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Hydrocortisone-induced anaphylaxis

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ABSTRACT: Two patients with asthma developed an anaphylactic reaction after the intravenous administration of hydrocortisone. In both cases, the reaction included the rapid development of airflow obstruction. Previous reports have suggested that the allergenic component may be hydrocortisone itself, rather than the diluents or preservatives. When administering hydrocortisone, one

should be aware of the possibility of such a reaction, even though it is uncommon. Although potentially life-threatening, particularly in an asthma sufferer, this reaction should be reversible with prompt recognition and appropriate management.

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HYDROCORTISONE is commonly used in the treatment of asthma and allergic reactions. It is not usually realized, however, that hydrocortisone itself can produce an anaphylactic reaction. Although there are isolated reports in the literature, this paper documents the first two cases to have occurred in Australia.

Case reports

Case 1. — An 81-year-old non-atopic man with chronic asthma first presented to The Prince Charles Hospital with status asthmaticus in 1979. He received bronchodilator therapy, which included intravenous injections of hydrocortisone (200 mg every four hours for three days) and aminophylline, and inhalations of nebulized salbutamol, with good effect. He required admission to hospital again in 1980 and, after receiving similar therapy, including a single dose of intravenously administered hydrocortisone (200 mg), he recovered. During his third admission to hospital in 1981, he required ventilation as well as the administration of aminophylline and adrenaline. He also received hydrocortisone by the intravenous route for six days and his condition gradually responded to this treatment. No adverse drug reaction was apparent on any of these occasions.

In 1982, he presented with severe asthma (FEV₁, 0.6 L; VC, 2.0 L). Approximately two minutes after the intravenous administration of hydrocortisone (200 mg), he very rapidly developed tachycardia, vomiting, increased bronchospasm and cyanosis. The inhalation of nebulized salbutamol produced little effect, and adrenaline was then administered subcutaneously after which the patient slowly recovered. Intravenous therapy with hydrocortisone was immediately discontinued, and replaced by oral therapy with prednisolone. The strong suspicion that the

hydrocortisone had caused an anaphylactic reaction had potentially grave consequences for the management of any future attacks in this patient. For this reason, informed consent for a formal challenge with hydrocortisone was obtained from the patient.

The minimum dose of intravenously administered hydrocortisone needed to cause an adverse reaction in hydrocortisone-sensitive patients is not known, but Dajani et al described such reactions in patients who received 100 mg of hydrocortisone by the intravenous route.¹ As a precaution, a low dose of 40 mg of hydrocortisone was chosen for our patient. This was administered by a slow intravenous injection over three minutes, under close medical supervision with resuscitation facilities available. A rapid fall in FEV₁, (see graph), together with wheezing and tachycardia promptly occurred. These symptoms resolved after the subcutaneous administration of adrenaline and inhalation of nebulized salbutamol.

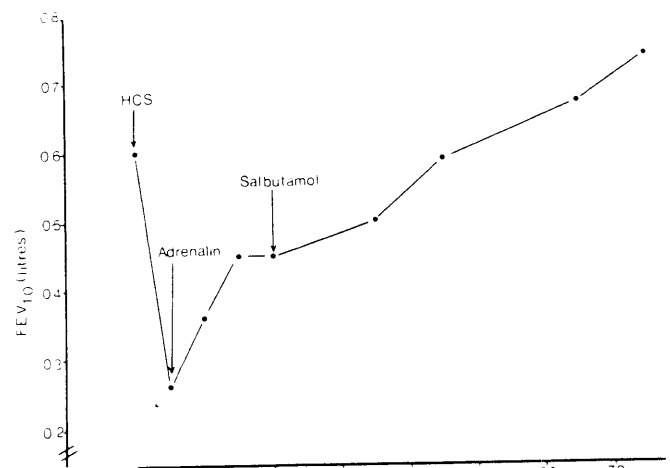


TABLE: Summary of reported adverse reactions to hydrocortisone in asthma

Study*	Sex	Reactions					Skin sensitivity to HCS	Allergy
		Bronchospasm	Angio-oedema	Rash	APLX	Atopy		
Mendelson et al., 1974 ⁴ (1)	M	Yes	Yes	Yes	Yes	Yes	Yes	HCS, MP
Kounis, 1976 ⁸ (2)	M	Yes	No	No	Yes	—	No	HCS
	M†	No	No	No	Yes	—	No	HCS
Hayhurst et al., 1978 ⁶ (2)	M	Yes	No	No	Yes	Yes	Yes	HCS
	F	Yes	Yes	No	No	—	No	HCS
Partridge and Gibson, 1978 ⁷ (2)	F	Yes	No	No	Yes	—	—	HCS, ASP
	F	Yes	No	Yes	No	—	—	HCS, ASP
Chapman et al., 1979 ⁵ (1)	M	Yes	No	Yes	Yes	—	Yes	HCS
Ashford and Bailey, 1980 ⁹ (1)	M	No	Yes	Yes	No	—	—	HCS
Dajani et al., 1981 ¹ (3)	F	Yes	No	No	No	No	No	HCS, ASP
	F	Yes	No	No	No	No	No	HCS, ASP
	F	Yes	No	No	No	No	No	HCS, ASP
Whitelaw, 1982 ¹⁰ (2)	M	Yes	No	No	Yes	—	—	HCS
	M	Yes	No	No	Yes	—	—	HCS

*Number of patients in parentheses.

†Chronic bronchitis.

APLX = anaphylaxis; ASP = aspirin; HCS = hydrocortisone; MP = methylprednisolone.

Case 2. — The second patient was a 47-year-old woman who had atopic asthma since childhood. She had experienced a previous anaphylactic reaction to tetanus toxoid. A prophylactic dose of hydrocortisone (100 mg) was administered intravenously before an intravenous pyelogram. Almost immediately, she developed severe bronchospasm, hypotension and tachycardia. The patient received adrenaline and aminophylline and was transferred to The Prince Charles Hospital for management. Because of continued airflow obstruction, she required aminophylline infusion and inhalation of nebulized salbutamol. Upon recovery, she declined a formal hydrocortisone challenge.

Discussion

Since the first documented case of an anaphylactic reaction to parenterally administered hydrocortisone was reported by King in 1960,² there have been nine further reports involving a total of 18 patients.¹⁻¹⁰ These are summarized in the Table. King,² and O'Garra,³ separately reported a total of four orthopaedic patients who developed anaphylaxis after intra-articular injections of hydrocortisone. These authors estimated the frequency of anaphylaxis after the intra-articular administration of hydrocortisone in non-asthmatic patients to be 1/2000 patients and 1/4000 patients, respectively. Although the frequency of this reaction in patients with asthma is unknown, its occurrence is obviously extremely uncommon.

The hydrocortisone sodium succinate preparation used in our two patients also contained sodium biphosphate anhydrous, dried sodium phosphate and benzyl alcohol added as a preservative. Mendelson et al. reported the case of a patient with asthma who developed an anaphylactic reaction following the intravenous administration of hydrocortisone and methylprednisolone.⁴ They demonstrated by means of separate intravenous challenge tests that the active allergenic component was the corticosteroid drug, and not the abovementioned diluents, preservative, or sodium succinate. These findings were also confirmed by Dajani et al. in a further three patients with asthma.¹ The hydrocortisone preparation used in our study, and in those of Mendelson et al. and Dajani et al., did not

circumstantial evidence suggests that hydrocortisone, and not its vehicle, was responsible for the anaphylactic reactions in our patients. However, it remains unclear why the patient in Case 1 did not develop a similar reaction on three previous occasions on which he also received intravenous therapy with hydrocortisone.

Other investigators have attempted to characterize this group of patients. King,² and Chapman et al.,⁵ found skin sensitivity to hydrocortisone in their patients, while this was found in two out of three patients by O'Garra,³ and in one of two patients by Hayhurst et al.⁶ On the other hand, the patients of Dajani et al. showed no sensitivity to hydrocortisone.¹ There is, thus, no consistent relationship between hydrocortisone-induced anaphylactic reactions and skin sensitivity to hydrocortisone. Several authors examined the atopic status of patients with hypersensitivity to hydrocortisone. The patient of Mendelson et al. was found to be atopic on skin testing,⁴ and Hayhurst et al. found atopy in one of their patients,⁶ whereas Dajani et al. had no atopic patients.¹ Dajani et al. electively challenged 11 aspirin-sensitive patients with asthma with intravenously administered hydrocortisone, and discovered that three patients developed bronchospasm. Partridge and Gibson also described two similar reactions in aspirin-sensitive patients with asthma.⁷ These cases may suggest that anaphylactic reactions to intravenously administered hydrocortisone are more common in such patients.

Our report draws attention to an infrequent complication of parenteral therapy with hydrocortisone. The practitioners who administer it should be aware that an anaphylactic reaction can occur, but that it should be reversible if oxygen, adrenaline and nebulized beta₂-agonists are available and promptly administered.

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Comment

Anaphylactoid reaction to hydrocortisone

THE REPORT by Chan et al. of two patients with asthma who developed anaphylactoid reactions after intravenous injections of hydrocortisone serves to remind us of this rare, but potentially life-threatening, adverse reaction which has also been observed with other corticosteroid agents, such as methylprednisolone and dexamethasone.¹ There appear to be few, if any, clinical pointers to identify susceptible individuals. Some of the 15 subjects with asthma reported to date in the world literature, who developed acute bronchospasm, were also sensitive to aspirin. Since up to 20% of the asthmatic population may be aspirin-sensitive,² it is evident that aspirin sensitivity alone is not a sufficient indication of predisposition. Furthermore, the results of skin tests with hydrocortisone are not positive often enough to be reliable predictors.

The mechanisms for these adverse reactions remain obscure. Hydrocortisone is an endogenous steroid hormone which these individuals synthesize and release from their adrenal glands without ill effects. Presumably, conversion to the succinate salt (which is a water-soluble form, and therefore suitable for intravenous injection) alters its acceptability to the body in some way. One refrains from using the term "antigenic transformation", because reaginic antibodies (those mediating anaphylactic reactions) to the succinate salt have not been convincingly demonstrated in all of these individuals. Preservatives or stabilizers, which are added to ampoules of corticosteroid agents to lengthen their shelf lives, may be responsible for some of these adverse reactions. Preliminary evidence in support of this intriguing possibility was obtained in a 23-year-old woman with acute asthma whose condition rapidly deteriorated during an intravenous infusion of dexamethasone, ampoules of which contain sodium bisulphite as a preservative. After her recovery, an oral challenge with sodium metabisulphite induced bronchospasm,¹ suggesting that she may also have been sensitive to sulphite salts administered intravenously.

Corticosteroid agents are valuable drugs in the management of asthma. Although the precise nature of their "anti-asthma" efficacy is not known, it is probably related to their anti-inflammatory activity, an effect which may be attributable, in part, to the production of an effector protein called macrocortin.³ Intravenously

acute exacerbations of asthma, at which time the patients also receive aminophylline by the intravenous route, and nebulized beta-adrenoceptor agonists. Under such circumstances, if airflow limitation increased after the intravenous administration of a corticosteroid agent, it would probably be interpreted as progression of the asthma.

Fortunately, the two patients reported by Chan et al., and those reported by the other authors, who have received prednisolone by the oral route tolerated it without untoward consequences. Therefore, these hapless individuals are not denied the beneficial effects of corticosteroids, albeit only as oral medication. Moreover, recent findings suggest that the inability to receive corticosteroids by the intravenous route may not place these patients at any particular disadvantage.⁴ In a study of hospital admissions for acute asthma, Harrison et al. found that the outcome was just as favourable for those patients who received prednisolone by mouth as for those who received prednisolone by mouth plus intravenously administered hydrocortisone.⁴ It would be inappropriate to alter the treatment regimens overnight on the basis of this single study, but it should offer reassurance to practitioners who may encounter patients with asthma who do not tolerate corticosteroid agents by the intravenous route.

These isolated case reports should not dissuade us from administering corticosteroid agents by the intravenous route to patients with severe asthma which is unresponsive to beta-adrenoceptor agonists. However, these reports should alert us to the rare possibility that intravenously administered corticosteroid agents may be a causative factor in some patients with acute asthma whose condition continues to deteriorate despite conventional therapy.

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