CASE REPORT

Worsening of Asthma with Systemic Corticosteroids

A Case Report and Review of Literature

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Despite widespread use for treatment of asthma and allergies, glucocorticoids may cause allergic reactions, even anaphylaxis. The incidence of adverse reactions to systemic glucocorticoids is 0.3%. The most commonly reported corticosteroids causing anaphylaxis like reactions are hydrocortisone, prednisone, and methylprednisolone. Most authors agree that allergic reactions to systemic corticosteroids are possibly immunoglobulin E mediated. We report a patient with asthma, aspirin allergy, and nasal polyps who developed bronchospasm following the administration of intravenous methylprednisolone sodium succinate during an acute asthmatic attack. We discuss the differential diagnosis of worsening asthma despite adequate treatment, and suggest corticosteroid-induced bronchospasm in our patient. Corticosteroid-induced bronchospasm should be considered when asthmatics fail to improve, or frankly deteriorate with systemic corticosteroid therapy, particularly when a history of aspirin allergy is present.

Teaching Point:

- Know the differential diagnosis for worsening of asthma despite adequate treatment.
- Consider corticosteroid-induced bronchospasm when asthmatics fail to improve, or frankly deteriorate with systemic corticosteroid therapy.
- Corticosteroid-induced bronchospasm is more commonly seen in asthmatics with a history of aspirin allergy.

KEY WORDS: allergy; asthma; corticosteroids.

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Despite widespread use for treatment of asthma and allergies, glucocorticoids may cause allergic reactions, even anaphylaxis. Sams and Smith¹ first described steroid-induced anaphylactic reactions and contact hypersensitivity in the 1950s. To date, allergic reactions have been reported with intramuscular,² intraarticular,^{3,4} periarticular,⁵ intralesional,^{6–8} oral,⁷ inhalational,^{9,10} and intravenous¹¹ routes of glucocorticoid administration. Type 4 (delayed) allergic reactions to topically applied glucocorticoids are frequently observed (2.9%).¹² However, type 1 (immediate) allergic reactions to systemic glucocorticoids are very rare (0.3%).² The most commonly reported corticosteroids causing anaphylaxis-like reactions are hydrocortisone, prednisone, and methylprednisolone. We report a patient with asthma, aspirin aller-

gy and nasal polyps who developed bronchospasm following the administration of intravenous methylprednisolone sodium succinate during an acute asthma attack.

CASE REPORT

A 64-year-old man with history of severe persistent asthma, aspirin allergy, diabetes, and hypercholesterolemia presented to the Emergency Department with a 2-week history of worsening dyspnea, wheezing, and productive cough. In the past, his asthma attacks were treated with intravenous hydrocortisone methyl succinate and oral prednisone. He was diagnosed with acute asthma exacerbation, and treatment started with nebulized albuterol, ipratropium, and intravenous infusion of methylprednisolone sodium succinate. Five minutes after the steroid infusion was started he developed diaphoresis with worsening dyspnea and wheezing. Physical examination revealed a heart rate of 140 beats per minute and diffuse loud wheezing throughout a prolonged expiratory phase. Steroid infusion was stopped promptly and his condition improved within 15 minutes without any additional intervention. Blood analysis showed a total white blood cell count of 6,800 cells per cubic millimeter (cmm) with 14% eosinophils. Chest radiograph revealed marked hyperinflation without any infiltrates. Electrocardiogram showed sinus tachycardia. Computerized tomogram of the sinuses showed polyposis and sinusitis. After recovering from this event, he was treated with oral prednisone without any adverse reactions, and discharged after 2 days of hospitalization. The patient was scheduled for an intradermal skin test with different steroids, but was lost to follow-up.

DISCUSSION

Acute asthma is a medical emergency. Goals of treatment include maintenance of adequate arterial oxygen saturation with supplemental oxygen, relief of airflow obstruction with rapid acting inhaled bronchodilators, and reduction of airway inflammation with systemic corticosteroids. Failure to respond to reasonable treatment, or decline despite appropriate treatment is a diagnostic dilemma. The differential diagnosis in such a scenario is summarized in the Table 1. Although skin prick test (SPT) could not be performed to confirm the diagnosis in our patient, we strongly suspect steroid-induced bronchospasm as he had worsening symptoms after administration of methylprednisolone sodium succinate, and prompt relief of symptoms on discontinuation of the steroid infusion.

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Table 1. Conditions That Can Cause Failure of Response, or Worsening of Symptoms Despite Standard Asthma Treatment

Pulmonary
Pneumothorax
Infection (pneumonia, bronchiectasis)
Respiratory muscle fatigue
Worsening hypoxia and/or hypercapnea
Vascular/cardiovascular
Pulmonary embolism
Congestive heart failure
Cardiac ischemia or arrhythmia
Metabolic
Electrolyte imbalance (hypokalemia, hypophosphatemia, etc.)
Other
Continuing exposure to allergen
Upper airway obstruction
Hyperventilation with panic attacks
Adverse drug reaction (aspirin, steroids, ACEi)
Steroid-unresponsive asthma (steroid-resistant asthma)

ACEi, angiotensin converting enzyme inhibitor.

Severe allergic reactions including anaphylaxis and death caused by systemic glucocorticoid have been reported over the past decades.^{13–21} Corticosteroid allergy is more commonly seen in patients with asthma and aspirin allergy with or without nasal polyps.^{20,22–24} The triad of nasal polyps, bronchial asthma, and aspirin allergy is seen in up to 3% of all asthmatics, and up to 20% of patients with severe asthma.²³ This could be because of the diversion of arachnidonic acid metabolism from the cyclo-oxygenase pathway to the 5-lipoxygenase pathway because of inhibition of cyclo-oxygenase by aspirin.²³

Most authors agree that allergic reactions to systemic corticosteroids are possibly immunoglobulin (IgE) mediated.¹⁵ The pathomechanism has, however, not been conclusively elucidated, and it is most likely that the pathogenesis is not homogenous. Pryse-Phillips et al.²⁵ demonstrated the presence of IgE (antibodies) to methylprednisolone in a patient with anaphylactic reaction after infusion of methylprednisolone. Ventura et al.²⁶ hypothesized that this mechanism is probably because of the formation of steroid glyoxal, a cortisol degradation product, which in an aqueous solution may be responsible for the presentation of the steroid carbon rings to the body immune system as a hapten. Succinate esters of hydrocortisone and methylprednisolone are the drugs that are most frequently responsible for type 1 (immediate) allergic reactions to systemic corticosteroids.¹⁷ Freedman et al.¹³ proposed that the immunogenic role of succinate esters could be attributed to their greater solubility in water, and to their higher affinity to serum proteins; thus changing the presentation of the steroid molecule from a hapten to a complete antigen. Wilkinson et al.²⁷ further demonstrated different affinities of hydrocortisone acetate, hydrocortisone sodium phosphate, and hydrocortisone sodium succinate to serum and cutaneous proteins. An independent immunologic potential of the esters have also been proposed.^{15,28} Patterson et al.²⁹ reported anaphylaxis induced by the carboxymethylcellulose component of an injectable steroid suspension.

Clinical manifestation of immediate reactions to corticosteroids includes urticaria, pruritus, sneezing, nausea, vomiting, dyspnea, bronchospasm, angio-oedema, hypotension, decreased consciousness, respiratory arrest, anaphylaxis, and even death. Bronchospasm is generally observed within

5 minutes of intravenous steroid administration in a dose-dependent fashion, and is most frequently observed with hydrocortisone sodium succinate and methylprednisolone sodium succinate.²³

SPT and in vitro measurement of IgE levels are generally used for confirming the allergic reaction to steroids. However, the efficient radioallergosorbent testing for specific IgE to cortisol and related compounds is lacking.³⁰ Treatment of corticosteroid hypersensitivity includes avoidance of causative drugs. Topical corticosteroids have been classified into four groups on the basis of chemical structure and cross-sensitivity; however, this classification does not seem to apply for immediate-type adverse reactions to systemic glucocorticoids.^{17,31} This would explain in part why our patient developed an allergic reaction to methylprednisolone preparation when he had tolerated systemic hydrocortisone and prednisone in the past. Because of strong possibility of cross-reactivity between hydrocortisone, methylprednisolone and prednisone, Ventura et al.²⁶ recommended avoidance of hydrocortisone, methylprednisolone, and prednisone in any formulation (succinate, acetate, or sodium phosphate) in patients with allergic reaction to systemic steroids. They suggested the emergency use of betamethasone and deflazacort as an alternative in such patients; however, intravenous forms of these medications are not available in United States. Dexamethasone has been suggested as an alternative in such patients²⁴; however, careful challenge testing would be the best way to identify glucocorticoids that are safe options for future therapy.^{32,33}

CONCLUSIONS

Corticosteroid-induced bronchospasm should be considered when asthmatics fail to improve or frankly deteriorate with systemic corticosteroid therapy, particularly when a history of aspirin allergy is present. Skin testing may be the best guide to safe alternative corticosteroid preparations in such patients.

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REFERENCES

1. Sams WM, Smith JG Jr. Contact dermatitis due to hydrocortisone ointment; report of a case of sensitivity to emulsifying agents in a hydrophilic ointment base. *J Am Med Assoc.* 1957;164:1212–3.
2. Borja JM, Galindo PA, Feo F, et al. Urticaria to methylprednisolone sodium hemisuccinate. *Allergy.* 2001;56:791.
3. Karsh J, Yang WH. An anaphylactic reaction to intra-articular triamcinolone: a case report and review of the literature. *Ann Allergy Asthma Immunol.* 2003;90:254–8.
4. Mace S, Vadas P, Pruzanski W. Anaphylactic shock induced by intra-articular injection of methylprednisolone acetate. *J Rheumatol.* 1997;24:1191–4.
5. Capdevielle P, Legros P, Darie H, et al. Shock following periarticular infiltration of methylprednisolone acetate. *Presse Med.* 1984;13:620–1.
6. Saff DM, Taylor JS, Vidimos AT. Allergic reaction to intralesional triamcinolone acetonide: a case report. *Arch Dermatol.* 1995;131:742–3.
7. Rasanen L, Hasan T. Allergy to systemic and intralesional corticosteroids. *Br J Dermatol.* 1993;128:407–11.
8. Lauerman AI. Screening for corticosteroid contact sensitivity. Comparison of tixocortol pivalate, hydrocortisone-17-butyrate and hydrocortisone. *Contact Dermatitis.* 1991;24:123–30.
9. McGivern DV, MacFarlane JT. Severe bronchoconstriction after inhalation of budesonide. *BMJ (Clin Res Ed).* 1984;288:447.

10. **Derrick EK, Price ML.** Contact dermatitis to pulmicort inhaler. *Br J Dermatol.* 1995;133:41.
11. **Mendelson LM, Meltzer EO, Hamburger RN.** Anaphylaxis-like reactions to corticosteroid therapy. *J Allergy Clin Immunol.* 1974;54:125-31.
12. **Dooms-Goossens A, Andersen KE, Brandao FM, et al.** Corticosteroid contact allergy: an EECDRG multicentre study. *Contact Dermatitis.* 1996;35:40-4.
13. **Freedman MD, Schocket AL, Chapel N, et al.** Anaphylaxis after intravenous methylprednisolone administration. *JAMA.* 1981;245:607-8.
14. **Escribano-Rodriguez MM, Gonzalez-Pol J, Munoz-Bellido FJ, et al.** Immediate reaction to methylprednisolone with tolerance of other corticosteroids. *Allergy.* 1997;52:677-8.
15. **Burgdorff T, Venemalm L, Vogt T, et al.** IgE-mediated anaphylactic reaction induced by succinate ester of methylprednisolone. *Ann Allergy Asthma Immunol.* 2002;89:425-8.
16. **Saito R, Moroi S, Okuno H, et al.** Anaphylaxis following administration of intravenous methylprednisolone sodium succinate in a renal transplant recipient. *Int J Urol.* 2004;11:171-4.
17. **Kamm GL, Hagmeyer KO.** Allergic-type reactions to corticosteroids. *Ann Pharmacother.* 1999;33:451-60.
18. **Butani L.** Corticosteroid-induced hypersensitivity reactions. *Ann Allergy Asthma Immunol.* 2002;89:439-45; quiz 445-6, 502.
19. **Thompson JF, Chalmers DH, Wood RF, et al.** Sudden death following high-dose intravenous methylprednisolone. *Transplantation.* 1983;36:594-6.
20. **Partridge MR, Gibson GJ.** Adverse bronchial reactions to intravenous hydrocortisone in two aspirin-sensitive asthmatic patients. *BMJ.* 1978;1:1521-2.
21. **Doezema D.** Anaphylaxis following administration of intravenous methylprednisolone sodium succinate. *Am J Emerg Med.* 1987;5:42-4.
22. **Preuss L.** Allergic reactions to systemic glucocorticoids: a review. *Ann Allergy Asthma Immunol.* 1985;55:772-5.
23. **Judson MA, Sperl PL.** Status asthmaticus with acute decompensation with therapy in a 27-year-old woman. *Chest.* 1995;107:563-5.
24. **Dajani BM, Sliman NA, Shubair KS, et al.** Bronchospasm caused by intravenous hydrocortisone sodium succinate (Solu-Cortef) in aspirin-sensitive asthmatics. *J Allergy Clin Immunol.* 1981;68:201-4.
25. **Pryse-Phillips WE, Chandra RK, Rose B.** Anaphylactoid reaction to methylprednisolone pulsed therapy for multiple sclerosis. *Neurology.* 1984;34:1119-21.
26. **Ventura MT, Calogiuri GF, Matino MG, et al.** Alternative glucocorticoids for use in cases of adverse reaction to systemic glucocorticoids: a study on 10 patients. *Br J Dermatol.* 2003;148:139-41.
27. **Wilkinson M, Hollis S, Beck M.** Reactions to other corticosteroids in patients with positive patch test reactions to budesonide. *J Am Acad Dermatol.* 1995;33:963-8.
28. **Fernandez S, Reano M, Vives R, et al.** 6-Methylprednisolone-induced bronchospasm. *Allergy.* 1997;52:780-2.
29. **Patterson DL, Yunginger JW, Dunn WF, et al.** Anaphylaxis induced by the carboxymethylcellulose component of injectable triamcinolone acetonide suspension (Kenalog). *Ann Allergy Asthma Immunol.* 1995;74:163-6.
30. **Rasanen L, Tarvainen K, Makinen-Kiljunen S.** Urticaria to hydrocortisone. *Allergy.* 2001;56:352-3.
31. **Dooms-Goossens A, Morren M.** Results of routine patch testing with corticosteroid series in 2073 patients. *Contact Dermatitis.* 1992;26:182-91.
32. **Asakawa H, Araki T, Imai I, et al.** Skin tests of steroid allergy. *Allergy.* 1999;54:645-6.
33. **Erdmann SM, Abuzahra F, Merk HF, et al.** Anaphylaxis induced by glucocorticoids. *J Am Board Fam Pract.* 2005;18:143-6.

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