Benzalkonium chloride and nasal mucociliary clearance: A randomized, placebo-controlled, crossover, double-blind trial

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ABSTRACT

Background: *Benzalkonium chloride (BKC) has been considered an innocuous preservative for prescription drugs.*

Methods: *We performed a double-blind, placebo-controlled, randomized, crossover, single-center trial with a 3-week washout period in 43 healthy volunteers comparing the effect of 3-week use of saline nasal spray containing BKC 0.01% to preservative-free saline t.i.d. on nasal mucociliary clearance rate. Evaluations were done at the beginning and the end of each period by γ-scintigraphy with technetium^{99m}-labeled strontium.*

Results: *Nasal mucociliary clearance rate was significantly impaired by BKC with a difference of 1.23 mm·min^{-1} ($p < 0.01$) between periods.*

Conclusion: *BKC in the concentration used in nasal preparations impaired mucociliary clearance in healthy individuals after 3 weeks of use. Presently, when preservative-free alternatives are available, BKC could be a risk without benefit.*

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Among available antimicrobial preservatives, benzalkonium chloride (BKC) was first introduced in 1935 as an antiseptic agent for clinical use and later was approved by the Federal Drug Administration, in 1982, as an innocuous ingredient for prescription drugs at concentrations up to 0.1%. It is the most commonly used agent to prevent bacterial contamination and to preserve pharmacologic activity in a wide range of prescription and over-the-counter products for a large array of indications—including several topical formulations for nasal use—with millions of units sold worldwide annually.[1–3]

Although considered inert, there still is a large uncovered debate in the literature about potential harmful effects of BKC. Recently, BKC effects on nasal mucociliary clearance (NMC), mucosal histology, ciliotoxicity, and neutrophil function were reviewed with conflicting findings.[2,3] Most studies evaluating the effect of BKC on NMC—one of the main nasal defense mechanisms—were done with methodologies that depend on subjective perception as the saccharine test, usually in solutions also containing topical steroids or oxymetazoline and in patients with atopic rhinitis, all of which can introduce serious bias on evaluation. The objective of this study was to investigate the effect of BKC 0.01% saline solution on NMC rate in healthy subjects in a controlled clinical trial.

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METHODS

Study Design and Population

This was a double-blind, placebo-controlled, randomized, crossover, single-center trial devised to investigate the effects of 3-week t.i.d. use of 0.9% saline spray with or without BKC 0.01% (BKC free) on NMC rate. A 3-week washout interval was adopted between both periods. We planned our study in accordance with CONSORT statements.[4] The Institutional Review Board of the Federal University of Pernambuco approved the study and written informed consent was obtained from all participants.

Healthy volunteers, 13–50 years of age, were recruited among relatives of children attending the Pediatrics Allergy Clinic at the University Clinical Hospital. Participants received no payment except transport and meal allowances. Inclusion and exclusion criteria are listed in Table 1.

Interventions

Subjects were screened according to selection criteria (Table 1) and submitted to a basal NMC rate determination. Then, they were submitted to a sequence of two periods of blinded medication use of 3 weeks each (periods 1 and 3), with a 3 weeks washout period of no medication use between them (period 2). At the beginning of periods 1 and 3 subjects received the solution containing atomizers and were instructed to use 1 spray in each nostril t.i.d. NMC rate determinations were done at the end of periods 1, 2, and 3. Any complaints were questioned at each visit, especially those related to symptoms of upper airway infection (upper respiratory infection [URI]), such as fever, sore throat, cough, stuffy/runny nose, and malaise.

BKC saline (Sorine Infantil; batch 0302304; Aché Laboratórios Farmacêuticos SA, São Paulo, Brazil) and preservative-free (Salsep; batch 31023; Libbs Farmaceutica do Brasil, São Paulo, Brazil) solutions were purchased from the market as commercial formulations, both approved by the Brazilian reg-