

ANAPHYLACTIC REACTION TO METHYLPREDNISOLONE

Author: Christy L. Ferrell, RN, CCRN, Richmond, VA

CE Earn Up to 8.0 CE Hours. See page 544.

The Centers for Disease Control and Prevention (CDC) reports that as of 2013, 22.6 million adults and children (7.3%) in the United States are living with asthma.¹ Acute asthma exacerbation is a presentation that is commonly seen in emergency departments, accounting for 2 million visits every year,² and it is ranked in the top 20 primary diagnosis groups in the 2011 National Hospital Ambulatory Medical Care Survey.³ The initial management of acute asthma exacerbation includes treatment with inhaled and systemic corticosteroids as the preferred initial drugs for symptom control.^{4,5}

Nurses administer methylprednisolone and other corticosteroids on a frequent basis in the acute care setting. Corticosteroids represent 3.1% of drugs given in emergency departments.³ Methylprednisolone is a steroid with both a greater anti-inflammatory potency and a lower risk of sodium and water retention than prednisolone.⁶ The majority of administrations of corticosteroids are without incident. However, this case report presents the rare incidence of a 51-year-old woman with asthma who responded with an anaphylactic reaction to methylprednisolone sodium succinate within minutes of intravenous (IV) administration.

Case Report

A 51-year-old woman presented to an emergency department in moderate respiratory distress. The patient's medical history included hypertension and asthma, and she had multiple previous ED visits for respiratory symptoms that had been effectively managed with nebulizer treatments of albuterol, albuterol-ipratropium, and IV methylprednisolone.

It is of note that the hospital carries only trade name medications, and the brand of methylprednisolone carried by the facility has not changed in more than 10 years. The patient had received this formulation of methylprednisolone at least 6 previous times. For this occurrence, the physician ordered the same treatment regimen as had been given before, including albuterol-ipratropium nebulizer treatments and IV methylprednisolone.

The patient received IV methylprednisolone, 125 mg over 60 seconds. Within minutes of administration, the patient reported itching and burning of the throat, followed by throat swelling. Epinephrine, diphenhydramine, and supplemental oxygen were immediately administered. However, the patient quickly progressed into severe respiratory distress requiring intubation, and she became hypotensive. A normal saline solution bolus was ordered and successfully treated the hypotension. Further treatment consisted of administration of lorazepam and magnesium sulfate. Extubation of the patient was performed the following morning, and hospital discharge occurred a day later. The consensus of the physicians on the patient's treatment team is that this patient experienced a reaction directly related to the methylprednisolone administration. The patient's documented allergies now include methylprednisolone, and the patient is aware of this allergy. However, she has not proceeded with any type of allergy testing that would determine the culprit allergen with any further certainty.

Literature Review

The term *anaphylaxis* has had many criteria in the past, but at the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium, Sampson and colleagues gave a definition that is now widely accepted.⁷ Anaphylaxis is present when 1 of the 3 following conditions exist. First, acute onset of the illness occurs with the involvement of skin and mucosal tissues with either respiratory compromise and/or decreased blood pressure and symptoms of end-organ dysfunction.⁷ Second, two or more rapidly occurring clinical manifestations are present after exposure of the allergen: involvement of

Christy L. Ferrell, member, ENA Chapter 118, is Registered Nurse, Emergency Department, Bon Secours Richmond Community Hospital, Richmond, VA. For correspondence, write: Christy Ferrell, RN, CCRN, Emergency Department, Bon Secours Richmond Community Hospital, 1500 N 28th St, Richmond, VA 23223; E-mail: Christy_Ferrell@bshsi.org.

J Emerg Nurs 2015;41:470-3.

Available online 18 August 2015

0099-1767

Copyright © 2015 Emergency Nurses Association. Published by Elsevier Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.jen.2015.06.010>

skin-mucosal tissue, respiratory compromise, decreased blood pressure, and persistent gastrointestinal symptoms.⁵ Third, blood pressure decreases after exposure to known allergens. In adults, the systolic blood pressure is <90 mm Hg.⁷

Doezema⁸ reports the case of a 27-year-old man who experienced respiratory arrest after administration of IV methylprednisolone sodium succinate. In subsequent allergy testing, the patient had positive tests for both methylprednisolone sodium succinate and hydrocortisone sodium succinate, but not to methylprednisolone acetate. The patient received a challenge with dexamethasone phosphate without further adverse events.⁸

Schonwald⁹ presents the case of a 17-year-old male patient with a history of asthma since he was 6 years old. This patient received IV methylprednisolone, and within 3 to 4 minutes, he experienced flushing, difficulty breathing, and generalized hives and required intubation. Shortly after the intubation, the patient experienced bradycardia, asystole, and a seizure. In this case, Schonwald⁹ attributes the adverse reaction to a rapid rate of administration: "125 mg Solu-Medrol over 15 or 30 seconds."

Moreno Escobosa et al¹⁰ report the case of a 32-year-old woman who had a reaction to an allergy vaccine, which worsened after administration of IV methylprednisolone hemisuccinate. This patient underwent both intradermal skin tests and intramuscular challenge to determine hypersensitivity to methylprednisolone. Intradermal skin test results were negative. However, within minutes of intramuscular challenge, the patient experienced itching of the throat, eyes, and nose, dry cough, and hives on both arms, requiring treatment with intramuscular epinephrine.¹⁰

Saito and colleagues¹¹ report the case of a 22-year-old man who received IV methylprednisolone, 500 mg, dissolved in 10 mL of normal saline solution in preparation for renal transplantation surgery. Within minutes, the patient experienced tachycardia, profound hypotension, and acidosis. The surgical preparations ceased until the patient recovered with administration of IV epinephrine and norepinephrine. Saito and colleagues recommend that transplant patients undergo skin testing for methylprednisolone prior to transplant to avoid reactions and indicate that lower administration rates and dosages are key in preventing severe reactions.¹¹

Walker et al¹² present the cases of 2 patients who both experienced immediate-type hypersensitivity reactions to corticosteroids. Both of these patients underwent subsequent allergy testing. Based on the history and test results of the patients, Walker and colleagues indicated that the diagnosis of immediate-type hypersensitivity to certain corticosteroids is likely to have an immunological basis.¹² These investigators

further state that the hypersensitivity was restricted to succinylated compounds, noting that various corticosteroids without a succinate attached were well tolerated during testing.¹² Walker et al¹² go on to discuss the possibility that patients who have immediate-type hypersensitivity reactions to corticosteroids may also have the same type of reaction to succinylated noncorticosteroid compounds. Walker and colleagues emphasize the importance of being alert to the possibility of these reactions and suggest that patients undergo allergy testing to identify the culprit compound.¹²

The Food and Drug Administration (FDA) maintains a voluntary database for reporting adverse drug events, but facilities and practitioners are not required to report an adverse drug reaction to the FDA.¹³ The FDA provided information in response to a query regarding adverse reactions to methylprednisolone. The recorded events are not specific to the form or route of the drug. An event tally report from January 1, 2004, to October 31, 2014, indicates a total of 7426 cases reported for methylprednisolone. Of these cases, there were 34 reported events (0.4%) of anaphylactic reaction, 6 reported events (0.1%) of anaphylactoid reactions, and 10 reported events (0.1%) of anaphylactic shock.¹³

Pfizer, the manufacturer of Solu-Medrol (methylprednisolone sodium succinate), indicated that as of September 30, 2014, spontaneous reports of anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and drug hypersensitivity have been received but that they are unable to calculate the incidence of these events or associated drug risk (C. Piperni, BPharm, written communication, December 2014).

Pathogenesis

It is clear that the same corticosteroids used to treat allergic reactions can also elicit them. Considering that corticosteroids are well known to have anti-inflammatory properties, Vatti et al¹⁴ offer several explanations for such a paradoxical response to these drugs. Typically, reactions to systemic corticosteroids can be classified as anaphylactic (allergic) or anaphylactoid (non-IgE-mediated). Both types of reactions present with clinical manifestations of urticaria, wheezing, shortness of breath, angioedema, hypotension, and/or abdominal pain.¹⁴ The anaphylactic response, more commonly known as the antigen-antibody or allergic response, involves a sensitization process.¹⁴ The position of the C21 hydrocortisone molecule in aqueous solution breaks down into a glyoxal, which is capable of bonding with the guanidino groups of arginine.¹⁴ This molecule further bonds with proteins, resulting in an immunologic agent capable of inducing an allergic reaction in re-exposed

individuals.¹⁴ When this process happens, the typical immune response is mediated by IgE antibodies, IgG antibodies, or memory T-lymphocytes.¹⁴ Once the number of antibodies are sufficient, mast cells are activated, resulting in the release of mediators such as histamine, leukotrienes, eosinophil chemotactic factor of anaphylaxis, neutrophil chemotactic factor of anaphylaxis, tryptase, and platelet-activating factor.¹⁴ Vatti et al¹⁴ note that sensitization through one route of administration does not eliminate the possibility of reaction if antigen exposure occurs through another route. Conversely, Vatti et al¹⁴ suggest that anaphylactoid, or nonallergic, hypersensitivity reactions to corticosteroids elicit minute involvement from the immune system. It is believed that the components of the immune system (mast cells, basophils, and the complement cascade) are directly activated by the exposure to the corticosteroids, and the inhibition of the cyclooxygenase pathway is the means of activation.¹⁴

Implications for Nursing Practice

Nurses frequently administer methylprednisolone, along with other corticosteroids, in the emergency department and other acute care areas.³ Although rare, an anaphylactic reaction to this drug is life threatening if it occurs. Therefore, it is vital for nurses to implement practices that minimize patient mortality in the case of such events.

REVIEW AND ADVOCATE

The nurse's diligence in performing a review of the patient's medical history, including a review of drug allergies, is vital to understanding how to care for the patient in a life-threatening situation. When patients do not know the name of a medication that they believe they are allergic to, nurses should attempt to obtain medical records from the facility where the reaction occurred. It is crucial to know if a patient has had a significant reaction to a succinylated medication before administering methylprednisolone sodium succinate. Not all forms of methylprednisolone, or other corticosteroids, have succinylated compounds attached. For example, if a patient has a known allergy to erythromycin ethylsuccinate, the nurse can advocate for a nonsuccinylated corticosteroid such as dexamethasone sodium phosphate rather than methylprednisolone sodium succinate in hopes of preventing another reaction if the succinate ester is the allergen culprit.¹² However, a lack of succinate ester on the corticosteroid does not entirely eliminate the possibility of a reaction. The Coopman (ABCD) system, validated by Baeck et al., provides a means of dividing corticosteroids into categories by molecular structure in order to display

cross-reactivity between them.^{14,15} Although it is well beyond the scope of the nurse to determine which medication serves as the best alternative for a particular corticosteroid, the Coopman system provides guidance to pharmacists or physicians who are faced with these challenging situations.

EARLY RECOGNITION AND IMMEDIATE ACTION

The nurse's ability to recognize small symptoms as an indicator of a much larger process is vital to the patient's survival in an anaphylactic reaction. In the case presented, the patient first reported pharyngeal itching and burning, which were not present prior to administration of the medication. Active listening by the nurse is essential to detect and act on these critical cues. When a nurse recognizes even subtle signs of a medication reaction, or is concerned that the patient has had a change, she should activate the hospital's Rapid Response Team and immediately notify the physician.¹⁶ If the patient continues to deteriorate, the nurse should activate the code team and be prepared to perform emergency interventions.

MANAGEMENT

The nurse must remain vigilant in observing the patient for a reaction after administration of IV methylprednisolone. The half-life of methylprednisolone ranges from 1.8 to 5.2 hours, but the therapeutic action of the drug can be expected to peak in 30 to 60 minutes from the time of administration.¹⁷ In this report, as well as in the other case reports reviewed, the chain of events that took place all happened within minutes after the administration of IV methylprednisolone sodium succinate or methylprednisolone hemisuccinate.⁷⁻¹² Patients receiving IV medications should remain under medical supervision for at least 20 minutes after administration. In the event of a suspected anaphylactic or anaphylactoid reaction, along with notifying the physician and engaging help, priority management is to control airway, breathing, and circulation. The ideal position of the patient is supine with the legs elevated. If this position is limited by the patient's respiratory status, the position should be modified to accommodate breathing. Supplemental oxygen should be administered. An accurate weight, if not already documented, should also be obtained, along with frequent vital signs. Epinephrine administration should occur simultaneously with the aforementioned procedures. For adults, subcutaneous or intramuscular administration is acceptable, and dosing is 0.3 to 0.5 mL (0.3 to 0.5 mg) of a 1:1000 solution. If a patient is extremely hypotensive, the first choice of treatment is rapid

infusion of a large volume (1000 to 2000 mL) of a crystalloid solution such as lactated Ringer's or normal saline solution. If IV fluid is ineffective at correcting hypotension, vasopressors may be considered. An important caveat to consider here is the hypotensive patient who is also receiving treatment with a β -adrenoceptor antagonist for baseline hypertension. In this case, the patient may require up to 7 L of fluid and glucagon administration may need to be considered for inotropic and chronotropic effects. The glucagon dose is 1 to 5 mg IV, according to response. This dose may be followed by a continuous IV infusion of 5 to 15 mcg per minute titrated to response. The cardiac effects of glucagon are seen as early as 1 minute after the start of infusion and are maximized at 15 minutes of infusion. Histamine receptor antagonist therapies are also recommended for treatment of anaphylaxis but are not considered lifesaving or a priority treatment. Clinical studies have demonstrated that a dual combination therapy of histamine H_1 and H_2 is more effective than either one alone. If wheezing persists after administration of the aforementioned treatments, consideration may be given to aerosolized β -adrenoceptor antagonists and aminophylline. After stabilization, the patient needs to be observed for at least 2 hours for mild reactions and at least 24 hours for severe reactions, given that biphasic episodes of anaphylaxis can occur and further treatment may be required.

Conclusion

This case presentation demonstrates an example of a rare anaphylactic reaction to methylprednisolone. An interesting aspect of this case is that no deviations from the manufacturer-recommended administration occurred to which the adverse event could be attributed. The dose of the drug was not high, and administration occurred over 60 seconds, which exceeds the 30-second recommendation by Pfizer.^{6,18} The patient previously had IV methylprednisolone prior to this event and responded with demonstrated improvement in her condition, and without incident. Although the patient in this case did not proceed with allergy testing because of limited financial resources, the physicians involved concluded that the safest approach would be to document methylprednisolone sodium succinate as an allergy and not administer it to her again. This case is one of the few case reports in the literature of the occurrence of anaphylaxis after administration of methylprednisolone sodium succinate. The scarcity of these case reports, combined with the small number of anaphylactic-type events recorded by the FDA, demonstrates that anaphylaxis is indeed an uncommon occurrence with methylprednisolone sodium succinate. Although rare, these phenomena are real and

potentially life threatening. Nurses must remain vigilant, quickly recognize such a situation, and intervene immediately to facilitate optimum patient outcomes.

REFERENCES

- Centers for Disease Control and Prevention. Most recent asthma data: prevalence. http://www.cdc.gov/asthma/most_recent_data.htm. Updated April 23, 2015. Accessed July 23, 2015.
- Asthma and Allergy Foundation of America. Asthma facts and figures. <https://www.aafa.org/display.cfm?sub=42&cid=8>. Accessed July 23, 2015.
- Centers for Disease Control and Prevention. National hospital ambulatory medical care survey: 2011 emergency department summary tables. http://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2011_ed_web_tables.pdf. Published 2011. Accessed July 23, 2015.
- National Heart, Lung, and Blood Institute, & National Institute of Health. Asthma care quick reference: diagnosing and managing asthma. http://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf. Revised September 2012. Accessed July 23, 2015.
- Albertson T, Sutter M, Chan A. The acute management of asthma. *Clin Rev Allergy Immunol*. 2015;48(1):114-125.
- Solu-Medrol [package insert], New York, NY: Pfizer; 2013.
- Lee J, Vadas P. Anaphylaxis: mechanisms and management. *Clin Exp Allergy*. 2011;41(7):923-938.
- Doezema D. Anaphylaxis following administration of intravenous methylprednisolone sodium succinate. *Am J Emerg Med*. 1987;5(1):42-44.
- Schonwald S. Methylprednisolone anaphylaxis. *Am J Emerg Med*. 1999;17(6):583-585.
- Moreno Escobosa M, Cruz Granados S, Moya Quesada M, Amat López J. Anaphylaxis due to methylprednisolone. *J Invest Allergol Clin Immunol*. 2008;18(5):407-408.
- Saito R, Moroi S, Okuno H, Ogawa O. Anaphylaxis following administration of intravenous methylprednisolone sodium succinate in a renal transplant recipient. *Int J Urol*. 2004;11(3):171-174.
- Walker A, R  wer H, Sieber W, Przybilla B. Immediate-type hypersensitivity to succinylated corticosteroids. *Int Arch Allergy Immunol*. 2011;155(1):86-92.
- Food and Drug Administration. Center for Drug Evaluation and Research Event Tally Report: methylprednisolone, 1/1/2004 to 10/31/2014, Silver Spring, MD: Food and Drug Administration; 2014.
- Vatti R, Ali F, Teuber S, Chang C, Gershwin M. Hypersensitivity reactions to corticosteroids. *Clin Rev Allergy Immunol*. 2014;47(1):26-37.
- Drain K, Volcheck G. Preventing and managing drug-induced anaphylaxis. *Drug Saf*. 2001;24(11):843-853.
- Baeck M, Chemelle J, Goossens A, Nicolas J, Terreux R. Corticosteroid cross-reactivity: clinical and molecular modelling tools. *Allergy*. 2011;66:1367-1374.
- Thomas K, Force M, Rasmussen D, Dodd D, Whildin S. Rapid response team: challenges, solutions, benefits. *Crit Care Nurse*. 2007;27(1):20-28.
- Pfizer New Zealand Ltd.. Data sheet, Solu-Medrol and Solu-Medrol Act-O-Vial (methylprednisolone sodium succinate). <http://www.medsafe.govt.nz/profs/datasheet/s/Solumedrolinj.pdf>. Published January 22, 2015. Accessed July 23, 2015.