

Correspondence

Preservation of nasal sprays

To the Editor:

Bernstein in reviewing aspects of the preservation of nasal sprays omitted or distorted issues that are critical to the subject reviewed to retain scientific balance (Bernstein L. Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? A cautionary note based on compromised mucociliary transport. 2000;105:39-44).

There are consistent findings *in vitro* that associate benzalkonium chloride (BKC) with effects on ciliary function. The situation *in vivo*, however, is very different. This difference is predictable. BKC is a quaternary ammonium compound. This property is the key to both its excellent antibacterial attributes and its high degree of safety when exposed to patients. The physical chemistry of BKC ensures that once in the nasal cavity (and of no further pharmaceutical use), it is strongly and irreversibly bound to the proteins in nasal mucus and subsequently cleared by mucociliary clearance and then swallowed. The *in vitro* studies reported use tissue samples that have been washed free of the protective nasal mucus.

This explains the apparent disparity between the *in vitro* and *in vivo* studies that have been reported and the absence of evidence of adverse events attributable to BKC, from long- and short-term clinical studies involving patients with rhinitis. The situation may be different in cases where BKC-containing decongestant nasal sprays are applied to the abnormal nasal mucosa of patients with pre-existing rhinitis medicamentosa.

Healthy cilia and normal ciliary function are consistently demonstrable in *in vivo* studies involving treatment with nasal corticosteroids.¹⁻⁵

One study cited by Bernstein⁶ purports to have shown a deleterious effect of BKC *ex vivo* in rats in the presence of nasal mucus. It is acknowledged that the micropipette technique used will wash off the nasal mucus when the BKC solution is applied to the rats' nasal cavities, and it is probable that the mucus subsequently visible in microscopic sections is new and has been secreted by goblet cells in the period between death and tissue fixation. Therefore these findings mimic the *in vitro*, not the *in vivo*, situation.

A key study was not cited by Bernstein. In this study,⁷ patients who were diagnosed with rhinitis medicamentosa attributed to overuse of decongestant nasal sprays were treated with either fluticasone or a placebo that contained BKC. There was a marked improvement in the condition of both treatment groups, with the response being faster in the fluticasone-treated group. The fundamental finding from this study is that the placebo (containing BKC) applied to the nasal mucosa of patients with rhinitis medicamentosa for 2 weeks improved their condition and not the reverse. Thus it remains unclear why Bernstein should wish to generate this cautionary note in the absence of any clinical evidence that would support his contention.

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Reply

To the Editor:

The chief purpose of the Rostrum review was to focus awareness of the medical community concerning the potential adverse effects of BKC, a commonly used preservative in nasal preparations. The article also adequately stressed current disparities and interpretative limitations between animal *in vitro/in vivo* data and several human clinical studies. As correctly noted by Richards, the degree of absorption of BKC by nasal mucus/protein is a key determinant in the development of possible BKC toxicity.¹ He is incorrect, however, in stating that the *in vivo* rat study by Berg et al was flawed because the micropipette technique of exposure may wash away nasal mucus.² In these experiments several topical nasal steroids (with and without BKC) were sprayed into rat nares through a micropipette twice daily for 21 days, a technique that mimics human exposure. To the best of my knowledge, there is no "acknowledged" precise method that detects significant changes in the mucociliary blanket before and after such applications. Nonetheless, even if it is assumed that each of the nasal applications would lavage away some mucus/protein, it can also be postulated that the mucociliary layer would be replenished before the next application. Regardless of the theoretic possibility that insufficient mucus was available for neutralization of BKC, Berg et al found unequivocal features of squamous cell metaplasia only in the nostrils treated with BKC-containing preparations.

Concerning Richards' assertion about "omitted or distorted issues," it was not possible to include all publications because of the Journal's editorial policy that restricts the number of Rostrum references. Moreover, several abstract articles cited by Richards did not investigate the effects of a BKC-placebo solution.^{3,4} In a 2-week study Hallen et al⁵ demonstrated that symptoms and objective index values of nasal obstruction in patients with rhinitis medicamentosa treated with BKC-formulated fluticasone propionate improved more and faster than in patients receiving the BKC-formulated placebo. It was noteworthy that improvement, as indexed by symptoms and objective tests, was slower in the BKC-placebo group, although symptom scores were lower in this group at the beginning of randomization. Although these results indicated that topical steroids were effective agents in this situation, they did not exclude the possibility that BKC might have been partially responsible for a slower response in the placebo

group. Thus, in contrast to Richards' contention, this particular study did not demonstrate to my satisfaction that BKC was unequivocally nontoxic.

Anecdotally, I continue to receive personal communications about patients who have epistaxis or irritant-like symptoms after use of nonsteroidal BKC-nasal preparations (eg, Ocean™) and I personally have observed similar clinical events. The "cautionary note" expressed in the Rostrum article is fully justified on the basis of current clinical evidence combined with complementary in vivo animal models that directly investigated histopathologic changes after exposure to BKC in a manner similar to clinical usage.² Ultimately, the controversial issue of BKC toxicity in nasal preparations will only be resolved by a long-term, controlled investigation of BKC in 0.9% saline solution compared with 0.9% saline solution alone.

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Issues of fluticasone nasal spray in seasonal allergic rhinitis

To the Editor:

I read with the interest the article by Jen et al (Jen A, Baroody F, deTineo M, Haney L, Blair C, Naclerio R. As-needed fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. 2000;105:732-8). There are some issues that I would like to raise.

First, statistically significant differences in symptom scores between the as-needed fluticasone and placebo groups did not become evident until treatment day 5. Currently available as-needed medicines provide symptom relief on day 1, some within minutes or hours.¹ Given this, it would be unlikely that the typical allergy patient or his or her physician would wait 5 days for an as-needed medication to begin working before wanting to try something else.

Second, no mention is made of how many of the subjects in the as-needed fluticasone group actually used their medication on each day of the 28-day study. Many patients may have used the medicine in the first few days although symptom scores were no better than with placebo until day 5. This point is important because fluticasone's package insert claims to decrease nasal symptoms in some patients in as little as 12 hours after initial treatment. I would like to

ask the authors to disclose how often and on which treatment days the as-needed fluticasone was actually used.

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Reply

To the Editor:

The letter by Stone raises two points about our study.

First, our study was designed to address use of medication over a 28-day period and not to assess the onset of action. There are multiple studies with fluticasone, triamcinolone, and budesonide that all show efficacy within 12 hours. All these studies enrolled larger numbers of patients than ours and all patients started medications on the same day. In contrast, our study had a rolling enrollment and thus the outdoor pollen counts during the study differed for each individual. Furthermore, the patients determined their medication use, implying that not all patients used medications on day 1. In fact, only 50% of the fluticasone group and 42% of the placebo group used medication on the first day in the study. It is for these reasons that our study did not show differences on treatment day 1. We suspect that if larger numbers of patients were enrolled efficacy would have been demonstrated on all days. It is also our premise that the onset of action is not the rationale for effectiveness in the as-needed use of intranasal corticosteroids in the management of seasonal allergic rhinitis because most patients take medications after symptoms develop and the symptoms would dissipate without treatment unless additional exposure occurs. Rather, it is our premise that, in such a design, treatment is targeted for the next exposure.

The second point, similar to the first, asks about medication during the study. Fig 1 shows a plot of the percentage of patients in the fluticasone and placebo groups versus day of treatment. Daily usage ranged from 30% to 70% with a mean of 50% in both groups.

We tried in a number of ways to determine what triggered the patients to use treatment. The percentage of patients using the drug on any given study day correlated with median total daily symptoms in the fluticasone group ($r_s = 0.66$, $P < .001$). The same correlation in the placebo group was less robust ($r_s = 0.35$, $P = .07$). We also correlated each patient's use of medication with the pollen count, his or her symptoms, and his or her medication use. Table I shows the correlation coefficients for these correlations (r_s), which were obtained with use of the Spearman rank test.

As shown, there was tremendous variability among the participants, but the strongest correlations appeared to be between symptoms and medication use. In fact, when all the patient points were analyzed together, there were highly significant correlations between symptoms and medication use for patients in both the fluticasone ($r_s = 0.32$, $P < .001$) and placebo groups ($r_s = 0.28$, $P < .001$). The observation that symptoms trigger medication use is anticipated. The predictive value, however, was low, suggesting that other factors must play a role. The lack of correlation between pollen and medication use probably relates to variable exposure to pollen on the same day because of each individual's different lifestyle. Multiple factors such as individual level of pollen exposure, tolerance of symptoms, planned activities, desire to use med-

ication, perceived benefit of medication, availability of medication when symptoms develop, and individual reactivity to pollen all contribute to the decision to use medication on any given day. Even looking over the individual data, we could not establish a consistent pattern for what triggered medication use, other than symptoms. The importance of the results of our study is that they demonstrate that use of an intranasal steroid as needed will provide positive effects on inflammation, symptoms, and the quality of life of patients with seasonal allergic rhinitis.

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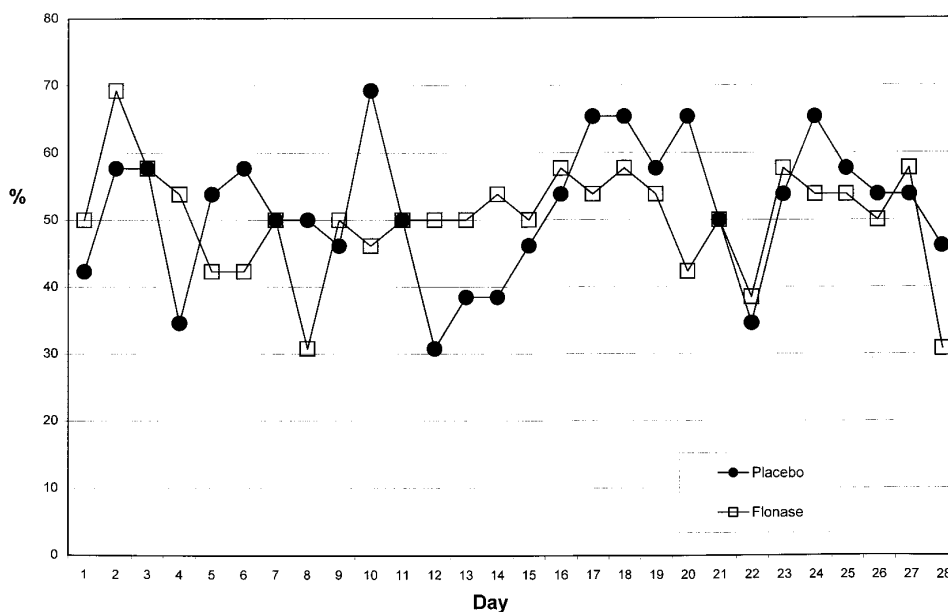


FIG 1. Percentage of patients in fluticasone and placebo groups versus day of treatment.

TABLE I. Correlation coefficients (Spearman rank test)

	Pollen vs symptoms (range [median])	Pollen vs medication use (range [median])	Symptoms vs medication use (range [median])
Placebo	-0.44 to 0.66 (0.25)	-0.49 to 0.39 (0.03)	-0.62 to 0.76 (0.33)
Fluticasone	-0.14 to 0.74 (0.22)	-0.26 to 0.60 (0.09)	-0.54 to 0.99 (0.34)