

Contact allergy to benzalkonium chloride in patients using a steroid nasal spray: A report of 3 cases

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Introduction

Benzalkonium chloride (N-alkyl-N-benzyl-N,N-dimethylammonium chloride; BAC) is a quaternary ammonium surfactant widely used as a preservative in nasal, cutaneous, pulmonary, and ophthalmic solutions. It is well known for its role in preventing bacterial contamination.¹ Nevertheless, some studies have cast doubt on BAC's reputation for safety. A discussion of this issue exists in the literature, especially with respect to BAC's allergenic and irritant properties.²⁻⁴

Many authors have investigated the ocular⁵ and cutaneous^{6,7} toxicity of BAC, but few studies have examined systemic allergic reactions induced by BAC after the use of steroid nasal sprays and nasal drops. In this article, we describe 3 cases of systemic BAC allergy following the use of a steroid nasal spray, and we discuss the epidemiology, clinical features, diagnosis, and treatment of these allergic reactions.

Case reports

Patient 1. A 58-year-old woman who had complained of chronic rhinosinusitis was referred to our otolaryngology department. She reported a 12-week history of rhinorrhea, nasal obstruction, and frontal pain. Nasofibroscope demonstrated nasal congestion, turbinate hypertrophy, and nasal polyps. A diagnosis of polypoid rhinosinusitis was established. Medical treatment was dispensed that included an endonasal spray of mometasone once a day for 90 days. Mometasone contains BAC.

Four weeks later, the patient returned complaining of increasing rhinorrhea and nasal obstruction. She underwent a standard test battery, read in 48 and 72 hours, which was positive on BAC 0.1% in water. No other allergy was detected by conventional methods (skin-prick test and radioallergosorbent test). The mometasone spray was stopped and replaced with a spray that does not contain BAC, and the patient's symptoms diminished after a couple of weeks. A list of products that contain BAC was supplied to the patient.

Patient 2. A 75-year-old woman was referred to us for evaluation of rhinorrhea, nasal tickle, and sneezing. Results of a standard skin-prick test revealed a mild sensitization to mites. The patient was prescribed mometasone nasal spray along with oral bilastine, which does not contain BAC.

A few days later, the patient developed pruritus, rash, and edema in her lower limbs along with an exacerbation of her rhinorrhea. She stopped the rhinitis treatment for 1 week, and her lower limb symptoms decreased, although her nasal symptoms persisted. At that point, she consulted a general physician, who switched her from mometasone to fluticasone spray. However, fluticasone also contains BAC, and a few days later, the same lower limb symptoms returned and her rhinorrhea worsened.

The patient was referred back to our department. A general examination revealed bilateral edema of the lower limbs and some superficial scratch lesions. An etiology of BAC allergy was highly probable, and we switched the patient from fluticasone to budesonide, which does not contain BAC. She tolerated the new treatment well, and her symptoms abated. Given her clinical

history, we determined that no other test was necessary to confirm the diagnosis of BAC allergy. This patient was also given a list of products that contain BAC.

Patient 3. A 74-year-old woman presented to our allergology department for evaluation of persistent postnasal drip, anterior rhinorrhea, and nasal obstruction, which had been present for a few months. Her history was remarkable for sensitization to several eye drops; she did not remember the name of the drops. A head and neck examination revealed a clear nasal discharge bilaterally, but no other relevant signs or ocular conjunctivitis. A standard skin-prick test was negative, but a standard European patch test was positive for BAC.

Several days after the patch test, we were surprised when the patient complained of generalized pruritus and exhibited cutaneous burns, which she attributed to BAC exposure. We recommended that she use budesonide spray as a nasal decongestant and avoid all products that contain BAC. The patient's follow-up was unremarkable, as she experienced no recurrence of her allergic reactions.

Discussion

The histories of these patients and the results of the European standard patch test in patient 3 point to a diagnosis of type IV hypersensitivity reactions caused by nasal sprays containing BAC.

Initially, BAC was used in various fields of industry, such as industrial chemistry (e.g., in the synthesis of dyes), metallurgy, cosmetics, agriculture, and textile manufacturing.⁸ In topical medications, this preservative compound is present in some disinfectants, medicinal gargle solutions, throat lozenges, and adhesive bandages, in addition to eye drops and nasal sprays.⁸

Cutaneous sensitization is rare, with an incidence of only 0.02 to 0.7%.^{6,9} Only a few reports have described type I and type IV hypersensitivity reactions attributable to BAC; these have occurred after the use of an asthma medication nebulizer,¹⁰ ophthalmic drops,¹¹ cutaneous agents,¹² and ear drops.¹³ The introduction of BAC into nasal sprays and nasal drops dates back a few decades, but only a few authors (several case reports and one prospective study) have described allergic reactions associated with their use.^{8,14}

Cases of contact allergy induced by BAC have been diagnosed on the basis of patch test results with BAC 0.1%. However, some authors have suggested that sensitivity reactions to BAC exposure actually represent a contact dermatitis rather than an allergy.¹⁵ It is essential to establish the relationship between BAC sensitivity and the symptoms experienced by the patient.

The most common ENT manifestations of BAC sensitivity are rhinorrhea, nasal congestion, and an endonasal burning sensation. BAC can also cause swelling of the nasal mucosa in cases of chronic use.¹⁶ General clinical manifestations range from skin dermatitis to angioedema. The diagnosis remains complicated, and the incidence of BAC sensitivity is probably underestimated. The few cases described in the literature have involved 1 patient with a type I reaction (anaphylactic reaction)¹⁰ and some type IV reactions^{14,17} after the use of nasal preparations.

Each of our patients experienced a type IV allergic reaction as a result of the activation of T cells that allow for the recruitment and activation of macrophages. From a pathophysiologic standpoint, the regular use of nasal sprays that contain BAC is known to damage the ciliated epithelium of the nasal fossa, leading to a greater permeability of the nasal mucosa.¹⁸ Indeed, it has been demonstrated in healthy patients that BAC in the concentrations used in nasal sprays and nasal drops impairs mucociliary clearance after 30 days of use, which can lead to the development of an inflammatory reaction and rhinitis medicamentosa.^{16,19}

In a type I reaction, BAC molecules penetrate the mucosa and induce an IgE-mediated reaction, inducing the release of histamine and other vasoactive amines from mast cells.⁸ The type IV reaction manifests as a classic sensitization phase and an effector phase that involves the activation of allergen-specific cytotoxic T cells that allow for the recruitment and activation of macrophages. Moreover, several animal studies have shown that BAC activates T2 helper cells, leading to an increase in total IgE and IgG1 levels in the blood and causing sensitization.²⁰ The development of these reactions increases the initial symptomatology.

Indeed, in a general way, if the use of an endonasal steroid spray prescribed to treat rhinitis causes a BAC allergy that in turn causes rhinorrhea, a clinician might misinterpret the rhinorrhea as a lack of response to the rhinitis treatment rather than a complication of it. Physicians usually suspect a BAC allergy on the basis of a medical history of similar allergic reactions to similar drugs or excipients.

Confirmation of a diagnosis of BAC allergy usually requires a standard patch test or skin-prick and intracutaneous tests, since determining specific BAC IgE is not feasible.⁸ A resolution of symptoms coinciding with the cessation of treatment suggests the diagnosis.

To the best of our knowledge, only one trial has looked at the potential effects of allergenicity of nasal spray components. Bennett et al conducted a prospective study of 30 patients who used an inhaled or nasal steroid and found that 3 of them (10%) experienced an allergic reaction and 1 had an irritant contact reaction; 2 of the 4 reactions were caused by BAC.¹⁴ The signs and symptoms of the allergic reactions and the irritant reactions were similar-redness, rhinorrhea, itching, pain, burning, nasal obstruction, dryness, and bleeding.

Each of our 3 patients experienced a type IV hypersensitivity reaction secondary to BAC exposure. Although the exact incidence of BAC allergy is not yet established, physicians who prescribe endonasal steroid sprays should take into consideration the possibility of an allergic reaction to BAC if a patient does not experience a resolution of symptoms or develops new nasal complaints.

In conclusion, endonasal solutions that contain a preservative excipient such as BAC are generally safe and well tolerated during short-, medium-, and even long-term use,²¹ but contact allergies leading to rhinorrhea are possible and should not be mistaken for a lack of response to treatment. Our 3 cases highlight the need to develop randomized, double-blind, controlled trials of the allergies and general toxicities caused by preservative agents included in endonasal steroid solutions.

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