

Brief report

## Systemic allergic reaction and diffuse bone pain after exposure to a preparation of betamethasone

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### Abstract

Allergic reactions to corticosteroids are unexpected as they seem to contradict their pharmacodynamic action. Nevertheless, they are not infrequent, with an estimated incidence of up to 4% for cutaneous reactions. Systemic reactions are rarely reported, but their incidence might be underestimated. We report here an unusual allergic reaction to betamethasone presenting with diffuse bone pain, erythema, and bronchoconstriction, which was confirmed by a positive rechallenge in a double-blind procedure. This is the first case report of a systemic reaction to betamethasone confirmed by a positive rechallenge. An impurity in betamethasone dipropionate cannot be excluded. As this substance is frequently used in rheumatologic soft-tissue injections, it is important to recognize this potentially life-threatening side effect. © 2005 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

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### 1. Introduction

Allergic reactions to corticosteroids are in apparent contradiction to their immunomodulatory and anti-inflammatory effects. Local and systemic allergic reactions have been reported since 1953 and most of the synthetic glucocorticosteroids have been involved. We report here a systemic allergic reaction to betamethasone with unusual clinical characteristics. This case report is the first description of a systemic reaction to betamethasone confirmed by a positive rechallenge and a further implicit inference of a substance group effect.

### 2. Case report

Ten minutes after receiving an intra-articular injection of betamethasone 14 mg (Diprophos<sup>®</sup>) and lidocaine 2%

(Xylocain<sup>®</sup>), a 42-year-old Portuguese female developed a sensation of fainting, heat, dyspnea, and intense diffuse bone pain, as well as a facial erythema. The symptoms regressed spontaneously within an hour. The injection was made in the right knee, where the patient suffered an effusion and acute pain in the context of chronic osteoarthritis. Arthritis of any other origin had been excluded.

A systemic reaction to one of the excipients was suspected. As the risk of inadvertent or voluntary iatrogenic re-exposure was judged to be high, the patient was assessed with Diprophos<sup>®</sup> and Xylocain<sup>®</sup> under close medical surveillance by the treating allergologist. Re-exposure to different doses of betamethasone (Diprophos<sup>®</sup>), lidocaine 2% (Xylocain<sup>®</sup>), and placebo (NaCl 0.9%) by intramuscular injection was performed under clinical monitoring (blood pressure, pulse rate, respiratory frequency, peak flow) in a double-blind procedure.

Injection of placebo and of different doses of lidocaine did not produce any symptoms or changes in the clinical parameters being monitored. Five minutes after the injection of 3.5 mg of betamethasone (Diprophos<sup>®</sup>), the patient felt intense pain localized mainly in the pelvic

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girdle, a sensation of fainting, dyspnea, and a facial erythema, along with sweating. The cardiovascular parameters remained in the normal range. The pulmonary parameters showed a decrease in peak flow to 240 L/min (400 L/min at baseline) and an increase in respiratory frequency to 20 breaths/min. Signs and symptoms regressed rapidly after the administration of adrenaline, salbutamol, and ketorolac, with a normalization of the peak flow after 20 min.

The patient was exposed to methylprednisolone (Depo-Medrol<sup>®</sup>), a corticosteroid belonging to another antigenic class. Administration of this substance was well tolerated at a dose of 40 mg (see Table 1 for excipients). To investigate the imputability of individual ingredients in the Diprophos<sup>®</sup> preparation, skin testing with a 1/1000 solution of betamethasone dipropionate in NaCl 0.9% was performed (lyophilized betamethasone dipropionate supplied by the manufacturer). Prick testing was negative. The intradermal reaction with the betamethasone solution resulted in a papule, 6 mm in diameter vs. 5 mm in diameter for the positive control, with 0.9% codeine. Oral exposition of the patient to benzoate (a mix of salts of benzoic acids–E210, E212, E213) was negative to 50, 100, and 250 mg.

The positive rechallenge test and the rapid regression of symptoms after stopping the drug allowed us to classify the imputability of the betamethasone (Diprophos<sup>®</sup>) as “certain” according to WHO criteria. The commercial preparation of betamethasone used (Diprophos<sup>®</sup>) contains several excipients that are listed in Table 1.

Table 1  
Ingredients of Diprophos<sup>®</sup> and Depo-Medrol<sup>®</sup> (kindly provided by Schering Plough and Pharmacia)

	Active substance(s)	Excipients
Diprophos <sup>®</sup>	Betamethasone dipropionate	Polysorbate 80
		Benzyl alcohol
	Betamethasone sodium phosphate	Sodium carboxymethylcellulose
		Polyethylene glycol 3350
		Methylparahydroxybenzoate
		Propylparahydroxybenzoate
		Disodium hydrogen phosphate dihydrate
		Disodium edetate
		Sodium edetate
		Hydrochloric acid for pH adjustment
Water for injection		
Depo-Medrol <sup>®</sup>	Methylprednisolone	Polyethylene glycol 3350
		Acetate
		<i>N</i> -myristyl-gamma-bicolinii chloride
		NaCl
		HCl, NaOH for pH adjustment
		Water for injection

### 3. Discussion

Hypersensitivity reactions are among the rare adverse drug reactions observed with glucocorticosteroids and can be life threatening. The apparent inconsistency between the pharmacodynamically expected effect and an immuno-allergic mediated drug-induced reaction could explain the underestimated incidence of allergic reactions to corticosteroids.

Virtually all glucocorticoids have been reported to produce allergic reactions, although the substances most often implicated remain preparations of hydrocortisone and methylprednisolone. A preparation of betamethasone has recently been demonstrated to be an alternative in case of an allergic reaction to these two substances [1], but it can itself be a cause of allergy, as our case demonstrates. Systemic extracutaneous reactions have been described and well documented, but they remain exceptional.

Our case report describes a systemic reaction to a preparation of betamethasone. An IgE-dependent mechanism is suspected. Three cases of systemic allergy to betamethasone have been suspected and reported in the literature [2]. Excruciating diffuse bone pain after glucocorticoids other than betamethasone have been described in three case reports and remain an unexplained finding: one patient experienced pain in the knees, ankles, and elbows [3], one had pain in the hips [4], and one experienced abdominal pain [5]. Pain after administration of glucocorticoids seems as incongruous as the immuno-allergic reaction when one considers the potent inhibition of cyclo-oxygenase-2 and the expected related analgesic effect.

The clinical symptoms experienced by our patient might be related to betamethasone itself, to an unknown metabolite, or to traces of impurities or additives in the preparation of betamethasone dipropionate. A recent publication [6] reports an anaphylactic reaction after injection of the polyethylene glycol (macrogolum) contained in the vehicle. In our patient, this excipient was well tolerated in the preparation containing a different steroid, and it can thus be excluded as the causative agent. Benzoates and carboxymethylcellulose are also frequently implicated in anaphylaxis, but our patient presented a negative oral re-exposition to benzoate and tested positive to betamethasone dipropionate alone in skin testing. The decision by the treating physician to re-expose this patient to betamethasone can be criticized, as a therapeutic alternative is available.

One can only speculate about the pathophysiologic mechanism of allergy to glucocorticosteroids as the direct experimental data remain sparse: the steroids might act as a hapten and need to combine with a protein to form the actual antigen. For some steroids, a complex with proteins produces antisera specific for the individual steroids, and passive transfer of reactivity to steroids has been reported. On the other hand, many of the deaths reported are not clearly immunologic in nature and include cardiovascular

collapse, cardiac arrhythmia, and other direct effects on heart and vascular muscle tone.

In summary, this case report is the first to demonstrate an unusual systemic adverse reaction to betamethasone confirmed by a positive rechallenge to betamethasone dipropionate. The potential of betamethasone preparations to induce allergic reactions is important to recognize, as the preparation is frequently used in rheumatologic soft-tissue injections and may be life threatening.

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