

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} Anderson et al reported a case of a 31-year-old female who presented to the emergency department with complaints of dyspnoea, eye redness and pain 20 minutes after using ophthalmic drops prescribed for allergic conjunctivitis.³ She had previously used the same drops and reported mild symptoms such as itching and burning sensations that responded well to diphenhydramine drops. She had presented to the emergency department a few years before this episode with symptoms of swelling around her eyes and dyspnoea approximately one hour after using eye dilator drops. She was treated with a cream and discharged only to be readmitted later in the day with progressively worsening dyspnoea. BAC was found to be present in the eye drops used for her conjunctivitis and pupillary dilatation as well as the cream used in the emergency department. She reacted immediately with itchy eyes, tightness of the throat and cough when a skin-prick test (SPT) was performed using BAC in normal saline, thereby confirming her diagnosis of severe BAC hypersensitivity. The authors did not report the concentration used for the SPT. Mezger et al reported another case of a 46 year-old female who developed airway symptoms 30 minutes after using a nasal spray containing BAC. She showed increasingly positive SPTs to BAC 0.1 per cent and 0.5 percent dilutions.⁶

Benzalkonium is more likely to cause irritant contact dermatitis compared to allergic contact dermatitis especially in healthcare workers who use disinfectants frequently. Nine per cent of healthcare workers had BAC-allergic contact dermatitis confirmed with atopic patch testing in this study.⁷

The prevalence of paradoxical bronchoconstriction with inhalation of nebuliser solutions is unknown as large studies are lacking; however, case reports have been documented and are supported by clinical studies in stable asthmatic patients.^{1,8,9,10} Clinical diagnosis can be very difficult due to the difficulty in determining if the patient's asthma is inherently worsening and not responding to treatment or is aggravated by the nebuliser solutions. Salbutamol nebulisation is the first line of treatment offered to the acute severe asthmatic according to the Global Initiative for Asthma (GINA) and the latest South African Asthma Guidelines.¹¹ The guidelines state that a salbutamol nebulisation should be given every 20 minutes for the first hour, then continuously as per the patient's progress. The salbutamol used in our hospital contains 5 mg of salbutamol and 200 mcg/ml of BAC in an economical multidose vial.

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.¹⁰ 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.⁸ 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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Report

ALLERGY SOCIETY OF SOUTH AFRICA DIETETIC INTEREST GROUP (ADIG): INITIAL REPORT

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ADIG was conceived at the ALLSA conference in 2015, where dietitians working in the field of allergy in southern Africa felt there was a need for networking and combined working in order to improve the quality of service being offered to allergy patients. The group was convened for the first time in April 2016 with the vision of forming a partnership between ALLSA and this group of dietitians.

The first task of the group was to assess the level of interest in the concept. In order to achieve this, ADIG sent out a survey to dietitians practising in southern Africa via the Association for Dietetics in South Africa (ADSA), the South African Society for Parenteral and Enteral Nutrition (SASPEN) and the Nutrition Society of South Africa (NSSA). We received 131 responses, of which 119 expressed an interest in allergy and a willingness to join ADIG. Fifty-five of these respondents have subsequently become members of ALLSA (information as at September 2016) and are therefore eligible to join the ADIG group as set out in our constitution. We currently have a provisional executive committee comprising nine dietitians and Professor Mike Levin as an honorary member. Once our membership base has been fully established, we intend to invite formal nominations and hold elections at the ALLSA AGM in 2017.

At present, the interim executive committee members are:

- Chairperson: Lindsay Archibald-Durham
- Secretary: Kerry Gibson
- Membership: Alison Campbell-Lang and Claire McHugh
- PR Officer: Sasha Watkins
- Research Officer: Idonette van Zyl

- Resource Officer: Linda Drummond
- Training/Sponsorship: Nicola Walters and Leigh-Ann Silber.

This group is in its infancy and we have many objectives, including:

- creating a support network for dietitians working in the field of allergy;
- improving dietitians' visibility and their promotion within the allergy multidisciplinary team;
- establishing CPD-accredited training in food allergies for dietitians and other health professionals in conjunction with ALLSA;
- establishing evidence-based guidelines and pathways to ensure consistency in work;
- disseminating recent research;
- improving allergy awareness among the general public;
- creating a database of information regarding allergens and allergen-free foods, leaflets and recipes;
- participating in research into food allergies;
- liaising with the food industry with regard to labelling legislation.

We are all incredibly excited about this new partnership with ALLSA and plan to launch the society officially at the ALLSA Congress in 2017. In addition, we already have a workshop planned for Cape Town in February 2017 and for Gauteng later that year. This is an exciting new era for dietitians working in the area of allergy and hopefully it will be one that brings about enhanced multidisciplinary collaboration. Should you have any queries or recommendations for this group, please do not hesitate to contact me.