

Casi clinici

Anaphylactic reaction to oral prednisone: a case report and review of the literature

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Reports of corticosteroid anaphylactic reactions are rare in the medical literature. We describe the case of a nonatopic 17-year-old girl with bronchial asthma and aspirin intolerance who developed a dramatic anaphylactic reaction to oral prednisone. She recovered with shock therapy and intravenous administration of diphenhydramine and hydrocortisone. Intradermal testing with a wide range of steroid preparations gave positive results to prednisone. No reactions occurred to methylprednisolone and hydrocortisone. This case and the brief review of the literature which follows emphasize the danger of prednisone administration in patients who have asthma and a history of drug intolerance.

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Introduction

Corticosteroids are widely used in the management of various inflammatory conditions, and oral prednisone in particular is one of the drugs of choice for acute exacerbations of bronchial asthma^{1,2}. Although well known side effects are frequently reported upon chronic dosing, anaphylactic reactions to corticosteroids are relatively uncommon^{3,4}. Hydrocortisone and methylprednisolone are the steroids most frequently involved in systemic adverse reactions, whereas prednisone, betamethasone, and dexamethasone are reported less often as causative agents³⁻⁵. These reactions may be immunologic or non-immunologic in nature, and the clinical signs of anaphylaxis may be seen with both types of reaction. It is somewhat paradoxical that, on rare occasions, steroids themselves can induce systemic adverse reactions.

The case presented describes such a reaction in a nonatopic girl with bronchial asthma and a history of previous allergic reaction to aspirin who developed severe systemic symptoms and loss of consciousness after a single dose of 25 mg prednisone. This case highlights the importance of considering uncommon side effects when oral prednisone needs to be used in asthmatic patients who require control of the acute exacerbations of their asthma, and particularly in those with a history of drug intolerance.

Case report

A 17-year-old girl with a long-standing history of intrinsic (results of allergy skin testing were negative on two separate occasions) asthma and aspirin intolerance (manifested as a cutaneous rash) was seen in the outpatient clinic with an acute exacerbation of her respiratory symptoms. A diagnosis of asthma was made when she was 7 years old,

and she remained well with inhaled salbutamol p.r.n. and beclomethasone dipropionate 250 µg two puffs bid. For the last 2 years she had only occasional exacerbations of her asthma, which resolved with standard nebulized therapy. The patient was not taking any other medicines or recreational drugs. She had received oral and intravenous steroids on a large number of occasions. There was no history consistent with food allergy. The family history for atopic disease was negative. Results of physical examination were entirely normal, except for the presence of widespread wheezing on auscultation of her chest. After consultation at the outpatient clinic, she was started on a short course of oral prednisone (25 mg/day) for better control of her asthma exacerbations. The following morning, approximately 40 min after prednisone dosing, she experienced an anaphylactic episode. This began with generalized flushing and hives. They were accompanied by intense hypogastric pain and abdominal cramps followed by vomiting and diarrhea. The patient lost consciousness, and arterial hypotension occurred. On admission to hospital, the pulse rate was 116 b/min, blood pressure 60/40 mmHg, and axillary temperature 36.6°C. Auscultation of her chest was unremarkable. Routine laboratory investigations were non-contributory. Symptoms were promptly reversed with standard shock therapy and intravenous administration of diphenhydramine and hydrocortisone. After 24-hour observation, she was advised to avoid systemic steroids, instructed in the use of autoinjectors of epinephrine to deal with any symptoms that might develop when medical attention was not available, and sent home. In addition, she was asked to increase her beclomethasone dipropionate 250 µg to two puffs qid. There were no subsequent problems with her asthma control.

Clinical and laboratory investigations

Two months after the incident, the patient was subjected to allergy testing. She and her parents received information about possible risks of challenge tests, and informed consent was obtained from the parents. Labo-

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ratory tests showed a normal complete blood count, serum IgE level, and C4 and CH50 values. A crushed prednisone tablet was tested after suspension in a drop of normal saline solution by means of the prick test technique without a positive result. Intradermal skin testing with increasing doses of pure prednisone (Miles, Inc.: Spokane, WA, USA) from 0.5 µg to 50 mg yielded a 3+ reaction at 500 µg. No reaction with intradermal prednisone was elicited in 3 control subjects. However, the results of intradermal skin testing to methylprednisolone and hydrocortisone from dilutions of 1:100 000 to 1:1 were negative. Oral challenge tests were performed under careful control. Challenges were performed with 1.25 mg, 2.5 mg, 5 mg, and 10 mg of commercially available prednisone (each 60 min apart). Twenty minutes after ingestion of 10 mg prednisone, the patient experienced flushing of the head and upper trunk, nausea, and dizziness. The pulse rate rose to 104 b/min, and blood pressure decreased slightly to 90/65 mmHg (her baseline values were 88 b/min and 105/75 mmHg). She recovered rapidly after intravenous administration of diphenhydramine and hydrocortisone. Additional challenges were performed with increasing doses of methylprednisolone and hydrocortisone administered intravenously. No reactions were observed. She was advised to take methylprednisolone in the case of an acute exacerbation of her asthma. The patient was not available for further investigations.

Discussion

The case of this girl with bronchial asthma and a history of previous allergic reaction to aspirin who developed severe anaphylaxis to oral prednisone emphasizes the danger of steroid administration, particularly in patients with a history of drug allergy. Intravenous therapy with hydrocortisone and methylprednisolone is sometimes associated with adverse reactions, whereas prednisone, betamethasone, and dexamethasone are rarely reported as causative agents³⁻⁵.

Although a few cases of urticaria (with or without angioedema) resulting from prednisone therapy have been published³⁻⁵, a complete search of the English literature with Medline did not bring to light any other reports of acute anaphylaxis induced by oral prednisone. In spite of the relative infrequency of adverse reactions to corticosteroids, it is possible that a low index of suspicion of an untoward reaction decreases the likelihood that such a reaction is correctly recognized. Bronchial asthma is a rather common illness, and oral prednisone is widely prescribed in a large number of individuals for acute exacerbations of their asthma, it is thus surprising that allergic reactions to prednisone have not been more frequently reported in the literature. A possible explanation is that either the treating physicians have not been aware of the worsening of asthma in their patients on oral steroids (which may be mild in most cases) or the adverse reaction described is a very rare one indeed. However, reactions to prednisone exist, and probably occur more often than we appreciate.

In these circumstances suspension of the offending drug and substitution with an alternative one is the logical approach. Since she would need steroid therapy for the management of the acute exacerbations of her asthma, it was very important to determine which corticosteroid could be tolerated by this patient. It is not advisable simply to rely on the results of intradermal skin testing in order to exclude sensitivity to corticosteroids, since positive wheal and flare responses may not always be present in susceptible individuals^{3,4,6}. It was therefore necessary to perform challenges with intravenous methylprednisolone and hydrocortisone.

The present case supports the view that systemic corticosteroids should be used with caution in asthmatics with a history of drug intolerance. It is widely acknowledged that corticosteroid-induced systemic adverse effects are more common in individuals with aspirin intolerance than in those with no clearly defined history of previous allergic reaction to aspirin^{7,8}. As corticosteroids do not usually cross-react with aspirin⁹, the reason for this phenomenon remains unclear.

Our patient report had a significant skin reaction to intradermal prednisone, and none to methylprednisolone and hydrocortisone. In addition, the specificity of this reaction was confirmed by the results of the oral and intravenous challenges with prednisone, methylprednisolone and hydrocortisone. It is possible that IgE sensitization to oral prednisone might have occurred in this girl. Although we did not measure IgE antibody specific to prednisone, the positive results of intradermal skin testing suggest that this case of acute anaphylaxis may be the result of either an IgE-mediated response or direct release of vasoactive mediators from mast cells or circulating basophils. An additional speculation is that prednisone could have inhibited the release of arachidonic acid which, in individuals with a history of aspirin intolerance such as our patient, may have deprived her of prostaglandins necessary to maintain the arterial tone and to support the cardiovascular system.

We have found over 30 reported cases of systemic reactions to steroid preparations to date. While most reactions are non-immune in nature, there are a few reports of a true IgE-mediated reaction¹⁰. The earliest reference to the possibility of steroid sensitivity comes from Brown et al.¹¹ who described 4 patients with urticaria after intra-articular injections of hydrocortisone acetate, but concluded that either the local anesthetic agent or the diluent was responsible for the reactions. Kendall¹² described 9 patients with similar reactions, although 4 received concomitant local anesthetic and hyaluronidase with the hydrocortisone. Several authors subsequently reported adverse reactions to a variety of steroids, but Mendelson et al.¹³ were perhaps the first to carry out a complete investigation of the phenomenon. The patient was a young asthmatic who developed urticaria and exacerbation of asthma on intravenous injection of methylprednisolone sodium succinate and hydrocortisone sodium succinate, and on oral challenge with methylprednisolone. Careful supervised chal-

lenges excluded the diluent as the cause of the reactions, and extensive skin testing confirmed that non-succinated steroids were responsible for the reactions. Since then, 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 seen in most cases, usually to intradermal injections, but occasionally to skin prick tests. Our patient had a positive skin reaction to intradermal prednisone, but not to skin prick testing. Despite reactions to intravenous preparations, patients do not commonly react to oral steroids, and aspirin sensitive

subjects may be overrepresented. Details of these cases are listed in Table I^{3,6,7,10-37}.

Our young patient with asthma and aspirin intolerance demonstrates that oral prednisone administration may lead to the development of severe anaphylaxis. Although rare, physicians should be aware of the possibility of dangerous systemic reactions upon steroid administration, particularly in patients with a history of drug allergy. In these instances the first dose should be administered under careful control, and epinephrine should be readily available as a rescue medicine.

TABLE I. Reported systemic reactions to corticosteroid preparation.

Patient details (age, sex, disease)	Corticosteroid preparation	Route of administration	Reaction	Test performed	Result
4 patients ¹¹	Hydrocortisone-?	Intra-articular	Urticaria	Intradermal	?
5 patients ¹²	Hydrocortisone-?	Intra-articular	Urticaria	Skin prick	?
50, F ¹⁴	Hydrocortisone + diluent	Soft tissue injection	Urticaria, petechiae, GIT bleeding	Intradermal	Positive for hydrocortisone
49, F ¹⁵	Hydrocortisone acetate	Soft tissue injection	Urticaria, angioedema	Patch/intradermal	Positive for hydrocortisone acetate
29, M ¹⁵	Hydrocortisone acetate	Soft tissue injection	Angioedema, petechiae	Intradermal	Negative for hydrocortisone acetate
39, M ¹⁵	Hydrocortisone acetate	Soft tissue injection	Petechiae, GIT bleeding	Intradermal	Positive for diluent
58, F ¹⁶	Prednisone Prednisone acetate	Oral Intra-articular	Rash Rash	Intradermal	Delayed positive for prednisone salt and prednisolone acetate
52, M ¹⁷	Triamcinolone Betamethasone	Topical Topical, intramuscular	Urticaria Urticaria	Intramuscular challenge	Positive for triamcinolone
17, M asthma ¹³	Methylprednisolone succinate	Intravenous	Urticaria, angioedema, bronchospasm	Intradermal	Positive for hydrocortisone and methylprednisolone
	Hydrocortisone succinate	Intravenous	Urticaria, angioedema, bronchospasm		
	Methylprednisolone	Oral	Urticaria, angioedema, bronchospasm		
50, M systemic lupus erythematosus ¹⁸	Prednisone succinate	Oral	Urticaria, angioedema	Intradermal	Delayed positive for hydrocortisone succinate and methylprednisolone
55, Waldenstrom's purpura ¹⁹	Prednisone	Oral	Urticaria, angioedema	—	—
	Dexamethasone phosphate	Oral	Urticaria	—	—
66, F aspirin sensitive asthma ⁷	Hydrocortisone phosphate	Intravenous	Bronchospasm	—	—
33, F aspirin sensitive asthma ⁷	Hydrocortisone succinate	Intravenous	Bronchospasm, urticaria, vomiting	—	—
21, F asthma ²⁰	Hydrocortisone + diluent	Intravenous	Bronchospasm	Skin prick	Positive for hydrocortisone succinate
41, M asthma ²⁰	Hydrocortisone + diluent	Intravenous	Bronchospasm, angioedema	Skin prick, intradermal	Negative for hydrocortisone succinate, methylprednisolone succinate and dexamethasone phosphate

TABLE I.

21, M asthma ²¹	Hydrocortisone succinate	Intravenous	Urticaria, bronchospasm	Intradermal	Positive for hydrocortisone succinate
31, M asthma ²²	Hydrocortisone succinate	Intramuscular	Urticaria, angioedema	—	—
56, F asthma ²³	Hydrocortisone succinate	Intravenous	Bronchospasm, cardiac arrest	Patch	Negative for hydrocortisone succinate
40, M asthma ²⁴	Methylprednisolone succinate	Intravenous	Bronchospasm, urticaria, hypotension	Skin prick, intradermal	Positive for hydrocortisone succinate and methylprednisolone succinate
3 patients with aspirin sensitive asthma ⁸	Hydrocortisone succinate	Intravenous	Bronchospasm	Skin prick, intradermal	Negative for hydrocortisone succinate and dexamethasone phosphate
41, M renal transplant ²⁵	Methylprednisolone succinate	Intravenous	Hypotension, urticaria, bronchospasm	Intradermal	Positive for methylprednisolone succinate
29, F ²⁶	Hydrocortisone succinate	Intramuscular	Angioedema, hypotension	Intradermal	Positive for hydrocortisone succinate
81, M asthma ²⁷	Hydrocortisone succinate	Intravenous	Bronchospasm, vomiting	Intravenous challenge	Positive for hydrocortisone succinate
47, F asthma ²⁷	Hydrocortisone succinate	Intravenous	Bronchospasm, hypotension	—	—
53, M multiple sclerosis ¹⁰	Methylprednisolone succinate	Intravenous	Urticaria, angioedema, hypotension	Skin prick, RAST	Positive for methylprednisolone
59, F chronic renal failure ³	Hydrocortisone	Intravenous	Urticaria, angioedema	Intradermal	Negative for hydrocortisone succinate and methylprednisolone succinate
6, F asthma ²⁸	Hydrocortisone succinate	Intravenous	Bronchospasm, urticaria	Intradermal	Positive for hydrocortisone succinate and methylprednisolone succinate
31, F asthma ²⁹	Hydrocortisone succinate	Intravenous	Petechiae, GIT bleeding, abdominal pain	Intradermal	Positive for hydrocortisone succinate, prednisolone, deflazacort and dexamethasone phosphate
66, F asthma ³⁰	Prednisolone		Urticaria		
	Methylprednisolone succinate	Intravenous	Vomiting, bronchospasm, hypotension	—	—
62, F asthma ³¹	Hydrocortisone succinate	Intravenous	Bronchospasm, urticaria, hypotension	Skin prick	Positive for hydrocortisone succinate and methylprednisolone
	Methylprednisolone succinate	Intravenous	Bronchospasm, urticaria		
64, M ³²	Hydrocortisone succinate	Intravenous	Bronchospasm, urticaria, coronary spasm	Intradermal	Positive for hydrocortisone succinate
27, M aspirin sensitive asthma ³³	Hydrocortisone succinate	Intravenous	Angioedema, bronchospasm	Intradermal	Positive for hydrocortisone succinate and methylprednisolone succinate
	Methylprednisolone succinate	Intravenous	Angioedema, bronchospasm		
23, F renal transplant ³⁴	Methylprednisolone succinate	Intravenous	Hypotension, bronchospasm	—	—

TABLE I.

60, F asthma ³⁵	Methylprednisolone succinate	Intravenous	Urticaria, bronchospasm	Skin prick	Positive for methylprednisolone, but negative for dexamethasone and prednisolone
43, M asthma ⁶	Hydrocortisone succinate	Intravenous	Vomiting, bronchospasm	Intradermal	Positive for hydrocortisone succinate and methylprednisolone succinate
				Skin prick	Negative for hydrocortisone succinate and methylprednisolone
27, F aspirin sensitive asthma ³⁶	Methylprednisolone	Intravenous	Vomiting, respiratory arrest	Intradermal	Positive for methylprednisolone succinate, hydrocortisone succinate, and dexamethasone phosphate
8, M asthma ³⁷	Methylprednisolone succinate	Intramuscular	Sneezing, urticaria, bronchospasm	Skin prick	Positive for methylprednisolone, but negative for hydrocortisone, dexamethasone, and prednisone

F = female; GIT = gastrointestinal; M = male; RAST = radioallergosorbent test.

Riassunto

Sono rari i casi di reazioni anafilattiche da assunzione di corticosteroidi riportati nella letteratura medico-scientifica. Noi descriviamo il caso di una ragazza di 17 anni con asma bronchiale intrinseco e intolleranza all'aspirina che ha sviluppato una grave reazione anafilattica dopo assunzione orale di prednisone. Tale evento è stato risolto con terapia anti-shock e somministrazione di difenidramina e idrocortisone per via endovenosa. Il test intradermico effettuato con diversi farmaci corticosteroidi ha evidenziato una risposta positiva al prednisone. Nessuna reazione veniva osservata con il metilprednisolone e l'idrocortisone. Questo caso e la succinta analisi degli altri rari casi osservati in letteratura enfatizza il pericolo della somministrazione di prednisone in pazienti con asma e anamnesi positiva per intolleranza ai farmaci.

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