate was withdrawn and a course of prednisone by mouth was completed without event. The patient continued to receive beclomethasone dipropionate with no apparent adverse effects. There was no history of previous exposure to corticosteroids given intravenously.

Method

Informed consent for skin testing and challenge was obtained from the patient. Skin prick tests were performed in a standard fashion by placing a drop of the test solution on the volar aspect of the forearm and applying a skin prick through the drop with a 26 gauge hypodermic needle. The response was read at 15 minutes. Intradermal tests were performed with a 26 gauge hypodermic needle. Sufficient quantity of the test solution was injected to raise a 3 mm bleb (0.02 mL) and results were read at 15 minutes. For both tests, the wheal size was expressed as two diameters at right angles, and a positive result was defined as a dimension exceeding that of histamine 1 mg/mL for skin prick tests and 1 µg/mL for intradermal tests. A control solution of saline 0.9% was used in each test.

Steroid concentrations of 5 mg/mL and 50 mg/mL were prepared. Although hydrocortisone sodium succinate, methylprednisolone sodium succinate, methylprednisolone acetate and dexamethasone sodium

phosphate were readily soluble in water, the other agents were not. Hence, quantities of powder were mixed with appropriate quantities of physiological saline, and suspensions of 5 mg/mL and 50 mg/mL were made by repeatedly drawing up and expelling the contents into a 2 mL syringe via a 21 gauge hypodermic needle. No preservatives were present in any of the steroid solutions or suspensions. All steroids were tested for non-specific irritation on a non-atopic control, and hydrocortisone sodium succinate, methylprednisolone sodium succinate and benzyl alcohol 0.9% (the soluble agents eliciting a positive response in the patient) were tested on a further four controls, two of whom were atopic. (Since it was unclear whether the Solu-Cortef causing the reaction contained preservative, it was thought necessary to investigate the possible role of benzyl alcohol in this reaction, hence its inclusion in the skin test battery.) Methylprednisolone acetate, the insoluble agent eliciting a positive response in the patient, was not further tested on these four controls because of the development of a small area of localised dermal atrophy in the first control. Radioallergosorbent test (RAST) was performed with hydrocortisone sodium succinate by means of a standard technique.¹

Results

Skin tests

Skin prick tests with common aeroallergens confirmed atopy with positive wheal reactions to grass pollens and fungal antigens.

Results of skin prick tests with steroids were negative and results of intradermal tests are shown in Table 1. Hydrocortisone sodium succinate, which was responsible for his acute exacerbation of asthma, also gave positive results on intradermal testing at a concentration of 5 mg/mL. Reactions were also noted with intradermal methylprednisolone sodium succinate (5 mg/mL),

TABLE 1: Results of intradermal tests with various steroid preparations in concentrations of 5 mg/mL and 50 mg/mL. Histamine response was a 7 x 4 mm wheal.

Corticosteroid preparation	Concentration	Wheal size
Methylprednisolone	50 mg/mL	0
Methylprednisolone sodium succinate	5 mg/mL	8 x 6 mm
Methylprednisolone acetate	50 mg/mL	7 x 4 mm
Hydrocortisone	50 mg/mL	0
Hydrocortisone sodium succinate	5 mg/mL	8 x 7 mm*
Hydrocortisone acetate	50 mg/mL	0
Dexamethasone sodium phosphate	5 mg/mL	0
Benzyl alcohol	0.9%	6 x 4 mm†

*One of 5 controls also reacted. †Irritant effect.

showed no significant reactions in four, but the other (who was atopic) developed a 7 x 5 mm wheal associated with a 30 x 30 mm flare. Four controls developed small areas of local swelling and erythema (3–7 mm diameter) to intradermal benzyl alcohol 0.9% similar to the response in the patient, suggesting local irritation. No response was obtained to methylprednisolone sodium succinate (5 mg/mL) in any of the controls. Results of skin testing with the insoluble agents were negative in the one control tested.

Challenges

Beclomethasone dipropionate

Several weeks after beclomethasone dipropionate by inhalation was withdrawn, a single-blind placebo-controlled aerosol challenge with this agent was performed, and no change in forced expiratory volume in one second occurred over a 60-minute period.

Dexamethasone sodium phosphate

Results of skin tests with dexamethasone sodium phosphate were negative and because of the potential need for an intravenous preparation should further acute attacks of asthma occur, an intravenous challenge with 5 mg of dexamethasone sodium phosphate was performed.

compared with control levels of 0.9% and 1.0% — a borderline negative result, although no positive control was available.

Discussion

This patient demonstrated anaphylactoid responses temporally related to injections of hydrocortisone sodium succinate, with positive results to skin tests with this steroid. Skin tests also demonstrated cross-reactivity with methylprednisolone sodium succinate and methylprednisolone acetate, although the clinical significance of this was not confirmed by challenge. Results of skin tests must be interpreted with caution in this setting as one of the controls, who had no history of previous exposure or reactivity, reacted significantly to hydrocortisone sodium succinate. The benzyl alcohol diluent induced a local response in both the patient and the majority of the controls suggesting an irritant effect, not likely to be relevant in the patient's systemic response. Results of skin tests with dexamethasone sodium phosphate were negative and it did not cause a reaction on intravenous challenge. Skin tests for sensitivity to corticosteroids may, therefore, have a role both in defining the positive reactions and in determining

a preparation which can be administered safely to the patient. However, further experience is necessary and patients should be challenged only where resuscitation facilities are available. The skin prick tests were insensitive compared with intradermal testing in detecting reactivity, a phenomenon which is not uncommon in other drug reactions.²

The nature of the reaction and the positive results of skin tests suggest either an IgE-mediated response or direct release of vasoactive mediators from basophils or mast cells. The result of RAST was negative, but this in itself leads to no firm conclusions as no control serum was available for the assay. The reaction occurred on the first known exposure of the patient to the drug, suggesting non-immune mechanisms, but this does not exclude the possibility of IgE sensitisation by occult exposure. Passive transfer experiments were not performed in this case, although Mendelson et al.,³ who reported a similar case, were not able to transfer reactivity, providing evidence against an IgE-mediated reaction.

There did not appear to be any particular chemical structure which consistently predicted reactivity (Figure). Although best correlation was obtained with the ester-

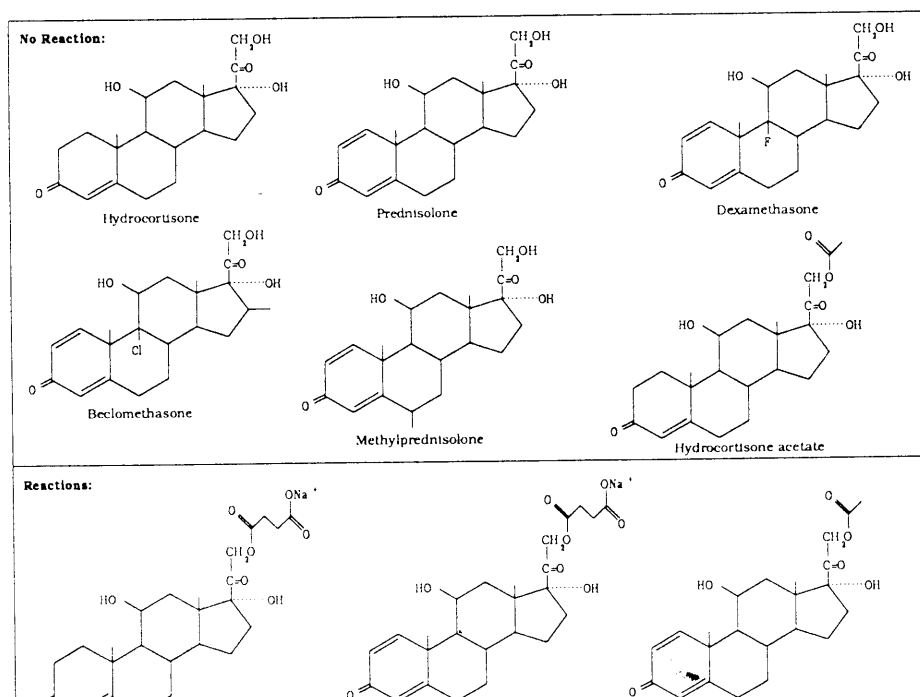


TABLE 2: Reported systemic reactions to corticosteroid preparations

Patient details (Age, sex, condition)	Corticosteroid preparation	Route of administration	Reaction	Test performed	Result
4 patients ^a	Hydrocortisone-?	IA	Urticaria	ID	?
5 patients ^a	Hydrocortisone ? diluent + local anaesthetic in 4 patients	IA	Urticaria	"Skin tests"	"Unsatisfactory"
50 F ¹³	Hydrocortisone + diluent	ST	Urticaria, petechiae GIT bleeding	ID	Positive for hydrocortisone
49 F ¹⁴	Hydrocortisone acetate	ST	Urticaria, angioedema	Patch/ID	Positive for hydrocortisone acetate
29 M ¹⁴	Hydrocortisone acetate	ST	Angioedema, petechiae	ID	Negative for hydrocortisone acetate and hydrocortisone acetate + diluent
39 M ¹⁴	Hydrocortisone acetate	ST	Petechiae, GIT bleeding	ID	Positive for diluent
58 F ¹⁵	Prednisone	O	Rash	ID	Delayed positive for prednisolone acetate, hydrocortisone and prednisone salt
52 M ¹⁶	Prednisolone acetate	IA	Rash	IM challenge	Positive for triamcinolone
	?Betamethasone	O	Urticaria		
	Triamcinolone	Top	Urticaria		
17 M Asthma ³	Betamethasone	Top, IM	Urticaria	ID	Positive for hydrocortisone and methylprednisolone
	Methylprednisolone sodium succinate	IV	Urticaria, angioedema, bronchospasm		
	Hydrocortisone sodium succinate	IV	Urticaria, angioedema, bronchospasm		
50 M ¹⁷	Methylprednisolone	O	Urticaria, angioedema, bronchospasm	ID	Delayed positive for methylprednisolone sodium succinate and hydrocortisone sodium succinate, results of skin biopsy showed delayed type hypersensitivity
	Prednisone	O	Urticaria, angioedema		
	Prednisone	O	Urticaria, angioedema		
55 M Waldenstrom's purpura hyperglobulinaemia ¹⁸	Dexamethasone sodium phosphate	O	Urticaria	—	—
66 F Asthma ¹¹	Hydrocortisone sodium phosphate	IV	Bronchospasm	—	—
33 F Asthma ¹¹	Hydrocortisone sodium succinate	IV	Bronchospasm, urticaria, vomiting	—	—
21 F Asthma ¹⁹	Hydrocortisone + diluent	IV	Bronchospasm	SPT	Positive for hydrocortisone sodium succinate
41 M Asthma ¹⁹	Hydrocortisone + diluent	IV	Bronchospasm, angioedema	SPT, ID	Negative for hydrocortisone, methylprednisolone sodium succinate and dexamethasone sodium phosphate
21 M Asthma ²⁰	Hydrocortisone sodium succinate	IV	Urticaria, bronchospasm	ID	Positive for hydrocortisone sodium succinate
31 M Asthma ²¹	Hydrocortisone sodium succinate	IM	Urticaria, angioedema	—	—
56 F Asthma ²²	Hydrocortisone sodium succinate	IV	Bronchospasm, cardiopulmonary arrest	Patch	Negative for hydrocortisone sodium succinate
40 M Asthma ²³	Methylprednisolone sodium succinate	IV	Bronchospasm, urticaria, hypotension	SPT/ID	Positive for hydrocortisone sodium succinate and methyl- prednisolone sodium succinate
36 F Asthma (aspirin sensitive) ¹²	Hydrocortisone sodium succinate	IV	Bronchospasm	SPT, ID	Negative for hydrocortisone sodium succinate, diluent and dexamethasone sodium phosphate
47 F Asthma (aspirin sensitive) ¹²	Methylprednisolone sodium succinate	IV	Bronchospasm	SPT, ID	
59 F Asthma (aspirin sensitive) ¹²			Bronchospasm	SPT, ID	
41 M Renal transplant ²⁴			Hypotension, urticaria, bronchospasm	ID	Positive for methylprednisolone sodium succinate
29 F ²⁵	Hydrocortisone sodium succinate	IM	Angioedema, erythroderma, hypotension	ID	Positive for hydrocortisone sodium succinate
81 M Asthma ²⁶	Hydrocortisone sodium succinate	IV	Bronchospasm, vomiting	IV challenge	Positive for hydrocortisone sodium succinate
47 F Asthma ²⁶	Hydrocortisone sodium succinate	IV	Bronchospasm, hypotension	—	—
53 M Multiple sclerosis ⁶	Methylprednisolone sodium succinate	IV	Urticaria, angioedema, hypotension	SPT RAST Passive cutaneous anaphylaxis test	Positive for methylprednisolone sodium succinate Positive for methylprednisolone sodium succinate Positive for methylprednisolone sodium succinate
59 F Chronic renal failure ⁵	Hydrocortisone	IV	Urticaria, angioedema	ID	Negative for methylprednisolone sodium succinate + diluent, hydrocortisone sodium succinate + diluent and diluent in hydrocortisone sodium succinate preparation
6 F Asthma ²⁷	Hydrocortisone sodium succinate	IV	Bronchospasm, urticaria	ID	Positive for hydrocortisone sodium succinate and methyl- prednisolone sodium succinate

TABLE 2: Reported systemic reactions to corticosteroid preparations (continued)

Patient details (Age, sex, condition)	Corticosteroid preparation	Route of administration	Reaction	Test performed	Result
66 F Asthma ²⁹	Methylprednisolone sodium succinate	IV	Vomiting, bronchospasm, hypotension	—	—
62 F Asthma ³⁰	Hydrocortisone sodium succinate	IV	Bronchospasm, urticaria, hypotension	SPT	Positive for hydrocortisone sodium succinate and methyl- prednisolone sodium succinate
64 M ³¹	Methylprednisolone sodium succinate	IV	Bronchospasm, urticaria	ID	Positive for hydrocortisone sodium succinate
	Hydrocortisone sodium succinate	IV	Bronchospasm, urticaria, coronary artery spasm		Positive for hydrocortisone sodium succinate
27 M Asthma (aspirin sensitive) ³²	Hydrocortisone sodium succinate	IV	Angioedema, bronchospasm	ID	Positive for hydrocortisone sodium succinate and methyl- prednisolone sodium succinate
23 F Renal transplant ³³	Methylprednisolone sodium succinate Methylprednisolone sodium succinate	IV	Hypotension, bronchospasm	—	—

Abbreviations: F = female; GIT = gastrointestinal; IA = intra-articular administration; ID = intradermal tests; IM = intramuscular administration; IV = intravenous administration; M = male; O = oral administration; RAST = radioallergen sorbent test; SPT = skin prick tests; ST = soft tissue injection; top = topical administration.

linked side-chain substitutions at C21, the lack of responsiveness to hydrocortisone acetate suggests that other factors are involved. It is of interest that no reactions to naturally occurring hydrocortisone were demonstrated, only reactions to chemically modified steroids.

There are over 30 reported cases⁴ of systemic reactions to steroid preparations to date. While most reactions are non-immune in nature,⁵ there is one report of a true IgE-mediated reaction (positive RAST and passive transfer of reactivity).⁶ The earliest reference to the possibility of steroid sensitivity came from Brown et al.⁷ and Hollander⁸ who described four patients with urticaria after intra-articular injections of hydrocortisone acetate, but concluded that either the local anaesthetic agent (three patients) or the diluent (one patient) was responsible for the reactions. Kendall⁹ described nine patients with similar reactions (one with bronchospasm alone), although four received concomitant local anaesthetic and hyaluronidase with the hydrocortisone. Several authors subsequently reported adverse reactions (urticaria, angioedema, rash) to a variety of steroids, but Mendelson et al.³ were perhaps the first to perform a thorough investigation of the phenomenon. The patient was a 17-year-old asthmatic who developed urticaria and an exacerbation of asthma on intravenous injection of methylprednisolone sodium succinate and hydrocortisone sodium succinate, and on oral challenge with methylprednisolone. Careful supervised challenges excluded

equilibrium existed between the succinated and the non-succinated steroids, and that the latter agents were causing the reactions. Our patient reacted to the succinate derivatives but not to the native compounds. Since this report, a number of similar cases of acute asthma, worsened by the administration of intravenous steroids, have been reported. A number of trends have been observed in these cases. Skin test reactivity has been observed in most cases, usually to intradermal injections, but occasionally to skin prick tests. Patients do not commonly react to steroids given orally despite reactions to intravenous preparations^{4,10} and aspirin-sensitive patients may be over-represented^{4,10-12} although the condition is too rare for one to draw definitive conclusions. Details of these cases are listed in Table 2.

This case demonstrates the rare phenomenon of steroid sensitivity with limited cross-reactivity between steroid preparations on skin testing. Intradermal testing was useful in defining the nature of the reactions and may have a role in predicting safe administration of alternative steroid agents for future use, although experience in this regard is limited. Physicians should be aware of the possibility of systemic reactions to these compounds.

Acknowledgements

We acknowledge the cooperation and assistance of Upjohn Pty Ltd in providing the various steroid substances for testing, and Mr D Harle and Dr B Baldo of the Kolling Institute, Royal North Shore Hospital.

reactivities of IgE antibodies to the muscle relaxants, gallamine, decamethonium, and succinylcholine (suxamethonium). *J Immunol Methods* 1985; 78: 293-305.

- Bousquet J. In vivo methods for study of allergy: skin tests, techniques and interpretation. In: Middleton EM (Jr), Reed C, Ellis E, et al., eds. *Allergy principles and practice*, 3rd ed. Missouri: CV Mosby Company, 1988: 424.
- Mendelson L, Meltzer E, Hamburger R. Anaphylaxis-like reactions to corticosteroid therapy. *J Allergy Clin Immunol* 1974; 54: 125-131.
- Preuss L. Allergic reactions to systemic glucocorticoids: a review. *Ann Allergy* 1985; 55: 772-775.
- Peller J, Bardana E. Anaphylactoid reaction to corticosteroid: case report and review of the literature. *Ann Allergy* 1985; 54: 302-305.
- Pryse-Phillips W, Chandra R, Rose B. Anaphylactoid reaction to methylprednisolone pulsed therapy for multiple sclerosis. *Neurology* 1984; 34: 1119-1121.
- Brown E, Frain J, Udell L, et al. Locally administered hydrocortisone in the rheumatic diseases. *Am J Med* 1953; 15: 656.
- Hollander J. Proceedings of 8th International Congress of Rheumatic Diseases. Geneva. *Med et Hyg* 1953; 143-145.
- Kendall P. Untoward effects following local hydrocortisone injection. *Ann Physical Med* 1958; 4: 170-175.
- Seale JP. Anaphylactoid reaction to hydrocortisone. *Med J Aust* 1984; 141: 446.
- Partridge M, Gibson G. Adverse bronchial reactions to intravenous hydrocortisone in two aspirin-sensitive patients. *Br Med J* 1978; 1: 1521-1522.
- Dajani B, Sirman N, Shubair K, et al. Bronchospasm caused by intravenous hydrocortisone sodium succinate (Solu-Cortef) in aspirin-sensitive asthmatics. *J Allergy Clin Immunol* 1981; 68: 201-204.
- King R. A severe anaphylactoid reaction to hydrocortisone. *Lancet* 1960; 2: 1093.
- O'Garra J. Anaphylactic reactions to hydrocortisone injections. *Br Med J* 1962; 1: 615.
- Comaish S. A case of hypersensitivity to corticosteroids. *Br J Derm* 1969; 81: 919-925.
- Maddin S. Urticaria following betamethasone. *JAMA* 1969; 207: 560.
- von Maur K, Rocklin R, Stevens M. Corticosteroid allergy in a patient with systemic lupus erythematosus. *Johns Hopkins Med J* 1974; 134: 356-364.
- Romankiewicz J, Franklin J. Allergic reactions to corticosteroid therapy. *JAMA* 1976; 236: 1939.
- Hayhurst M, Braude A, Benatar S. Anaphylactoid-like reaction to hydrocortisone. *S Afr Med J* 1978; 53: