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OVERUSE OF OXY- AND XYLOMETAZOLINE NASAL SPRAYS

Changes in nasal mucosal swelling and histamine sensitivity in healthy subjects and in patients with rhinitis medicamentosa

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ABBREVIATIONS

BC	Benzalkonium chloride
DNS	Deviated nasal septum
ENT	Ear, nose and throat
NA	Noradrenaline
NANH	Non-allergic nasal hyperreactivity
NAR	Nasal airway resistance
NPY	Neuropeptide Y
PPA	Phenylpropanolamine
RM	Rhinitis medicamentosa
URI	Upper respiratory infection
VAS	Visual analogue scale
VIP	Vasoactive intestinal peptide

Historical background

Intranasal medications for the alleviation of nasal stuffiness have been used since the dawn of civilization. The Talmud speaks of the dung of white dogs mixed with myrrh, and the ancient Hindus used pepper, mustard, orris root and asafoetida to relieve nasal stuffiness. In China 5000 years ago, a herb containing ephedrine was used (Kully 1945; Toohill et al. 1981) but not until 1887 was the alkaloid ephedrine isolated. In 1895, Oliver and Shafer demonstrated the vasoconstrictive effect of epinephrine and, since then, many topical vasoconstrictors have been available. Barger and Dale discovered Neo-synephrine and synephrine in 1910. In 1930, Benzedrine was introduced and in 1931 Privine (naphazoline) was developed (Baldwin 1977).

Hünerman was the first to point out that prolonged use of topical vasoconstrictors could induce nosedrop abuse (Hünerman 1942) and in 1944, it was reported that more than 30 patients had become addicted to Privine (naphazoline) (Gollom 1944). In 1945, Kully described rebound swelling after the long-term use of sympathomimetic drugs (Kully 1945) and he pointed out that, due to "advertising of the patient nostrum in the press and radio" at least 240 vasoconstrictor compounds were available. Re-evaluation of the indications of the use of vasoconstrictors was needed.

Apart from α- and β-receptor activity, ephedrine has an indirect action by releasing noradrenaline (NA) from nerve terminals. Tolerance has been explained as exhaustion of the vasopressor mechanism due to overuse of ephedrine because less NA is released from nerve terminals. In view of experiences from the 1940s regarding RM and tolerance, it was recommended that topical vasoconstrictors should be used no longer than 7-10 days. In the 1960s, modern vasoconstrictors such as oxy- and xylometazoline (imidazoles), acting directly on α-adrenoreceptors, were synthesized from the imidazole naphazoline. Initially, it was believed that these drugs had characteristics close to those required by ideal nasal decongestants (Mayer 1966;Young 1967):

1. A prompt onset of action followed by a long duration, without a decreased vasoconstrictive effect on repeated use
2. No rebound swelling after long-term use
3. No adverse effect on the mucociliary apparatus in the nose
4. No systemic side-effects

The decongestive effect of oxy- and xylometazoline lasts about 7 to 9 hours and they both have a rapid onset of action, with maximal decongestive effect within 30 minutes (von Knothe and Rietshek 1976; Juto and Lundberg 1983). They do not affect other organ systems (Bertler and Drettner 1967; Cohen and Duffy 1969; Empey and Medder 1981; Kuhn 1966), but as regards RM, The Council of Drugs in the American Medical Association points out that, like other topical vasoconstrictors, these drugs may induce rebound swelling after long-term use (A.M.A. 1965). Oxy- and xylometazoline

are chemically and pharmacologically very similar and clinically no difference between the two drugs in the tendency to develop RM has been observed (Rijntjes 1985).

Vascular physiology of the nasal mucosa and vasoconstrictor action

The vascular bed in the lamina propria of the nasal mucosa may be divided into arteries and arterioles (resistance vessels) and a subepithelial capillary network which drains into veins and venous sinusoids (capacitance vessel) (Cauna 1970). Mucosal swelling is due to pooling of blood in the venous sinusoids which is regulated by the capacitance vessels. Both the resistance and the capacitance vessels are surrounded by adrenergic sympathetic nerve fibres that innervate adrenoreceptors (Dahlström and Fuxe 1965; Änggård and Densert 1974) via the neurotransmitter noradrenaline (NA). There are two major types of adrenergic receptors, α and β, where α-receptor stimulation induces vasoconstriction and β-receptor stimulation results in vasodilatation (McGrath 1981) with a functional predominance of α-receptors in the nasal mucosal blood vessels. The α-adrenoreceptors are subdivided into α_1- and α_2-receptors and initially it was suggested that the α_1-receptors were localized postsynaptically, whereas the α_2-receptors were involved in the presynaptic release of NA (Langer 1981). However, the classification of adrenoreceptors based on their anatomical localization is not sufficient because α_2-receptors have also been found postsynaptically (Berthelsen and Pettinger 1977). The nervous control of vasoconstriction resulting in decongestion of the nasal mucosa is induced by an increase in the constant vasomotor tone via the cervical sympathetic chain that acts through the α-receptors. Simultaneously, the parasympathetic activity decreases. To induce vasodilatation, the opposite occurs (Hall and Jackson 1968; Konno et al. 1982).

The two main groups of topical vasoconstrictive drugs are sympathomimetic amines (ephedrine, phenylpropanolamine (PPA)) and imidazoline derivatives (oxy- and xylometazoline) which are α-adrenoreceptor agonists. The sympathicomimetic amines act mainly on the α_1-receptors and the imidazoles are more selective α_2-agonists (Starke 1981). These vasoconstrictors act either by directly stimulating the α-receptors because of their resemblance to NA (imidazoles), or by indirectly stimulating the α-receptors via release of NA presynaptically (PPA) (Bertler and Drettner 1967). Moreover, it has been suggested that NA regulates its own release by acting presynaptically, inducing an inhibitory feedback mechanism through α_2-receptors (Lacroix 1989).

The subdivision of the α-receptors is important regarding the action of topical decongestive drugs. The amines and the imidazoles are powerful decongestants, and the capacitance vessels responsible for mucosal congestion are regulated by α_1- and α_2-receptors (Andersson and Bende 1984). However, it has been shown that oxymetazoline, but not phenylephrine, an α_1-selective sympathomimetic amine, constricts

nasal resistance vessels. This results in a reduction in mucosal blood flow, which was more pronounced in patients with acute rhinitis than in healthy subjects (Bende 1983). The data suggest that the resistance vessels are regulated mainly by α_2-receptors (Andersson and Bende 1984). In the pig nasal mucosa, it has been shown that α_2-adrenoreceptor mechanisms dominate in the regulation of mucosal blood flow and capacitance vessel function (Lacroix and Lundberg 1989).

Physical exercise has a decongestive effect on the nasal mucosa (Broms et al. 1982; Juto and Lundberg 1984a; Richerson and Seebohm 1968) but, unlike oxymetazoline, it does not influence mucosal blood flow (Paulsson et al. 1985). During physical exercise both sympathetic nerve activity and circulating adrenaline levels are increased. It seems possible that NA from adrenergic nerves acts primarily on the α_1-receptors in the nasal mucosa, and circulating adrenaline from the adrenal medulla acts on α_2-receptors (McGrath 1982). If so, the effect of physical exercise on the nasal mucosa would be due to NA. Moreover, it has been shown that PPA, an α_1- and β-adrenoreceptor stimulator, which also acts indirectly by releasing NA, has no blood flow-reducing effect on the nasal mucosa (Bende et al. 1984).

Regarding the β-adrenoreceptors, it is established that they exist in the nasal mucosa in pig and cat (Lacroix and Lundberg 1989; Malm 1974). In the pig nasal mucosa, β-receptor-mediated vasodilatation was seen in resistance vessels, but not in the capacitance vessels (Lacroix and Lundberg 1989). Topical application of the β_2-adrenoreceptor agonist terbutaline had no influence on the human nasal mucosa blood flow, suggesting that β-receptors are of minor importance in the nasal vascular function in man (Andersson and Bende 1984).

Data have been presented indicating the occurrence of non-adrenergic vasoconstrictive mechanisms in the nasal mucosa. By pretreatment of the nasal mucosa with adrenoreceptor blocking agents, it has been shown that NPY, among other substances induces vasoconstriction (Lacroix 1989). In the cat, parasympathetic activation results in atropine-resistant vasodilatation, suggesting that VIP may be a mediator (Änggård 1974). However, there is no evidence that the presently used topical vasoconstrictors interact with NPY or VIP (Malm and Änggård 1993).

Benzalkonium chloride as a preservative

Most nasal drops and sprays are multi-dose preparations that contains a preservative to prevent the growth of microorganisms. There is a risk that gram-negative bacteria will grow in solutions without preservatives, since a large variety of microorganisms have been found in the nasal mucosa of healthy volunteers (Savolainen et al. 1986). Bacterial contamination may result in an infection in the subject, a decrease in the concentration of the drug or instability of the solution (Van de Donk et al. 1980). The

preservative BC, a quarternary ammonium compound, has a bacteriocidal effect since it damages the cell wall of the microorganisms (Richards and Cavill 1976). It is used in nebulizer solutions for the lungs, in nasal sprays, such as vasoconstrictors and corticosteroids, and in eye- and eardrops. In nasal solutions, BC is ordinarily used in concentrations of 100 mg/l or 200 mg/l (Håkansson et al. 1989 a, b).

The use of BC has been questioned because of its reported bronchoconstrictive effects when inhaled by asthmatic patients (Miszkiel et al. 1988 a, b). It has also been shown that exposure to 0.01% BC for 2 minutes damages the corneal epithelium by cellular destruction (Tönjum 1975) and BC-induced contact allergy has been reported in patients with chronic external otitis (Fräki et al. 1985). Moreover, 0.1% BC applied to the serosal surface of the intestine of the rat for 30 minutes has been found to injure intramural nerve elements selectively, resulting in aganglionosis (Sato et al. 1978). Benzalkonium chloride (0.2 mM) also induces irreversible depolarization of the cell membrane of the muscle after a few minutes which injures the muscle cells (Bonciocat 1975). *In vitro* studies in the nose have shown that BC is toxic to the cilia (Batts et al. 1989; Van de Donk et al. 1980, 1981). Moreover, it has been reported that compounds in nasal decongestant preparations, such as oxymetazoline, xylometazoline and BC, have deleterious effects on granulocyte chemotaxis and phagocytosis (Håkansson et al. 1989 a, b) and other important defence functions of the neutrophils *in vitro* (Bjerknes and Steinsvåg 1993). The effects of such compounds on the mucociliary transport rate are not yet clear, since conflicting results have been reported (Petruson and Hansson 1982; Saketkhoo et al. 1978; Simon et al. 1977).

RHINITIS MEDICAMENTOSA

Definitions

Regarding the term rhinitis medicamentosa, various definitions are found in the literature and opinions differ as to what is meant by RM. As far back as 1946, Lake coined the expression "rhinitis medicamentosa for the condition of the nasal membranes resulting from overuse of nasal vasoconstrictors" (Lake 1946). RM has also been referred to as "chemical rhinitis" (Stephens and Boggs 1968). Baldwin defined RM as a "chronic inflammatory condition of the nasal mucous membranes secondary to the prolonged use of topical vasoconstrictor agents" (Baldwin 1977). However, Rijntjes prefers to employ the term rhinopathia medicamentosa because in his studies on patients who had overused topical vasoconstrictors no inflammatory infiltrate was found in the nasal mucosa (Rijntjes 1985). Other authors, focusing on the clinical picture rather than on the histological findings, describe RM as "a condition

characterized by symptoms of rhinitis caused by the same decongesting nosedrops as the patient uses to relieve the symptoms" (Åkerlund and Bende 1991).

According to Feinberg, there always remains a compensatory vasodilatation after the vasoconstrictive effect of the drug has disappeared. This makes the patient use the nosedrops again, and with each cycle the congestion increases. Over time, the only way to alleviate the rebound swelling is to stop using the decongestants. When the problem "is *recognized,* it is apt to be called rhinitis medicamentosa" (Feinberg and Feinberg 1971). Other authors have extended the term RM to mean "the syndrome of RM" (Stride 1967). In this syndrome, tolerance must develop for the term RM to be employed. By using the definition "symptomatology of RM", Fleece and co-workers emphasize that in many cases the chronic use of nasal vasoconstrictors is a true addiction (Fleece et al. 1984).

Pathophysiology

The pathophysiology of the rebound swelling in RM is not known. However, several theories have been postulated some which are more plausible than others. According to Baldwin (1977), secondary vasodilatation may develop because all sympathomimetic amines have both α- and β-receptor activity. The β effect, although not so pronounced, outlasts the α effect and causes rebound swelling. Beside α- and β-receptor activity ephedrine has an indirect action by releasing NA from nerve terminals. Tolerance has been explained as exhaustion of the vasopressor mechanism due to overuse of ephedrine because less NA is released from nerve terminals. However, oxy- and xylometazoline act selectively on the α-receptors, but the long-term use of these drugs also induces rebound swelling. Moreover, it has been shown that the decongestive effect remains unchanged during long-term use of xylometazoline (Petruson 1981b; Åkerlund and Bende 1991).

It has further been suggested that the rebound swelling occurs because of tissue hypoxia resulting in reactive hyperaemia which is manifested as vasodilatation (Baldwin 1977; DeBernardis et al. 1987). This is improbable because the resistance vessels regulating mucosal blood flow are affected mainly by α_2-adrenoreceptor agonists (Andersson and Bende 1984). Unlike the imidazoles, the α_1-selective sympathomimetic amines cause decongestion without reducing nasal mucosal blood flow (Andersson and Bende 1984). However, the sympathomimetic amines induce rebound swelling after long-term use (Osguthorpe and Reed 1987).

The rebound swelling has also been attributed to long-term use of α_2-receptor agonists that may stimulate the negative feedback mechanism presynaptically, resulting in reduction of endogenous NA (Lacroix 1989). The α-adrenergic tone would then persist only so long as the topical α_2-receptor agonist is used. When the action of the drug disappears, rebound swelling follows (Malm and Änggård 1993). This theory is

supported by evidence that, in the dog, nasal mucosa pretreatment with an α_2-receptor agonists reduces the response to sympathetic nerve activation (Berridge and Roach 1986). However, vasoconstrictors without α_2-receptor action also induce rebound swelling.

Finally, the rebound phenomenon has been ascribed to alteration in the vaso-motor tone with increased parasympathetic activity, vascular permeability and oedema formation (Osguthorpe and Reed 1987). This hypothesis is in accordance with a study in guinea pigs which received naphazoline for 4 months (Elwany and Stephanos 1983). An increased activity of the choline esterase enzyme in the cholinergic nerves around the blood vessels was found which was interpreted as parasympathetic hyperactivity. Marked vascular dilatation and oedema were also present, indicating an increased vascular permeability. Similar results have been reported by Talaat and co-workers (1981) while no such histological changes were found in studies performed by others (Petruson and Hansson 1982; Rijntjes 1985).

Epidemiology

Rhinitis medicamentosa is more common in young and middle-aged adults than in children and old people, but there is no difference between men and women (Baldwin 1977; Toohill et al. 1981). The lowest incidence is reported in a study by Toohill who reviewed the charts in their otolaryngological practice over a 10-year period. One per cent (130 patients) had overused phenylephrine, oxymetazoline and xylometazoline, in that order (Toohill and et al. 1981). In another large survey, 119 physicians answered a questionnaire about RM (Fleece et al. 1984). Using Baldwin´s definition of RM (see p. 12), 6.7% of the patients examined by these physicians fitted that definition. In Great Britain it has been estimated that many ENT units may have an incidence rate of up to 5% among their out-patients (Stride 1967). Feinberg and Feinberg (1971) in their private allergy practice, examined the records of the last 500 new patients suffering from severe nasal obstruction. In this selected group of patients, the nasal obstruction was presumed to be due to nasal allergy. However, the major problem was RM in 46 of them (9.2%), the majority having overused oxymetazoline. In a prospective study, 100 consecutive adult patients with nasal obstruction were studied (Mabry 1982). Patients with infections were excluded and of these 100 patients, 52 with typical RM had used nosedrops for more than 14 days, according to the author.

It should be pointed out that in the study by Toohill, the average duration of the nosedrop overuse was 21.4 months indicating that more severe, chronic cases of RM were included in that study, unlike in the study by Mabry. Moreover, patients with RM are often unaware of the origin of the nasal stuffiness and unless they are directly asked a question regarding their use of vasoconstrictors, the diagnosis may easily be

overlooked. Therefore, retrospective studies probably tend to underestimate the incidence of RM.

The general impression is that RM is common in Northern Europe and North America. Many patients also point out that their nasal symptoms improve in summer or when they travel to warm, humid countries. Although allergy is often cited as a predisposing factor, no difference in incidence was found between high and low ragweed areas in North America (Fleece et al. 1984). The incidence of RM in a servey from Canada was 6.1% (134 of 2185 patients) where patients with asthma or rhinitis were studied (Toogood 1990). A high prevalence of asthma (59.7%) among the patients with RM was found. Similar data have not been reported previously and, according to the author, the association was presumably correlative rather than causal.

Predisposing factors

Patients with some underlying chronic nasal obstruction run a greater risk of developing RM. Often the basic underlying nasal disorder is not apparent at the initial examination, but it usually becomes clear when treatment has begun. Frequently, the patients do not remember or do not know why they initially started to use the topical decongestant. In the study by Toohill, 43 of 130 patients had deviated nasal septums (DNS) that led to the overuse of topical decongestants (Toohill et al. 1981). An upper respiratory infection (URI) was the cause of nasal obstruction in 33 of the patients, while 20 had allergy, seven had vasomotor rhinitis and 6 had rhinitis associated with pregnancy as the underlying nasal disorder. In the study by Baldwin (1977), 14 of 22 patients had allergy, two had allergy and deviated septums, two had deviated septums without allergy. Three patients had URIs which precipitated their nasal obstruction and one had used antihypertensive medication (reserpine). In 1952, Walker presented a study on RM in which 20 patients had overused nose drops (17 used naphazoline and three used phenylephrine) (Walker 1952). In that study, 10 patients had an URI, three had allergy, two were pregnant, one had purulent sinusitis, and four had nasal obstruction of unknown aetiology.

Symptoms and diagnosis

Nasal blockage is the dominating symptom in patients with RM. Nasal obstruction without discharge should immediately alert one to the possibility of RM (Walker 1952). The patients who suffer from both nasal blockage and rhinorrhoea often have allergy or vasomotor rhinitis as an underlying nasal disease. Severe nasal blockage may lead to oral breathing and a dry, sore throat. Other common features are insomnia, snoring and disturbed sleep with excessive sweating. The complications of RM include chronic ethmoiditis, nasal polyposis and atrophic rhinitis (Black and Remsen 1980; Toohill et al. 1981). The abuse of topical vasoconstrictors in neonates can be life-

threatening. Infants are obligate nasal breathers up to 2 months of age and it has been reported that RM may cause respiratory distress, polycythaemia and cardiomegaly (Osguthorpe and Reed 1987).

Clinically, one cannot distinguish between RM, nasal allergic and vasomotor rhinitis (Blue 1968; Feinberg and Friedlaender 1945; Kully 1945; Stride 1967). Patients suffering from RM are often unaware of the origin of the stuffiness and therefore one must ask all patients with chronic nasal obstruction about their use of topical vasoconstrictors.

It is not known why some subjects continue to use topical decongestants, sometimes for years. It has been suggested that RM develops in predisposed individuals after long-term use of topical decongestants, implying that RM does not occur without an underlying nasal disorder (Åkerlund and Bende 1991). Moreover, some authors believe that nosedrop abusers do not tend to increase the dose or the number of daily doses. Although they need to continue the medication to relieve the nasal stuffiness, and though discomfort occurs when the nosedrops are not available, these authors prefer to use the term habituation rather than addiction (Rijntjes 1985; Åkerlund and Bende 1991). Others claim that the symptomatology of RM is, indeed, an addiction since the long-term use of topical decongestants induces drug tolerance, an abstinence syndrome and psychological dependence (Fleece et al. 1984). Many authors emphasize the patients´ tendency to use additional doses of the vasoconstrictor in gradually increasing larger doses as an expression of tolerance (Baldwin 1977; Feinberg and Feinberg 1971; Lekas 1991; Osguthorpe and Reed 1987). An abstinence syndrome on cessation of the decongestants has been seen, including headache, restlessness, anxiety and dysphoria (Fleece et al. 1984; Walker 1952) and cases of psychological dependence have also been reported (Snow et al. 1980).

On rhinoscopy, the appearance of the mucous membrane varies from congested, hyperaemic and granular in the early stages, to pale and anaemic in the late stages. The diagnosis is established by a history of prolonged use of nasal decongestants, constant nasal obstruction and poor shrinkage of the nasal mucosa on examination (Walker 1952). To verify the diagnosis, Mabry applied a powerful vasoconstrictor (4% cocaine) to the nasal mucosa which acts by blocking re-uptake of NA. He states that this does not usually induce vasoconstriction in patients with RM (Mabry 1982).

Need for studies of RM

Clinically, one cannot distinguish between vasomotor rhinitis and RM because the medical history of patients with RM resembles that of patients having vasomotor rhinitis with blockage as the main symptom. Using rhinostereometry to record the nasal mucosal reaction in terms of congestion (Juto 1985), a histamine provocation model has recently been presented, standardizing the nasal mucosal reactivity. With the histamine

challenge test one can distinguish between healthy subjects and patients with vasomotor rhinitis, independently of the predominant symptom of nasal blockage, sneezing or enhanced secretion (Hallén 1994). The hypothesis in this study was that the nasal stuffiness in patients with RM may be due to the development of nasal hyperreactivity induced by the long-term use of decongestant sprays. Patients with RM may have had an increased histamine sensitivity prior to their overuse of nosedrops. The histamine sensitivity during long-term use of nasal decongestant sprays therefore has to be evaluated first in healthy subjects.

Symptom score tables have frequently been used in clinical trials to estimate nasal patency. However, contradictory results have been reported regarding the correlation between the subjective sensation of nasal stuffiness and nasal resistance to airflow as measured with Yolten meter and rhinomanometry (Fairley et al. 1993; Jones et al. 1989). Thus it is important to investigate whether the estimated stuffiness correlates with objective nasal mucosal swelling, as measured with rhinostereometry.

Hitherto, knowledge about RM has been based on case reports and a few surveys. Some animal studies on the subject have also been published (Elwany and Stephanos 1983; Fox 1931; Talaat et al. 1981). However, with rhinomanometry no rebound swelling has been found in healthy subjects after the long-term use of xylometazoline nosedrops (Åkerlund and Bende 1991; Petruson 1981 b). Moreover, opinions vary as to whether tolerance exists with modern decongestants (Lekas 1991; Petruson 1981b) and systematic follow-up of patients with RM after vasoconstrictor withdrawal has been lacking. There is therefore a great need for objective, long-term studies regarding RM in healthy volunteers and in patients.

It has been suggested but never confirmed, that the severity of the rebound swelling and RM are directly proportional to the period during which the drug is used, to the frequency of its use and to the amount of drug administered (Baldwin 1977; Chignell 1972; Fleece et al. 1984; Kully 1945). To determine what is an adequate amount of vasoconstrictor, the investigations have hitherto focused on the effectiveness of the drugs (Connell 1969; Meurman and Rantanen 1975; Åkerlund et al. 1989). However, no studies have been performed to evaluate the effects of various amounts of the vasoconstrictors on the development of RM. Moreover, it has always been assumed that the vasoconstrictor alone is responsible for the development of RM. No *in vivo* studies have yet been performed to investigate whether benzalkonium chloride in nasal decongestant solutions affects the development of rhinitis medicamentosa.