Case Study

ALLERGIC REACTIONS RELATED TO BENZALKONIUM CHLORIDE

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INTRODUCTION

Benzalkonium chloride (BAC) is a preservative commonly found in different medications and disinfectants used in clinical practice. Allergic and pseudoallergic adverse reactions have been reported in both patients and healthcare workers and are supported by data in various studies. We present a case of a 15-year-old female who was admitted with a severe asthma exacerbation and clinically deteriorated to a life-threatening exacerbation presumed to be due to BAC contained in the salbutamol nebulisations.

CASE REPORT

MM, a 15-year-old female, was admitted to the Red Cross War Memorial Children’s Hospital with complaints of an acute onset of wheeze and chest tightness. She was a known asthmatic well controlled on a salmeterol/fluticasone metered-dose inhaler at 25/250 mcg 12 hourly and montelukast 10 mg once daily. No trigger for the exacerbation was identified from her history. Three hundred micrograms of a short-acting beta 2 agonist (Asthavent®) had been administered at home prior to arrival at the hospital, with no discernable improvement in symptoms. On examination she was alert, able to speak only single words, saturating at 80 per cent in room air, tachypnoeic at 30 breaths per minute with increased work of breathing, decreased air entry bilaterally with wheezing and crepitations on auscultation plus a pulsus paradoxus. Her blood gas showed an uncompensated respiratory acidosis with a pH of 7.28, pCO₂ 7.2 kpa, pO₂ 22 kpa, lactate 0.6 and HCO₃ of 23.1. Treatment was initiated with three doses of 10 mg salbutamol and 250 mcg ipratropium bromide nebulisations (2 ml of each) within the first hour and 40 mg of oral prednisone followed by continuous salbutamol nebulisations. A single dose of 50 per cent magnesium sulphate was administered IVI as she did not appear to respond to initial treatment and an ICU bed was sought for continued management.

Repeat blood gas readings taken in ICU showed an increase in hypercarbia to 8.9 kpa and IV salbutamol was commenced in addition to continuous salbutamol nebulisation and high-flow oxygen at 40 ℓ/min with an FiO₂ of 50 per cent. She subsequently developed confusion and decreased level of consciousness necessitating intubation and mechanical ventilation. While on the ventilator, she developed two discrete and severe episodes of worsening bronchospasm lasting about 20 minutes requiring an increase of peak inspiratory pressure from 50 to 60. An urgent bronchoscopy to the level of the carina ruled out a foreign body. It was during the second episode of bronchospasm that it was noted that the deterioration occurred during nebulisation with salbutamol and improved once this was stopped. Further investigation revealed that the salbutamol used since admission came from a multidose vial that contained BAC as a preservative. A presumptive diagnosis of BAC sensitivity was made. Preservative-free salbutamol (IV solution) was used for subsequent nebulisation resulting in improvement in her bronchoconstriction and she was successfully weaned off the ventilator.

Plans have been made for a drug-provocation challenge to confirm or refute the diagnosis of BAC hypersensitivity.

DISCUSSION

BAC or N-Alkyl-N-benzyl-N, N-dimethyl ammonium chloride is a mixture of quaternary benzyl dimethyl alkyl ammonium chlorides. It is one of many quaternary ammonium chloride compounds (QACs) used as preservatives.¹ The hydrophobic and cationic groups of BAC destroy both gram-positive and negative bacteria by changing the permeability of their cell walls. Edetate disodium (EDTA) further enhances the germicidal activity of BAC and the two are commonly found together in multidose vials of nebuliser solutions.² BAC is also found in ophthalmic and nasal medications, antiseptics, disinfectants and cosmetics.¹,³,⁴ The American College of Toxicology has recommended a concentration of up to 0.1 per cent can be used safely as a microbial agent.⁴ Commercial preparations may contain mixtures of QACs with varying lengths of carbon chains attached to the R position of the benzyl group. Unclear labelling of the actual QACs contained can make it difficult to recognise the culprit responsible for hypersensitivity reactions.

Although BAC has been deemed safe since its introduction as a preservative in 1935, it has been implicated in a
wide array of hypersensitivity reactions. Examples of allergic reactions include allergic contact dermatitis and case reports of anaphylaxis, whereas irritant contact dermatitis, ciliostasis with reduced transport, rhinitis medicamentosa, neutrophil dysfunction and paradoxical bronchoconstriction are examples of non-allergic reactions found in some patients.\(^2\)\(^3\)\(^5\)\(^6\)\(^7\) Byoung et al showed that the bronchoconstrictive effect of BAC reached a plateau after a dose of 1 200 micrograms and that this effect responded readily to short-acting beta agonists.\(^8\) Miszkiel et al reported that histamine was seven times stronger with a faster bronchoconstrictive onset of action compared to BAC which caused a slower and more persistent effect lasting up to 45 minutes. Benzalkonium’s bronchoconstrictive effect was only partially attenuated by selective H1 antagonists unlike histamines and other mechanisms such as mast cell-derived prostaglandin D2 and stimulation of non-myelinated C fibres are thought to play a role.\(^9\) Stable asthmatics with higher bronchial hyper-responsiveness during a methacholine provocation challenge were found to be significantly more sensitive to BAC compared to those with less hyper-responsiveness.\(^10\)

**CONCLUSION**

BAC is widely available in various products and has been found to cause many different adverse reactions including anaphylaxis. With regard to paradoxical bronchoconstriction, careful monitoring of the patient’s response to nebulisation during the first hour is crucial as this appears to be when the condition of an affected patient may deteriorate. Most severe asthmatics receive a BAC-cumulative dose of 1 200 mcg during the first hour as they receive three 10 mg doses of salbutamol (6 ml nebuliser solution) during this period. Clinicians should ensure that common causes of acute severe exacerbations are ruled out even as they initiate management for suspected BAC-induced paradoxical bronchoconstriction as shown in the case above. If BAC bronchoconstriction is suspected, then a change to a preservative-free, short-acting bronchodilator may be warranted and a response to a BAC-free preparation may help support the diagnosis with further testing once the patient is stable. Currently, no blood test can assist in the diagnosis of BAC reactions and a drug-provocation challenge is required to confirm the diagnosis of paradoxical bronchoconstriction.

**DECLARATION OF CONFLICT OF INTEREST**

The authors declare no conflict of interest.

This article has been peer reviewed.

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