



# Paradoxical bronchospasm from benzalkonium chloride (BAC) preservative in albuterol nebulizer solution in a patient with acute severe asthma. A case report and literature review of airway effects of BAC



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## ABSTRACT

Nebulized bronchodilator solutions are available in the United States as both nonsterile and sterile-filled products. Sulfites, benzalkonium chloride (BAC), or chlorobutanol are added to nonsterile products to prevent bacterial growth. Bronchoconstriction from inhaled BAC is cumulative, prolonged, and correlates directly with basal airway responsiveness. The multi-dose dropper bottle of albuterol sulfate solution contains 50 µg BAC per/2.5 mg of albuterol, which may be below or at the lower limit of the threshold dose for bronchoconstriction. However, with repeated albuterol nebulization, the effect can be additive and cumulative, often exceeding the bronchoconstriction threshold. We report a case of a 17 years old patient, who received 32 mg of BAC via nebulization over a period of 3.5 days that probably caused persistent bronchospasm evidenced by failure to improve clinically and to increase peak expiratory flow rate (PEFR) from 125 L/min (27% of predicted value) to 300 L/min (68% of predicted value) within 2 hours of withdrawing BAC. The patient's respiratory status and PEFR improved dramatically once the nebulization solution was switched to BAC free lev-albuterol solution. The pediatric providers, particularly the emergency department physicians, intensivists and pulmonologists need to be aware of this rare albeit possible toxicity to the respiratory system caused by BAC used as a preservative in albuterol nebulizer solution.

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## 1. Introduction

Sulfites, BAC, or chlorobutanol is added to nonsterile products to prevent bacterial growth, but there have been reports of contaminated solutions containing preservatives [1]. All of the additives can induce bronchospasm in a concentration-dependent manner. Bronchoconstriction from inhaled BAC is cumulative, prolonged, and correlates directly with basal airway responsiveness [2]. The multi-dose dropper bottle of albuterol sulfate contains 100 µg BAC/ml (50 µg/2.5 mg of albuterol), which is below the threshold dose for bronchoconstriction whereas the screw cap unit-dose vial contains 600 µg/ml, which is above the threshold dose for many patients. We report a case where the patient received approximately 32mg of BAC mixed in albuterol solution over 3.5 days and

did not have bronchodilator response to the continuous albuterol nebulization. Her clinical status dramatically improved once the BAC containing albuterol was replaced with BAC free lev-albuterol solution.

## 2. Case report

A 17 years old female with moderate persistent asthma and atopic dermatitis presented to the pediatric emergency department with shortness of breath for a few hours. She took albuterol 2 puffs with spacer two times daily for 4 days at home with minimal improvement in her symptoms prior to her arrival at ED.

In the emergency department (ED), she was reported to be in severe respiratory distress with a tripod posture and was unable to speak in full sentences. Vital signs revealed temperature of 97.6F, respiratory rate of 50 per minute, heart rate of 95 beats per minute, and oxygen saturations of 97% on room air. Physical exam revealed nasal flaring, diffuse bilateral wheezing with severe suprasternal,

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intercostal and subcostal retractions. She received 4 treatments of nebulized albuterol with each dose containing 5 mg of albuterol sulfate. She also received 2 g of magnesium sulfate intravenously, one liter of normal saline bolus, two subcutaneous injections of epinephrine 0.3mg each, and 125mg of methylprednisolone intravenously. Due to deterioration in her respiratory status, she was initiated on bi-level positive airway pressure (BiPAP) with inspiratory and expiratory pressures of 14 and 6 cm H<sub>2</sub>O respectively and a FiO<sub>2</sub> of 50%. She was subsequently admitted to the pediatric intensive care unit (PICU) for management of acute respiratory failure secondary to status asthmaticus.

In the PICU, the BiPAP was continued and she received continuous albuterol nebulization at the rate of 20 mg per hour. Due to persistent poor air entry with diffuse biphasic wheezing and severe suprasternal retractions, she was administered another 2 gm of magnesium sulfate, a terbutaline bolus (10mcg/kg) and started on a terbutaline drip (0.4 µg/kg/min). However, her respiratory condition continued to deteriorate with oxygen saturations of 90% on FiO<sub>2</sub> 60% on BiPAP. Her peak flow rate measured twice at 12 hour interval on the first PICU day was 125 L/min (28% of predicted value) each time. A chest X-ray was unremarkable.

On the second PICU day, the terbutaline dose was increased to 0.6 µg/kg/min, but had to be discontinued due to tachycardia in the range of 140–150 beats per minute with ST changes on the electrocardiogram. Despite continued albuterol nebulization, her peak flow still remained at 130 L/min (30% of the predicted value) and had persistently poor air entry. She received a third bolus of magnesium sulfate and anticipated intubation for mechanical ventilation.

On fourth PICU day, a question was raised whether the preservative in the albuterol solution, benzalkonium chloride (BAC) may be responsible for failure to improve her respiratory status. BAC concentration in the multi dose albuterol solution was 100 µg/ml (0.1 mg/ml). By this time, she had received a cumulative dose of 3 g of albuterol, of which 1.5 g was BAC containing albuterol; with the total BAC that she received cumulatively was approximately 32 mg. Her albuterol therapy was then switched to lev-albuterol nebulizer solution, which was BAC free. She received it for 8 hours, at a rate of 10 mg per hour for the first 4 hours and 7.5 mg/hour for the next four hours. This switch resulted in a rapid improvement in her respiratory status with increased air entry and decreased work of breathing. Her peak flow rate increased dramatically from 130 L/min (30% of predicted value) to 300 L/min (68% of predicted value) within 2 hours of the switch from albuterol to lev-albuterol. The peak flow rate increased even further to 400 L/min (91% of the predicted value) 5 hours after the switch.

She was subsequently weaned to albuterol nebulization every 2-h and BiPAP was discontinued. She was transferred to the pediatric floor within 24 hours of switching to BAC free lev-albuterol nebulization. The corticosteroids were continued for a total of 7 days when she was discharged home. She was given a follow up appointment to pediatric pulmonology clinic but she failed to keep the appointment.

### 3. Discussion

Benzalkonium chloride (BAC) is a mixture of quaternary benzyl dimethyl alkylammonium chlorides. It is added for its bactericidal properties and until recently, was an ingredient in many commercially available nebulizer solutions including albuterol and ipratropium bromide. The multi-dose solution of albuterol that is used for continuous nebulization contains BAC at 50 µg per dose of albuterol 2.5mg. Furthermore, a pharmacist compounded inhalant solution of albuterol, ipratropium, or cromolyn from bulk chemical grade powder contains BAC since they are generally not

compounded or packaged in sterile manner. Albuterol used for our patient was the non-sterile multi-dose vial of albuterol, containing 50 µg of BAC per 2.5 mg of albuterol.

Concern over BAC might be responsible for the development of bronchoconstriction initially came from reports that isotonic ipratropium bromide inhalation solution containing BAC causing significant drop in forced expiratory volume in 1 second (FEV<sub>1</sub>) and failed to produce bronchodilator response [1,2]. Several case reports followed and studies were conducted where patients received inhalation challenge with increasing concentration of BAC, which produced dose dependent bronchoconstriction [3–5].

Although the mechanism of BAC induced bronchoconstriction is uncertain, one possibility is the release of spasmogenic mediators from mast cells within the bronchial wall. Mast cells release in excess of 90% of their histamine content when exposed to BAC in a concentration of 30 µg per ml as shown in a mice model [6]. In that study, it was also shown that BAC inhibited histamine release induced by polyamines, bradykinin, curare, guanethidine, polyline, polymyxin B, poly-THIQ, protamine and stilbamidine. Histamine release is induced by a lytic effect resulting from the surface-active properties of the hydrophobic and cationic group of the molecules. Other animal studies have shown that BAC may also enhance IgE dependent release of the preformed mediator 5-hydroxytryptamine from rat serosal mast cells [7]. Histamine is one of the prominent preformed mediator in mast cell and it is thus possible that bronchoconstriction induced by BAC results from endogenous release of histamine. However, the study conducted by Miszkiet al [4] showed findings suggestive of alternate mechanism to histamine release. In that study of 12 patients (mean age 29 ± 4 years), it was shown that the bronchoconstriction response of BAC was blocked by H<sub>1</sub> antagonist terfenadine but very briefly. Overall bronchoconstrictor response to BAC was inhibited only 13% by terfenadine, a H<sub>1</sub> antagonist, compared to 86% inhibition of bronchoconstriction caused by histamine exposure. Therefore, it is assumed that BAC also causes the release of lipid derived mediators into the airways. Mast cells release substantial amount of prostaglandin D<sub>2</sub> when stimulated and it is hypothesized that BAC caused mast cells to degranulate and release the prostaglandin D<sub>2</sub>. An alternative possibility is that BAC stimulates non-myelinated C fiber endings or myelinated rapidly adapting irritant receptors of airway, which will enhance the bronchoconstriction properties. Alternatively, BAC could stimulate the cholinergic ganglia directly. This was demonstrated by another paper by Miszkiet al [8], where 9 patients with mild atopic asthma recruited for the study showed inhibition of bronchoconstriction by BAC after pretreatment with ipratropium bromide and sodium cromoglycate, a muscarinic antagonist and mast cell stabilizer respectively. This suggests that airway response to BAC is mediated both by bronchoconstriction effect of mediator release within airways and also by stimulation of central and/or local neural reflex pathways. The PC<sub>20</sub> of BAC (provocation concentration causing a 20% fall in FEV<sub>1</sub>) in the above study was 4.99 mg/ml. However, this figure varied between different studies, ranging between 0.3 and 5 mg/ml [2]. In asthma patients, the PC<sub>20</sub> of BAC was much lower as shown by same author in 6 asthma patients whose PC<sub>20</sub> ranged from 0.13 to 2.0 mg/mL [1]. Zhang et al. has demonstrated the PC<sub>20</sub> range of 0.1–1.57 mg/ml [5]; for reference, the concentration of BAC in the albuterol solution that our patient received was 0.1 mg/ml. The lethal dose of oral BAC, where mortality was reported, was in the range of 100 mg/kg [9].

Another respiratory toxic effects of BAC is chemical pneumonitis from ingestion of pharmaceutical products constituted in BAC; a 2-day-old full-term neonate was inadvertently given 2 teaspoonful of antiseptic solution (container was similar to sterile water bottle) containing 10% BAC and developed inspiratory and expiratory stridor, respiratory acidosis (pH 7.13, PaCO<sub>2</sub> 72.1 mmHg, PaO<sub>2</sub> 58.7);

and edematous epiglottis requiring intubation and mechanical ventilation. Patient eventually recovered and discharged on day 33 [10]. The caustic properties of BAC in concentration of greater than 1% on skin and mucous membranes are well known. In the 1970s when the BAC was used as a topical treatment for candidiasis, John et al. reported a case of infant twins who sustained severe circumoral and pharyngeal burns, and chemical pneumonitis from an 11% solution of BAC dispensed in formulation error by the pharmacist (rather than the requested concentration of 1:50,000) for the treatment of candidiasis [11]. Other effects of BAC in the airway include local irritation of airway causing rhinitis medicamentosa, burning, irritation, dryness, epistaxis and deficits in mucociliary transport. The mucociliary dysfunction secondary to BAC has been shown in animal study where the authors demonstrated 30% reduction of mucociliary beat frequency after a 20-min exposure [12].

In our patient, the lack of bronchodilator response to continuous albuterol nebulization could possibly be from beta adrenergic receptor polymorphism and/or tachyphylaxis [13,14]. Genetic polymorphisms affecting amino-acids at positions 16 and 27 within beta-2 -adrenoceptor gene have been implicated in the asthma phenotypes and influence on the variability observed in response to beta-agonists used for the treatment of asthma. A study conducted by Carroll et al. showed that children with the Arg16Arg and Arg16Gly genotypes, as compared to Gly16Gly genotype, had longer pediatric ICU and hospital stay [12]. Chronic exposure to  $\beta$ -agonists causes tolerance to their bronchodilator effects, which has been demonstrated during acute bronchoconstriction [15]. Our patient has been taking albuterol MDI frequently for 2–3 weeks preceding the hospitalization; however, there is no evidence that any partial tolerance that could have developed contributes to complete failure to respond to continuous albuterol nebulization. Lactic acid can cause metabolic acidosis and compensatory tachypnea; its contribution to bronchoconstriction and increased airway resistance has been demonstrated in animal and in vivo studies. Administration of albuterol either by bolus or continuously can cause lactic acidosis in patients; however, we did not determine lactic acid levels or arterial blood gases for our patient [16,17]. Finally, it is worth mentioning that toxic properties of an aerosolized agent depends on the agent's particle aerodynamic characteristics affecting its impaction, sedimentation, diffusion and tidal volume. We do not have any data on particle spectrum of BAC containing albuterol used for our patient [18].

According to Naranjo's Adverse Drug Reaction (ADR) scale [19], the score was 6 for this case indicating a probable cause (>9 = definite ADR, 5–8 = probable ADR, 1–4 = possible ADR and 0 = doubtful ADR). The quick improvement in her clinical status and increase in PEFr after the BAC was withdrawn is suggestive of bronchospasm induced by BAC.

Limitations of our report include a lack of serum or aerosol measurements of BAC levels, not obtaining spirometry and arterial blood gases when patient was acutely ill and not testing for genetic polymorphism for beta agonist which may have contributed to the prolonged severe airflow obstruction in this patient.

It is important for the clinicians to be cognizant of the great

variability of BAC content in albuterol nebulizer solutions they use for their sick patients. For example, a 2.5 mg dose of albuterol from a sterile-filled unit-dose vial contains no BAC, whereas a 2.5 mg dose from the unsterile multi-dose bottle contains 50  $\mu$ g BAC, and a 2.5 mg dose from the unsterile screw cap vial contains 300  $\mu$ g of BAC [3].

When albuterol nebulizer therapy is administered repeatedly for a patient with severe airway obstruction not responding optimally to albuterol therapy, the cumulative effect of BAC can cause significant bronchoconstriction and may be the cause of a blunted bronchodilator response. The problem can be altogether avoided by using only the preservative-free products [3].

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