

CLINICAL COMMUNICATION

Anaphylaxis with use of eye-drops containing benzalkonium chloride preservative

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Benzalkonium chloride (BAC) is a bactericidal preservative found commonly in cosmetics, disinfectants, nebuliser solutions, spermicides and eye-drops.¹ BAC is reported as the most commonly used quaternary ammonium compound.² Numerous cases of contact sensitivity have been reported,^{2,3} including alarming cases of paradoxical bronchoconstriction and anaphylaxis (an acute multi-system and very severe Type I hypersensitivity reaction) with BAC in nebuliser solutions.² In 1997, Chiambaretta, Pouliquen and Rigal³ reported two cases of contact sensitivity and a third case of immediate hypersensitivity involving chemosis and angioneurotic oedema. Chemosis and angioneurotic oedema are associated with anaphylaxis but differ from our case because the patient had established anaphylaxis to another member of



Figure 1. Skin testing to epinastine ophthalmic drops. Prick testing done on the left of the arm, while intradermal testing was done on the right. Results show wheal/flare in mm for each component and control: Histamine (H)- prick 13/36, intradermal not performed; Saline and BAC (SB)- prick 3/14, intradermal 15/>45; Epinastine ophthalmic (contains BAC) (EB)- prick 0/0, intradermal not performed; Control (C)- prick 0/0, intradermal 7/0.

Epinastine HCL 0.5 mg/mL (0.05%)	Active
Benzalkonium chloride 0.01%	Preservative
Edetate disodium*	Inactive
Purified water*	Inactive
Sodium chloride*	Inactive
Sodium phosphate, monobasic*	Inactive
Hydrochloric acid*	To adjust pH to approx. 7
Sodium hydroxide*	To adjust pH to approx. 7

*Elemental, considered inert

Table 1. Ingredients of epinastine ophthalmic per millilitre⁴

the quaternary ammonium compound family.³ We report a case of anaphylaxis following an ophthalmologic administration containing BAC with confirmatory testing.

CASE REPORT

A 31-year-old Caucasian female presented to the emergency department with difficulty breathing, eye redness and pain. The symptoms began 20 minutes after using epinastine ophthalmic allergy prescription drops (Elestat; Boehringer Ingelheim, Ingelheim Germany) given as samples and used bilaterally for dryness with contact lenses and as empiric treatment of allergic conjunctivitis (Table 1). She reported having used the same eye-drops six times over the previous three months prior to this episode. She knew she was sensitive to the eye-drops, having experienced mild symptoms (for example, flushing, itching, burning eyes) with prior use that responded well to diphenhydramine (Benadryl; Johnson and Johnson).

She had had a similar episode in 2002 with swelling and difficulty breathing approximately 75 minutes after receiving eye dilator drops. This resulted in a visit to the emergency department, where she was given a cream as treatment. She was discharged from the emergency department but returned shortly after the initial presentation with further swelling and difficulty breathing. BAC was identified as an ingredient in both the dilator drops and

the cream used for treatment, though allergy testing was not pursued at that time. Our patient also suffered from gastro-oesophageal reflux disease and hypothyroidism, for which she was taking metoclopramide, levothyroxine sodium and OCPs. She reported no other allergies and no significant family history. She does not smoke and consumes alcohol occasionally.

On presentation at the emergency department triage, her temperature was 36.8°C, respiration 24 per minute, pulse 90 bpm and BP 129/85 mmHg. Physical examination noted conjunctival injection bilaterally, though greater in the right eye. Slitlamp examination demonstrated a superficial central corneal abrasion in the right eye, without evidence of ulceration, while the left eye was normal. Anaesthetic drops were not given as they contained BAC. Lungs were clear with no stridor, which ruled out active oedema of the airways, suggesting that the airways were stable and ventilator support was not required. She was subsequently treated with diphenhydramine (an antihistamine for early phase reaction), prednisone (a steroid for late phase reaction) and albuterol (for prophylaxis of bronchospasm). This relieved the feeling of throat closure, tightness in the chest and eye discomfort. She was given gentamicin ophthalmic ointment (for empiric coverage of bacterial infection) and hydrocodone bitartrate and acetaminophen with instructions to follow-up with an ophthalmologist and an allergist.

During follow-up with the allergist, skin testing was conducted with histamine, saline with BAC, epinastine ophthalmic and a saline control (Figure 1). The results were determined by measuring the raised area of skin (wheal) and the erythematous area (flare). There was no reaction to the prick test using epinastine ophthalmic, probably because it contains an antihistamine. There was a strong reaction to the saline with BAC test, resulting in the patient having itchy eyes, cough and throat tightness. This required intervention with diphenhydramine and triamcinolone diacetate 100 mg IM (steroid; for late phase reaction). The symptoms resolved after one hour. In addition, immunoglobulin testing for IgG, IgM, IgA and IgE yielded results within normal limits. IgE, the antibody associated with allergy, was actually at the lower end of normal at 20 IU/mL with the reference range at zero to 180 IU/mL. The low value of IgE indicates that patient is not atopic, as we would expect the IgE levels to be high in the presence of many different allergies. This was confirmed when skin testing with 60 of the most common allergens yielded negative results with the exception of the positive control sample. All skin testing was performed approximately one month after the ED presentation.

Taken together, the test results strongly suggest that the episode of anaphylaxis was secondary to BAC exposure. The differential diagnosis may include allergies to a different preservative; however the skin testing confirmed reactions to BAC. Further confirmatory testing with a radio-allergosorbent test (RAST), a blood test to determine IgE specificity against certain antigens with BAC was not available. The patient declined further *in vivo* challenge with BAC due to established anaphylaxis on exposure. The patient was counselled on avoidance of BAC and switched to a peroxide-based eye-drop solution.

DISCUSSION

The strong history on two separate occasions involving a BAC-containing eye-drop suggests that BAC was responsible for the anaphylactic reaction. Skin testing con-

firmed this diagnosis with positive results and symptoms consistent with her previous presentation. The possibility of the anaphylactic reaction being caused by another component of the eye-drops or another agent such as food, drug or an environmental allergen is unlikely due to the skin test yielding strong positive anaphylactic symptoms to saline with BAC. A response to BAC following ophthalmic administration has been described previously³ in a patient with known anaphylaxis to a quaternary ammonium compound, which is in the same chemical family as BAC. No discussion of allergy testing or follow-up was included, however, avoidance of the allergen was recommended to the patient. Kim and Ahn² presented a case of anaphylaxis to BAC in a nebuliser solution, with subsequent confirmation of BAC as the causative agent with skin testing.² Our case is consistent with information reported in previous cases and further emphasises that although useful to confirm the cause of anaphylaxis, a safe dose of BAC for the purposes of skin testing has yet to be established.

CONCLUSION

We have described a case of rare allergic reaction to a preservative contained in ophthalmic drops with confirmatory testing. The early signs of anaphylaxis are important to recognise due to the possibility of rapid progression to a fatal outcome secondary to airway occlusion or vascular collapse.⁵ If a detailed history does not reveal the cause of the anaphylaxis, medications and their preservatives should be considered. Skin testing to determine the cause is useful; however, safe testing doses have yet to be established as evidenced by at least two reported cases of anaphylaxis with BAC skin testing. In these cases, the most effective approach to both prevention and treatment is patient counselling on avoidance of BAC-containing medications and instructing the patient to report similar reactions to other agents immediately. Additionally, health-care providers, regardless of speciality, should be prepared with basic medical supplies in the

event that a patient experiences anaphylaxis during testing or administration of suspected allergens.⁵

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