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Anaphylaxis Caused by Benzalkonium in a Nebulizer Solution

Benzalkonium chloride (BAC) is commonly used as a bactericidal preservative in nebulizer solutions, and can cause paradoxical bronchoconstriction following nebulizing therapy in some asthmatics. We describe a case of anaphylactic shock in a 23-yr-old asthmatic woman following an intradermal skin test with a salbutamol solution containing BAC. Since she complained of cough and dyspnea after inhalation therapy with a nebulizer solution, we conducted an intradermal skin test using the same solution, which contained BAC. About 10 min later, the patient reported dizziness, palpitations, and dyspnea. On examination, tachycardia, tachypnea, and hypotension were found. She was resuscitated with a subcutaneous injection of epinephrine and an infusion of saline. One month later, we conducted a bronchial provocation test with BAC, and she showed a positive response.

Key Words : *Anaphylaxis; Preservatives, Pharmaceutical; Skin Tests; Adrenergic beta-agonist*

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INTRODUCTION

Nebulizer solutions are widely used in the treatment of asthma and chronic obstructive pulmonary disease. A number of bronchial and nasal nebulizer preparations contain benzalkonium chloride (BAC) (1). Quaternary ammonium compounds are used as antiseptics, disinfectants, detergents, and preservatives, and of these BAC is the most frequently used. BAC-induced contact allergy and bronchoconstriction have been documented (2). We report a 23-yr-old woman presenting with anaphylactic shock following an intradermal skin test with a nebulizer solution containing BAC. As far as we could ascetain from available literatures, this is the first reported case of anaphylaxis caused by benzalkonium in a nebulizer solution.

CASE REPORT

A 23-yr-old woman who had complained of exacerbation of cough and dyspnea after inhalation therapy with a nebulizer solution was referred to our outpatient clinic. She had been diagnosed with asthma 3 yr previously and treated with a metered dose of a short-acting b2-agonist inhaler as needed. She had no history of anaphylaxis, urticaria, or drug allergy.

On admission, a complete blood count, blood chemistry, and serologic tests were normal. Chest radiographs revealed no abnormalities. Her white cell count was 7,400/μL with 5% eosinophils and the serum total IgE was 256 IU/mL by the EIA method. On spirometry, her forced vital capacity and forced expiratory volume in 1 sec were 3,520 mL (90% of the predicted value) and 2,700 mL (86% of the predicted value), respectively. She underwent skin prick tests with a panel of 10 common inhalant allergens and histamine (Allergopharma Co., Hamburg, Germany) and serial dilution of nebulizer solution containing BAC (Ventolin®, GlaxoSmithKlein, U.K.). The skin prick test was positive only for house dust mites species (*Dermatophagoides farinae* and *D. pteronyssinus*). Subsequently, an intradermal skin test with a serial dilution of her nebulizer solution was performed. A positive reaction was observed with 1:10 solution (wheal: 4×5 mm in diameter, flare: 18×20 mm). About 10 min later, she presented with dizziness, palpitations, and dyspnea. Her blood pressure was 70/30 mmHg, and her pulse was 120-140 per minute. Electrocardiography showed no abnormal findings, except for tachycardia. She was resuscitated with a subcutaneous injection of epinephrine (0.5 mg), an intravenous infusion of saline, and oxygen. She recovered fully 3 hr later. After obtaining oral informed consent, two healthy women without atopy or allergies underwent intradermal skin tests with the same nebulizer solution. Both control subjects were negative on tests. One month later, we conducted a bronchial provocation test with BAC following the method used by Asmus et al. (1). The patient inhaled 3 mL of 0.9% NaCl solution containing 600 μg of BAC (benzalkonium chloride, Sigma, St. Louis, U.S.A.). The solutions were prepared using aseptic techniques and stored at 2°C in an Eppendorf tube. The solutions were allowed to warm to room temperature immediately before use. Each 3 mL dose was inhaled using normal tidal breathing through a DeVilbiss 646 nebulizer (DeVil-

biss Co., Somerset, PA, U.S.A.). Spirometry was performed at the beginning of the test and 15 min after inhalation of each dose began. On BAC bronchial challenge, a drop in FEV_1 of 23% was noted after inhalation of 1,800 μg BAC. The patient refused skin test with BAC since she was aware of her anaphylactic reaction.

DISCUSSION

This patient's history and the results of the skin test and BAC bronchial provocation test are consistent with anaphylaxis caused by a nebulizer solution containing BAC. Our case showed a positive skin test to nebulizer solution and developed an anaphylactic reaction. This nebulizer solution contained salbutamol and BAC. Although a positive bronchial provocative response to BAC is not specific to diagnosis of BAC-induced anaphylaxis, the immediate development of symptoms and bronchoconstriction in response to BAC were significant in this case. This result suggested BAC-induced anaphylaxis.

BAC is one of the best known etiologic causes of contact dermatitis and occupational asthma. It is found in cosmetics, soaps, baby lotions, body lotions, and skin care products, as well as in medical products, such as eye drops, ointments, and solutions. Some bronchial nebulizer solutions contain BAC as a bactericidal preservative, and it causes paradoxical bronchoconstriction in some asthmatics when inhaled. The mechanism of the allergic reaction caused by BAC and other chemicals remains controversial (3). The previous reports on BAC-induced asthma suggest that it induces anaphylaxis via either IgE-mediated or non-IgE mediated mechanisms. Our case showed a positive intradermal test, suggesting that an IgE-mediated mechanism played a role in causing the reaction. However, this does not exclude the possibility that BAC also causes non-specific histamine release from mast cells via surface activation. This is supported by previous reports of dose-dependant histamine release from rat mast cells, and antihistamine inhibition of the bronchoconstriction caused by BAC (4, 5). In conclusion, our patient had an anaphylactic reaction caused by the intradermal injection of benzalkonium chloride in her nebulizer solution. Although this is not a common complication, such reactions may occur in patients treated with nebulized solutions containing BAC.

REFERENCES

1. Asmus MJ, Barros D, Liang J, Chesrown SE, Hendeles L. *Pulmonary function response to EDTA, an additive in nebulized bronchodilators. J Allergy Clin Immunol 2001; 107: 68-72.*
2. Bernstein JA, Stauder T, Berstein DI, Bernstein IL. *A combined respiratory and cutaneous hypersensitivity syndrome induced by work exposure to quaternary amines. J Allergy Clin Immunol 1994; 94: 257-9.*
3. Purohit A, Kopferschmitt-Kubler MC, Moreau C, Popin E, Blaumeiser M, Pauli G. *Quaternary ammonium compounds and occupational asthma. Int Arch Occup Environ Health 2000; 73: 423-7.*
4. Read GW, Kiefer EF. *Benzalkonium chloride: selective inhibitor of histamine release induced by compound 48/80 and other polyamines. J Pharmacol Exp Ther 1979; 211: 711-5.*
5. Miszkiel KA, Beasley R, Rafferty P, Holgate ST. *The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. Br J Clin Pharmacol 1988; 25: 157-63.*