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# Effect on the Nasal Mucosa of Long-Term Treatment With Oxymetazoline, Benzalkonium Chloride, and Placebo Nasal Sprays

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A parallel, randomized, double-blind study was performed in 30 healthy subjects to investigate the effects on the nasal mucosa of a 1-month treatment with nasal sprays. Ten subjects received oxymetazoline nasal spray; 10 subjects used a nasal spray containing the preservative benzalkonium chloride, and the others were treated with a placebo nasal spray. The three variables that were studied—nasal mucosal swelling, symptom scores, and nasal reactivity—were estimated by histamine challenge before and after 28 days of treatment. Rhinostereometry was used to measure nasal mucosal swelling and nasal reactivity.

After 28 days of use, benzalkonium chloride spray alone induced an increase in nasal mucosal swelling. At the end of the month, the score for nasal stuffiness was significantly higher for the group treated with oxymetazoline than for those treated with benzalkonium chloride. Oxymetazoline nasal spray induced a pronounced increase in nasal reactivity, which was significantly greater than that induced in the placebo group. Long-term use of placebo and benzalkonium chloride nasal sprays also caused an increase in nasal reactivity, but not to the same extent as with the nasal sprays containing oxymetazoline.

The authors concluded that long-term use of oxymetazoline induces a sensation of nasal stuffiness, which may be due to unconscious exaggeration of the degree of nasal stuffiness, induced nasal hyperreactivity, or a combination of both. These factors are probably the main reasons for the prolonged use of nasal decongestive sprays and the development of rhinitis medicamentosa. Benzalkonium chloride induces mucosal swelling, which explains why the presence of this preservative in a decongestant spray aggravates rhinitis medicamentosa.

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## INTRODUCTION

In the early part of this century, topical nasal decongestants were mainly derived from ephedrine. During the 1940s, the abuse of nose drops was reported in a few studies,<sup>1,2</sup> and in 1945 some authors found that rebound swelling (*i.e.*, rhinitis medicamentosa) developed after the protracted use of topical vasoconstrictors.<sup>3</sup>

In the 1960s, the vasoconstrictors xylometazoline and oxymetazoline were synthesized from naphazoline, an imidazole. In 1965, the Council on Drugs of the American Medical Association stated that xylometazoline and oxymetazoline might induce rebound swelling after prolonged use.<sup>4</sup> In 1985, an association between rebound swelling and the protracted use of these agents was demonstrated.<sup>5</sup> Later studies on healthy volunteers found that rhinitis medicamentosa developed after 4 weeks of oxymetazoline and xylometazoline treatment.<sup>6,7</sup> Other studies, however, found no rebound swelling in healthy volunteers after the long-term use of these vasoconstrictors.<sup>8-10</sup> The latter studies<sup>8-10</sup> used rhinomanometry to evaluate the mucosal swelling, whereas the former studies<sup>6,7</sup> evaluated the mucosal swelling with rhinostereometry. It seems possible that rhinomanometry is less accurate than rhinostereometry in determining changes in the nasal mucosa swelling.

Since 1981, the use of nasal vasoconstrictors has increased in Sweden, and sales of multidose preparations climbed dramatically in the late 1980s.<sup>11</sup> Unlike single-dose preparations, all multidose preparations on the Swedish market contain the preservative benzalkonium chloride. Since the beginning of the 1990s, the number of patients with rhinitis medicamentosa has increased,<sup>12</sup> and the roles of vasoconstrictors and preservatives in this condition have been discussed.

The effects of benzalkonium chloride have been evaluated in many studies, both *in vitro* and *in vivo*. There have been reports of damage to cilia in the respiratory mucosa of the frog palate<sup>13</sup> and cellular destruction of corneal epithelium in the rabbit.<sup>14</sup> One study of asthmatic patients showed that benzalkonium chlo-