Advisory 18-02 Dexamethasone Dilution

To: All ALS Agencies and Providers

From: Jeremy T. Cushman, MD, MS, EMT-P, FACEP, FAEMS
Regional Medical Director

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Since the addition of Dexamethasone to the EMS Collaborative Protocols, we have observed a number of cases where during or immediately after Dexamethasone administration the patient (most commonly female) experiences a significant perineal or whole body burning sensation. An article summarizing this phenomenon is attached.

A few important take-aways: This phenomenon, although more common in women, does occur in men. The reaction is not an allergic or anaphylactic one and will self-resolve. There is no indication for the administration of diphenhydramine.

Based on the observations, and the disturbing adverse effect encountered by some patients, we recommend diluting Dexamethasone in 50 mL normal saline and administering over 5-10 minutes.

With any questions, please do not hesitate to contact this office.

web www.mlrems.org
phone (585) 463-2900
fax (585) 473-3516

office
44 Celebration Drive, Suite 2100
Rochester, NY 14620

mailing
601 Elmwood Avenue, Box 655
Rochester, NY 14642

Dexamethasone-Related Perineal Burning in the Prehospital Setting: A Case Series

Layne Dylla, MD, PhD, Nicole M. Acquisto, PharmD, Francis Manzo, RN, BSN, EMT-P, Jeremy T. Cushman, MD, MS, EMT-P

Abstract

Dexamethasone is frequently used in the treatment of allergic reactions and airway inflammation because of its potent anti-inflammatory effects and long duration of action. As prehospital use becomes more common, it is important for providers to be aware of unique and potentially distressing associated adverse effects. We report eight cases of intravenous dexamethasone administration associated with perineal or diffuse burning sensation in female patients.
Key words: dexamethasone; medication reaction; emergency medical services

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Introduction

Inflammation is a key driver in the pathophysiology of asthma, chronic obstructive pulmonary disease (COPD), and anaphylaxis. Systemic corticosteroids are part of the treatment algorithms in all three cases. Specifically, systemic corticosteroids in addition to inhaled corticosteroids and beta-2 agonists are the basis of treatment for moderate to severe asthma exacerbations (1). In recent years, dexamethasone has gained popularity after studies indicating that 2 doses of dexamethasone are as effective as a 5-day course of prednisone for adult asthma exacerbations and may confer an added benefit of increased compliance (2). Given the role of airway inflammation in COPD, it is not surprising that systemic corticosteroids, especially when initiated early in the exacerbation course, benefit patients with an acute COPD exacerbation through decreased length of hospital stay and improved respiratory function (3, 4). Dexamethasone can be found as part of prehospital protocols and emergency department (ED) treatment of allergic reactions and anaphylaxis, despite weak evidence suggesting that corticosteroids may decrease the risk of prolonged reactions and biphasic reactions (5, 6).

Upstate New York utilizes a common set of patient care protocols, and in March 2017 intravenous (IV) dexamethasone 10 mg (concentration 10 mg/mL) given as a slow push over 2 minutes replaced methylprednisolone 125 mg IV for the management of allergic reactions, asthma, and COPD exacerbations due to its relatively long duration of action compared to other corticosteroids. According to manufacturer recommendations, dexamethasone can be administered undiluted and there are no specific directions regarding the method of administration (7). Following this protocol change, providers in our emergency medical services (EMS) system noted 2 cases of a unique adverse reaction following administration of dexamethasone in which female patients reported a severe burning sensation located in the perineum. This potential adverse drug reaction was not known to our EMS community and prompted a review of prehospital records. From March 2017 to October 2017 there were 294 cases (164 female; 130 male) of dexamethasone administration. Of these, there were 8 (2.7% overall incidence; 4.9% incidence among females) adverse reactions documented. This report describes the cases, reviews the available literature, and offers suggestions to mitigate this idiopathic adverse reaction associated with dexamethasone administration.

Cases

Group 1: Allergic Reactions

There were 5 cases of allergic reaction in which patients received dexamethasone (Table 1). The patients were all females between the ages of 17 and 51 years. Three of the patients (patients 1, 2, and 5) reported no significant medical history, including no history of anaphylaxis or allergies. Three patients (patients 1, 2, and 3) had no known exposures, with the remaining 2 patients (patients 4 and 5) reporting being stung by bees. Four patients (patients 1, 2, 3, and 5) reported

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Address correspondence to Jeremy T. Cushman, Division of Prehospital Medicine, University of Rochester, 601 Elmwood Avenue, Box 655, Rochester, NY 14642. E-mail: Jeremy_Cushman@urmc.rochester.edu

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TABLE 1. Description of individual reactions to dexamethasone

Patient Number	Gender	Past Medical History	Dexamethasone Indication	Initial Vital Signs				Reaction	Concomitant Medications	Repeat Vital Signs			
				Heart Rate (minute)	Blood Pressure (mmHg)	Respiratory Rate (minute)	SpO_2			Heart Rate	Blood Pressure	Respiratory Rate	SpO_2
1	Female	None	Allergic Reaction	106	164/96	24	100%	Burning	Diphenhydramine	94	149/86	22	100%
2	Female	None	Allergic Reaction	134	128/90	20	96%	Burning in groin	Diphenhydramine	85	116/73	18	100%
3	Female	Anaphylaxis to bees	Allergic Reaction	115	132/80	18	99%	Diffuse burning	Diphenhydramine	115	130/70	16	99%
4	Female	Severe Allergy to bees	Allergic Reaction	75	168/141	18	96%	"Stinging in groin"	Diphenhydramine; Epinephrine	77	149/96	18	96%
5	Female	None	Allergic Reaction	126	171/119	22	96%	Severe burning in groin	Diphenhydramine; Epinephrine	116	186/115	25	99%
6	Female	Asthma	Respiratory Distress	123	147/80	50	88%	Feeling "on fire"	Albuterol; Ipratropium	126	133/97	26	98%
7	Female	Asthma, COPD	Respiratory Distress	177	144/103	28	80%	Genital Burning	Albuterol; Ipratropium	211	147/97	24	94%
8	Female	COPD	Respiratory Distress	100	130/90	30	63%	"My Vagina's on Fire" and diffuse burning	Albuterol; Ipratropium	89	114/83	14	Not documented

Note. COPD, chronic obstructive pulmonary disease.

hives and itching. Two patients (patients 2 and 5) reported facial swelling and/or throat itching. Two patients (patients 4 and 5) were noted to have evidence of respiratory distress. While none of the patients had evidence of hemodynamic instability, 2 patients received intramuscular epinephrine for suspected anaphylaxis prior to dexamethasone administration. In all 5 cases, patients were placed on cardiac monitors, peripheral IV access was obtained, and diphenhydramine 50 mg IV was administered followed by dexamethasone 10 mg IV. Immediately during or after dexamethasone administration, all women reported a reaction that included either a severe, diffuse "burning sensation" throughout the body or significant perineal burning or stinging sensations. A 51-year-old woman (patient 5) receiving treatment for a bee sting had such a significant reaction that EMS stopped the administration of dexamethasone and the patient only received 5 mg. In no case did the patient receive IV fluids or medications following the administration of dexamethasone. All patients remained hemodynamically stable without changes in their vital signs and the sensation spontaneously resolved in 1 to 10 minutes.

Group 2: Respiratory Distress

Three women with a history of asthma and/or COPD presented with shortness of breath and respiratory distress (Table 1). The patients were aged 43, 66, and 70 years. All 3 women were placed on cardiac monitors and started on a combination of albuterol and ipratropium nebulized solutions. Two of the women were also provided supplemental oxygen for hypoxia. All had IV access established and were subsequently given dexamethasone 10 mg IV. Two women immediately reported profound perineal burning and one reported whole-body burning. The 66-year-old woman (patient 7) was in rapid atrial fibrillation with a heart rate of 160 to 170 bpm prior to the dexamethasone administration and heart rate immediately increased to the 200s; however, her blood pressure and mentation remained normal and the tachycardia resolved without intervention within 10 minutes. One woman (patient 8) received diphenhydramine 50 mg IV following the reaction to dexamethasone given the provider's concern for a possible allergic medication reaction; however, she had no other allergic symptoms such as hives, facial swelling, itching, or worsening of her respiratory symptoms. Her symptoms fully resolved in several minutes.

DISCUSSION

This represents the first case series describing the adverse effect of perineal burning or a diffuse burning sensation immediately during or following IV dexamethasone administration in prehospital patients

receiving treatment for allergic reactions or respiratory distress associated with acute asthma or COPD exacerbations. Although all our patients did receive diphenhydramine or nebulized albuterol and ipratropium, we could not identify any reports in the literature of these medications being associated with burning or perineal irritation and can therefore conclude that this effect is associated with dexamethasone administration.

Dexamethasone-induced perineal burning and pruritus have been reported when the drug was given for postoperative nausea and vomiting during the induction of general anesthesia (8–12). Similar to our cases, these reports of dexamethasone-induced perineal pain or burning are in females, onset is immediate, and duration is short. Specifically, three separate reports describe an onset of 10 to 40 seconds and a duration of 30 seconds (8–10, 12). Three randomized prospective trials investigated the incidence of this adverse effect in both females and males when dexamethasone 8 mg IV was administered prior to the induction of general anesthesia for postoperative nausea and vomiting (10–12). Perron et al. randomized 20 patients (10 female and 10 male) and found an incidence of 100% and 30% in female and male patients, respectively (10). All described pain in the perineal region within 40 seconds of administration. Similarly, Singh et al. described the incidence of perineal pain in 17 of 30 (56.7%) females and 9 of 30 (30%) males and perineal pruritus in 23.3% and 16.7%, respectively (12). Severity of pain was quantified based on a 10-cm visual analog scale and severe pain (≥7) occurred in 8 of 17 (47%) female and 5 of 9 (55.6%) male patients. Another report described these symptoms as excruciating and very distressing, which is consistent with our providers' and patients' experiences of this adverse reaction to dexamethasone (8).

The largest evaluation of dexamethasone-induced perineal pain occurred in a prospective randomized trial of 200 patients (100 female and 100 male) (11). Within these groups, half received fentanyl 1 mcg/kg IV or placebo pretreatment followed by dexamethasone 8 mg IV 5 minutes later. Overall, the incidence and severity of pain was greater in females than in males. Perineal-region adverse effects were described as itching (62%), burning (13%), or both (25%). Pretreatment with fentanyl reduced the incidence of pain and also the severity and duration (11). Treatment with fentanyl 100 mcg and midazolam 2 mg was also associated with resolution of symptoms within 30 seconds in one report (8). However, it is difficult to conclude that these symptoms did not spontaneously resolve irrespective of pharmacologic intervention during this time frame given the short symptom duration without treatment in other reports.

There is no clear understanding of the association between dexamethasone and perineal irritation. It is thought to be related to the corticosteroid phosphate ester of dexamethasone sodium phosphate since this adverse effect has also been described with hydrocortisone-21-phosphate sodium and prednisolone phosphate, but not with other noncorticosteroid phosphate drugs (13). Further supporting this is that incidence and severity seem to increase as the corticosteroid organic phosphate concentration increases (9). The short duration of pain and irritation may represent the time required to hydrolyze the ester bond to dexamethasone and phosphate ions (13), and repeated administrations can also cause similar effects, suggesting this as a potential etiology (14). Unfortunately, there are no potential explanations for the predilection of female patients to have a higher incidence of this adverse reaction.

The incidence of dexamethasone-induced perineal irritation in our cases series is lower (2.7% overall; 4.9% in females) than described in the anesthesia literature (30%–100%) (10–12). As these other reports were prospective randomized trials in which investigators were specifically asking patients whether symptoms occurred, this could represent reporting bias. As providers in our system self-reported these events, our incidence likely represents a conservative estimate. To date, we are not aware of a case in our system in which a male has experienced these symptoms.

Given the conservative estimate of 1 in 20 women having this brief but extremely unpleasant adverse effect of dexamethasone administration, EMS systems may wish to adjust their protocols to reflect administering dexamethasone diluted and by slow IV infusion (13, 14). Specifically, one author recommends diluting in 50 mL of fluid and administering over 5 to 10 minutes (10). While there is a paucity of high-quality evidence regarding specific mechanisms to prevent this adverse reaction, the correlation of increased incidence of reactions with increased concentrations of the corticosteroid organic phosphate suggests that administration of a more diluted dose over a longer period of time may minimize these reactions. Changing to a dilution in 50 mL of fluid and administering over 5 to 10 minutes could also prevent the potential confounder in our administrations in which 1 mL of the 10-mg/mL concentration of dexamethasone could be inadvertently administered more quickly than currently recommended in our protocols (over 2 minutes). Our system is considering this change; however, its true effect on decreasing the incidence of this effect is unknown.

Conclusion

Dexamethasone-associated perineal irritation is a unique adverse effect that can be extremely unpleasant and disturbing to patients. Prehospital providers may be unaware of this reaction and it is important to recognize that it does not represent an allergic reaction; it is self-limiting and thankfully brief in

duration. Our series found that the prevalence was more common than initially recognized among female patients and diluting dexamethasone and infusing over a longer period may reduce its incidence and severity.

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