Rostrum

Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? A cautionary note based on compromised mucociliary transport

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Background: Topical nasal solution and suspension delivery systems are available for short- and long-acting vasoconstrictors, ipratropium, cromolyn, azelastine, and glucocorticosteroids. The use of intranasal glucocorticosteroids has increased substantially because the efficacy of these agents has been well established for the treatment of perennial and seasonal allergic rhinitis. Adverse local effects of burning, irritation, and dryness are occasionally associated with glucocorticosteroid nasal preparations. Benzalkonium chloride (BKC) is a quaternary ammonium antimicrobial agent included in some nasal solutions (including glucocorticosteroids) to prevent the growth of bacteria. Some reports suggest that BKC in nasal sprays may cause adverse effects, including reduced mucociliary transport, rhinitis medicamentosa, and neutrophil dysfunction.

Objective: This article summarizes recent literature about possible adverse biologic effects associated with BKC as a nasal spray preservative by examining its effects on the following properties of mucociliary transport: ciliary motion, ciliary form, ciliary beat frequency, electron microscopy, and particle movement/saccharin clearance tests.

Conclusion: Both animal and human in vitro data suggest that BKC promotes ciliostasis and reduction in mucociliary transport that may be partially masked by absorption and dilution effects occurring in respiratory mucus. These possible confounding factors may account for several disparate human in vivo results. The use of BKC-free glucocorticosteroid formulations should be considered, particularly in patients who complain of nasal burning, dryness, or irritation. (J Allergy Clin Immunol 2000;105:39-44.)

Key words: *Allergic rhinitis, topical nasal drugs, preservatives, benzalkonium chloride, mucociliary transport*

Topical nasal aqueous and suspension delivery systems are available for vasoconstrictors, ipratropium, cromolyn, azelastine, and glucocorticosteroids (Table I). Intranasal corticosteroid therapy is recognized as the most significant advance in the treatment of allergic rhinitis since the advent of antihistamines.[1] Treatment with corticosteroid-containing nasal sprays is recommended when nasal symptoms are not controlled with antihistamines.[1] Topical corticosteroids have proved highly effective by decreasing cellular inflammation in the nasal mucosa.[1,2]

Abbreviation used
BKC: Benzalkonium chloride

Formulation of nonpropellant mucosal delivery systems often requires preservatives for inhibition of microbial growth. Both toxic and allergic effects of these agents have been reported.[3,4] Among available antimicrobial preservatives, benzalkonium chloride (BKC) is commonly used to prevent bacterial contamination in various nasal formulations (Table I). Adverse local effects of these products (eg, rhinitis medicamentosa, burning, irritation, dryness, and epistaxis) have generally been attributed to the active therapeutic agents. Nevertheless, the possibility that BKC could contribute to adverse responses should be reconsidered further in view of recent reports that this agent may affect mucociliary function.

BKC AS A PRESERVATIVE: STRUCTURE/FUNCTION AND MECHANISM OF ACTION

BKC has been used to prevent bacterial contamination and to preserve pharmacologic activity in multidose topical aqueous drops and sprays.[5,6] BKC is a mixture of quaternary benzyldimethylalkylammonium chlorides. Its germicidal activity is attributed to surface-active properties of its hydrophobic and cationic groups, which are bactericidal against a wide variety of gram-positive and gram-negative bacteria at low concentrations.[5] This activity is accomplished by altering the permeability of cell walls of microorganisms.[7] EDTA enhances penetration of BKC into the bacterial cell wall and is often recommended as a BKC coadditive.[7] It is postulated that the cationic surfactant properties of BKC promote strong binding to nasal tissue, thereby increasing the viscoelastic nature of the mucus gel with attendant toxicity.[8,9]

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TABLE I. Excipient profiles of nasal preparations used in the United States

Class of drugs	Generic name	Trade name	BKC	CFC	EDTA	Surf	Alc	Hg	PG	G	PS-80	BA	MC
Vasoconstrictor-short	Phenylephrine HCl	Neosynephrine	+	–	–	–	–	+	–	–	–	+	–
	Phenylephrine HCl, naphzoline HCl, pyrilamine maleate	4-Way Fast Acting nasal spray	+	–	–	–	–	–	–	–	–	+	–
Vasoconstrictor-long	Oxymetazoline	Afrin	+	–	+	–	+	–	+	–	+	+	–
	Oxymetazoline	4-Way Long Lasting nasal spray	+	–	–	–	–	–	–	–	–	+	–
Antihistamine	Azelastine	Astelin	+	–	+	–	–	–	–	–	–	+	+
Anticholinergic	Ipratropium bromide	Atrovent nasal spray 0.03% and 0.06%	+	–	+	–	–	–	–	–	–	+	–
Mast cell stabilizer	Cromolyn sodium	Nasalcrom solution	+	–	+	–	–	–	–	–	–	–	–
Glucocortico-steroid	Triamcinolone acetonide	Nasacort inhaler	–	+	–	–	+	–	–	–	–	–	–
		Nasacort AQ	+	–	+	–	–	–	–	–	+	+	+
	Flunisolide	Nasalide nasal solution	+	–	+	–	–	–	–	–	–	–	–
		Nasarel nasal solution	+	–	+	–	–	–	–	–	–	–	–
	Dexamethasone	Decadron Turbinaire	–	+	–	–	+	–	–	–	–	–	–
	Beclomethasone dipropionate	Beconase AQ	+	–	–	+	–	–	–	–	–	–	–
		Beconase aerosol inhaler	–	+	–	–	–	–	–	–	–	–	–
		Vancenase AQ	+	–	–	–	+	–	–	–	–	–	–
		Vancenase nasal inhaler	–	+	–	–	–	–	–	–	–	–	–
	Fluticasone proprionate	Flonase	+	–	–	–	+	–	–	–	+	–	+
	Budesonide	Rhinocort	–	+	–	+	–	–	–	–	–	–	–
	Mometasone furoate	Nasonex nasal suspension	+	–	–	–	+	–	–	+	+	+	+

BKC, Benzalkonium chloride; *CFC,* chlorofluorocarbons; *Surf,* surfactant; *Alc,* alcohol; *Hg,* mercurial preservatives; *PG,* propylene glycol; *G,* glycerin; *PS-80,* polysorbate-80; *BA,* buffering agents; *MC,* methylcellulose compounds; +, present; –, not present.

Although ophthalmic mucositis[10] and contact dermatitis[11] resulting from BKC have been documented, allergic effects of BKC in nasal sprays have not been reported. In the current article the possibility that BKC may exert adverse effects on mucociliary transport is discussed.

ADVERSE MUCOCILIARY EFFECTS OF BKC

Three techniques are available to assess mucociliary function. These include (1) ciliary form and motion, (2) mucus production and properties, and (3) measurement of the efficiency of the combined ciliary activity and mucus production.[12] All these parameters have been examined to investigate biologic effects of BKC. However, the effect of BKC on rheologic properties of mucus has not been investigated because a reliable clinical test is not available.[12]

Ciliary motion

The effects of BKC on nasal mucosal motility have been studied in several animal and human models.[13-16] A major strength of this method is the ability to harvest cilia readily from the inferior turbinate for in vitro examination in a mucus-free environment[12] that excludes confounding factors such as stress, hormone secretion, or inflammatory mediators.[16] In contrast, in vitro cultures of cilia may not be representative of how they behave in the body. For example, ciliary dysfunction in patients with cystic fibrosis may not be demonstrated in culture.[17] To measure ciliary motion, the ciliary beat frequency of randomly selected areas is measured photometrically in the presence and absence of BKC for periods ranging from minutes to hours. The photosensitive cell converts the reflected light from the beating cilia to an electric current that is then amplified to an oscilloscope display.[12,18] In vitro, ciliary beating occurs in a coordinated manner at 10 to 20 Hz with an effective stroke perpendicular to the mucosal surface.[18]

Animal studies. BKC was chosen as a prototypical polar compound to examine the in vitro ciliary beat frequency of chicken embryo tracheas compared with lipophilic (eg, chlorocresol) and mercuric compounds (eg, thimerosal).[13] BKC (0.1% wt/vol) in the presence of

EDTA (0.05% wt/vol) caused a reduction of beat frequency of about 30% after a 20-minute exposure. Longer BKC exposure led to more pronounced reductions in beat frequency and ciliostatic effects. The $t_{50\%}$ (frequency time 50% of control) and $t_{0\%}$ (complete loss of motility) was 1.13 and >2 hours, respectively. Chlorhexidine gluconate, a nonquaternary ammonium polar compound, was more toxic. Nevertheless, van de Donk et al[13] recommended BKC (0.01% wt/vol) and EDTA (0.05% wt/vol) as nasal drop additives because these agents had fewer ciliotoxic effects at these concentrations than did chlorhexidine gluconate or thimerosal.

The effect of BKC on the ciliary beat frequency in rat and guinea pig tracheal epithelial tissues was studied by Joki et al.[15] In rat tracheal explants, decrease in ciliary beat frequency was dependent on both duration and concentration of BKC exposure. At concentrations of 0.01% (wt/vol) ciliary activity ceased by 5 minutes, whereas about 30 minutes were required to abrogate beat frequency at lower concentrations (0.00125% wt/vol and 0.0025% wt/vol).

In guinea pig tracheal preparations a dilute concentration of BKC (ie, 0.0025% wt/vol) led to a 27% decrease in ciliary beat frequency by 60 minutes, whereas a slightly higher concentration of 0.005% (wt/vol) irreversibly stopped ciliary activity after 40 minutes. In fact, these in vitro studies revealed that BKC had higher toxicity than three other common preservatives used in nasal formulations.

Human studies. Stanley et al[19] demonstrated a dose-dependent ciliostatic response of BKC in ciliated epithelial preparations obtained by brushing the inferior nasal turbinates of healthy human volunteers. A maximal ciliostatic response was observed by 5 minutes in the presence of 0.01% to 0.02% (wt/vol) and by 60 minutes in the presence of 0.002% (wt/vol). At a concentration of 0.0008% (wt/vol) the ciliostatic response was 57% of control by 60 minutes. These data convincingly indicated the in vitro ciliotoxic nature of BKC.

Significant retardation of ciliary beat frequency of human nasal mucosa by BKC was confirmed in patients with nasal polyposis, chronic sinusitis, or sinus pseudocysts.[15] Reduction of ciliary beat frequency by BKC (0.0012%-0.005% wt/vol) was detected in mucosal explants for periods of 10 to 60 minutes. At 0.005% (wt/vol), BKC irreversibly reduced the ciliary beat frequency by 60%. However, the magnitude of inhibition of ciliary beat frequency by BKC was not as pronounced as that found in mucosal preparations from rat and guinea pig.

In a recent study the effect of several BKC-containing nasal sprays on ciliary beat frequency of human nasal mucosa in vitro was compared with one without BKC.[16] Ciliary beat frequency was slowed down dramatically or irreversibly arrested by 3 of the 4 agents (ie, fluticasone propionate, azelastine, and levocabastine) that contained BKC. In contrast, only mild and transient reduction in beat frequency was observed in the one preparation without BKC, (ie, budesonide). These investigators also demonstrated that BKC alone caused an irreversible arrest of ciliary beat frequency.

Other preservatives used in nasal aqueous solutions of corticosteroids similarly have been shown to be harmful. Propylene glycol (20% wt/vol), a main preservative of flunisolide, caused reversible inhibition of human nasal ciliary beat frequency in vitro.[20] Thimerosal (0.005% wt/vol), a preservative found in some formulations of glucocorticosteroidal nose drops containing either betamethasone alone or betamethasone with neomycin, was ciliostatic within 5 minutes.[19]

Nasal and ciliary histologic features

In addition to routine nasal mucosal morphologic examination, ciliary histologic features can be assessed quantitatively by electron microscopy. A normal columnar cell displays 200 whip-like cilia 6 to 8 μm in length on its surface.[12] These assessments include the number of compound cilia, central and peripheral microtubule defects, inner and outer dynein arms per cilium, and ciliary orientation.[12] A ciliary angle may be determined against a perpendicular ciliary axis line drawn through the centers of the 2 central microtubules.[12]

Animal in vivo and ex vivo studies. Intranasal administration of BKC in rats has been associated with the development of nasal lesions.[21] BKC (0.01, 0.05, and 0.10% wt/vol) was administered to a nasal cavity of rats 8 times for 1 day. Epithelial desquamation, degeneration, edema, or neutrophilic cellular infiltration were demonstrated in the nasal mucosa of rats administered BKC at higher concentrations (0.05 and 0.10% wt/vol) than are used in many nasal sprays (0.01% wt/vol).

Berg et al[22] found that BKC is potentially toxic to nasal mucosa in vivo. In this study rats were exposed to nasal steroids with and without BKC twice daily for 21 days. The structure of the mucosal lining of all parts of the nose was then investigated in serial frontal sections. Squamous cell metaplasia was observed in rats exposed to either beclomethasone or flunisolide containing BKC (0.031% and 0.022%, respectively). These alterations were found in anterior regions of the nose and included reduced epithelial cell height, pleomorphism of individual epithelial cells, fewer cilia, reduced number of goblet cells, and loss of mucus covering the epithelial cell layer. In contrast, pathologic changes were not found in nasal tissues exposed to either nasal steroid without preservative (ie, budesonide) or saline solution alone.

Ainge et al[23] studied the in vivo effect of corticosteroid sprays on monkey and rat nasal ciliated epithelia for 28 days. Cynomolgus monkeys were treated intranasally 8×0.1 mL per day with fluticasone propionate (0.05% wt/vol) containing BKC (0.02% wt/vol) or control (5% glucose). Rats received either beclomethasone dipropionate aqueous spray containing BKC (0.01% wt/vol) in a inhalation chamber for 1 hour per day or air. A BKC control group was not studied. At the end treatment periods ciliated cells were counted, and both scanning and transmission electron microscopy were performed on monkey inferior turbinate and rat intermediate turbinate sites, respectively. There was no difference in the number of ciliated cells in the corticosteroid-treated group versus the

control group. Scanning electron microscopy revealed intact turbinate surfaces with normal ciliated respiratory epithelia. Likewise, transmission electron microscopy analysis showed no ultrastructural abnormalities, suggesting that the effects of BKC-containing corticosteroid sprays were not deleterious.

Human studies. Steinsvag et al[6] demonstrated destruction of human in vitro nasal mucosa preparations by topical nasal steroids containing BKC. In explant cultures of adenoid tissue, corticosteroid nasal sprays (ie, beclomethasone dipropionate, fluticasone propionate, and flunisolide) containing BKC or BKC alone decreased the number of beating cilia in chronic studies of once-daily administration. Assessment by inverted-phase microscopy and scanning electron microscopy showed a gradual transition from a continuous epithelial lining to a rough, irregular surface. After 10 days of exposure, cilia were no longer present on the exposed tissue fragments. The kinetics of morphologic changes seemed to correlate with the levels of BKC present in various nasal sprays. For example, tissue explants exposed to flunisolide containing 0.031% (wt/vol) BKC exhibited histogic changes earlier than preparations of beclomethasone and fluticasone propionate containing 0.022% and 0.02% (wt/vol) BKC, respectively.[6] In contrast, tissue fragments exposed to steroid sprays in the absence of BKC retained beating cilia at all times during the 10-day treatment period. These data support the hypothesis that BKC is responsible for in vitro toxic effects on human respiratory mucosa.

Berg et al[24] studied the in vitro effects of exposure time and concentration on human respiratory mucosa treated with BKC-containing nasal spray. Ten-day cultures of adenoid tissue fragments were exposed to a 14-day treatment of oxymetazoline with BKC (0.015% wt/vol) for 1, 3, 10, or 30 minutes and neat, 30%, 10%, and 3% concentrations of oxymetazoline with BKC (0.015% wt/vol) for 10 minutes. Morphologic and functional assessments were done by electron microscopy and ciliary beat frequency, respectively, for each trial regimen. In the group exposed to daily oxymetazoline for 30 minutes, adenoid fragments exhibited a black, nonpellucid appearance within 3 days. When daily exposure was continued for 14 days, scanning electron microscopy revealed absence of epithelium, basal lamina, defects in cell and nuclear membranes, stromal components of collagen fibrils, autophagosomes, dying cells, and cell remnants. Similar but later-onset findings were observed after shorter exposure times or with more dilute preparations. In addition, the number of beating cilia corresponded to the loss of the continuous epithelial lining in a concentration- and exposure time–dependent manner.

In contrast, Braat et al[25] failed to demonstrate an effect of BKC on the function and morphologic features of cilia in human nasal epithelium. This double-blinded study included 22 patients with allergic rhinitis who received one of the following for 6 weeks: fluticasone propionate aqueous nasal spray (200 μg) with BKC (0.02% wt/vol), BKC (0.02% wt/vol) alone, or placebo. Functional assessment was performed by a saccharin transport test performed before, during, and after treatment. Anatomic evaluation was also performed by electron microscopy of biopsy specimens taken 2 cm behind the anterior tip of the inferior turbinate before and after treatment. The ciliary transport time, as measured by the saccharin test, was unchanged at all time points examined. No difference was observed in the number of ciliated cells between treatment groups, although there were large variations within and between treatment arms. Considerable variation was also observed in the ultrastructure of the ciliated epithelial cells, including the appearance of swollen mitochondria and cytoplasmic vacuoles. However, significant differences were not noted between treatment groups, possibly because of the small number of cohorts in each treatment arm. Despite these variations that may reflect the allergic rhinitis population under study, this negative BKC in vivo and ex vivo study contrasts with previous in vitro observations.

As suggested by Berg et al,[22] the study by Braat et al[25] was not directly comparable because (1) the biopsy samples were limited to the inferior turbinates, (2) significant variation was present in the control populations, and (3) the patients under study had perennial rhinitis with excessive mucus, which may have masked detrimental effects of BKC on the nasal mucosa.

Measurement of the combined effects of the mucus and ciliary systems

As recently summarized by Lale et al,[12] when studying the combined effects of the mucus and ciliary systems it is necessary to distinguish between mucociliary transport and mucociliary clearance. Mucociliary transport represents the movement of particles in an anatomically defined location in an animal model. This may be measured by movement of graphite particles over a defined length of frog palate.[9] Mucociliary clearance measures elimination of inhaled or insufflated aerosols and is typically performed by a saccharin test.[12] The test involves placing one fourth of a saccharin tablet on the anterior end of the inferior turbinate.[17] The patient is asked to sit quietly (without sniffing, sneezing, eating, drinking, or moving the head forward) until the first perception of sweet taste is experienced. Normal saccharin clearance times range from 7 to 15 minutes, with greater than 20 minutes indicative of pathologic mucociliary transport.[12]

Animal in vitro studies. In a model designed to examine the mucociliary transport rate of the frog palate, Batts et al[9] showed BKC to be tolerated poorly. In this model a small volume of the solution was applied to the palate for 10 minutes, followed by measurement of the transport rate of graphite particles over a given distance of the palate for up to 200 minutes. BKC (0.01% wt/vol) halted transport irreversibly after 1 or 2 applications. Unlike other in vitro models, the frog palate system has a ciliated epithelium protected by mucus that may better reflect the in vivo situation in that damage attributable to BKC

may include alterations in the viscoelastic nature of the protective mucus layer.

Human in vivo studies. The immediate and short-term effect of BKC on human nasal mucosa in vivo was examined by McMahon et al.[26] In 34 healthy volunteers subjected to a saccharin clearance test, a 10-minute exposure to BKC (0.02% wt/vol) led to a significant increase in the mean clearance time (762.7 ± 459 seconds) versus that observed with saline solution alone (620 ± 437 seconds). Despite these abnormal single-dose findings in healthy volunteers, these investigators did not detect a difference of saccharin clearance in a double-blind multidose study comparing saline solution, fluticasone propionate plus BKC, and BKC alone administered for 2 weeks at 2 puffs per day.

Van de Donk et al[27] examined the effect of BKC on human nasal mucociliary clearance but failed to see an increase in transport time, indicating normal ciliary beat frequency. These data may not be comparable because the BKC concentrations used were at least 2 log orders more dilute than concentrations used in clinical preparations.

OTHER ADVERSE BIOLOGIC EFFECTS OF BKC

Bronchoconstriction

In addition to its ability to retard ciliary beat frequency and mucociliary clearance, BKC as a preservative has been associated with other adverse biologic effects. This was first reported when paradoxic bronchoconstriction occurred after inhalation of nebulizer solutions of ipratropium bromide and several $\beta_2$agonists.[28] In preservative-free formulations of ipratropium bromide, the expected increase in FEV_1 was observed after inhalation, whereas in the presence of BKC patients actually had bronchoconstriction with a fall in FEV_1 after inhalation. The mechanism of action by which BKC promotes bronchoconstriction may involve histamine release because an H_1 antihistamine blocked BKC-induced bronchoconstriction.[28] Inclusion of BKC (0.01% wt/vol) in albuterol sulfate and metaproterenol sulfate solutions may also counteract the bronchodilating properties of these drugs in some asthmatic patients.[28] In contrast, the presence of BKC did not cause bronchoconstriction in single-dose nebulizer solutions of salbutamol, albeit at lower concentrations than that found in ipratropium bromide (0.01% vs 0.025% wt/vol, respectively).[28]

Rhinitis medicamentosa

BKC has been shown to potentiate rhinitis medicamentosa in healthy volunteers treated with a decongestant nasal spray. Graf et al[29] found an increase of mucosal swelling after use of BKC-containing oxymetazoline 3 times daily for 30 days. In a subsequent study the same investigators determined that the nasal swelling caused by BKC may last for 3 months.[30]

Neutrophil dysfunction

Human neutrophil function was compromised by exposure to BKC-preserved glucocorticosteroid nasal sprays such as flunisolide and beclomethasone.[6] Several index values of neutrophil function, including actin polymerization, degranulation of azurophilic granules, and oxidative burst, were depressed in a time- and concentration-dependent manner. Flow cytometric analysis demonstrated neutrophil disintegration at concentrations of BKC greater than 0.001% (wt/vol). In contrast, exposure of neutrophils to flunisolide or beclomethasone dipropionate in the absence of BKC did not affect neutrophil function.

BKC has been demonstrated to affect leukocyte response to local inflammation. Hakansson et al[8] found that human granulocyte migration was inhibited by BKC at a concentration as low as 0.00008% (wt/vol). In that study, BKC was found to be more deleterious than thimerosal at respective preservative concentrations in nasal drops (ie, BKC [0.02% wt/vol] and thimerosal [0.0024% wt/vol]).[8]

LIMITATIONS OF STUDIES

Discordant results between in vitro and in vivo studies may reflect the protective mechanisms of the respiratory mucosa against topically applied toxic substances, including BKC, found in vivo.[6,26] The preservative may be diluted by nasal secretions covering the nasal mucosa or removed by absorption to the mucociliary layer.[19] Ainge et al[23] postulate that proteins in the mucous blanket may inactivate BKC on the basis of the ability of protein and organic material to rapidly inactivate quaternary ammonium compounds. These naturally occurring palliative events may vary from individual to individual depending on the volume and the physiochemical properties of secretions.

The pH of a BKC solution may be an important factor in accounting for disparate results of different in vitro studies. In this regard, van de Donk et al[13] suggested that a modest decrease in the pH of BKC may markedly reduce ciliary movement of guinea pig trachea. Moreover, a reduction of BKC solution pH from 7.4 to 6.0 decreased the duration of ciliary movement from 1.33 to 1 hour. Whether pH is indeed an important variable in BKC toxicity will require further study.

The extent of BKC toxicity may vary from one site to another within the nasal bed. Areas directly challenged by the impact of the nasal spray, particularly the anterior part of the nasal septum, the tips of the inferior and middle turbinate, and the anterior aspect of a polyp, would be exposed to high concentrations of preservative.[20] This could lead to reduction in ciliary beat frequency and mucosal clearance in specific nasal loci.

The failure to demonstrate deleterious effects of BKC in morphologic studies may also be due to biopsy site.[22] For example, Ainge et al[23] limited their study to the examination of the inferior turbinate and were unable to demonstrate BKC toxicity. In contrast, Berg et al[22] found BKC to be harmful in vivo when the total nasal mucosal lining was investigated histologically by serial frontal sections.

The toxic effects of BKC may be more prevalent in

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