Rhinitis Medicamentosa

JT Ramey,[1] E Bailen,[2] RF Lockey[1]

[1] Division of Allergy & Clinical Immunology, University of South Florida & James A. Haley VA Medical Center, Tampa, Florida, USA
[2] University of Louisville School of Medicine, Louisville, Kentucky, USA

Abstract. Rhinitis medicamentosa (RM) is a condition induced by overuse of nasal decongestants. The term RM, also called rebound or chemical rhinitis, is also used to describe the adverse nasal congestion that develops after using medications other than topical decongestants. Such medications include oral ß-adrenoceptor antagonists, antipsychotics, oral contraceptives, and antihypertensives. However, there are differences in the mechanism through which congestion is caused by topical nasal decongestants and oral medications.

Very few prospective studies of RM have been performed and most of the knowledge about the condition comes from case reports and histologic studies. Histologic changes consistent with RM include nasociliary loss, squamous cell metaplasia, epithelial edema, epithelial cell denudation, goblet cell hyperplasia, increased expression of the epidermal growth factor receptor, and inflammatory cell infiltration. Since the cumulative dose of nasal decongestants or time period needed to initiate RM has not been conclusively determined, these medications should only be used for the shortest period necessary. Validated criteria need to be developed for better diagnosis of the condition. Stopping the nasal decongestant is the first-line treatment for RM. If necessary, intranasal glucocorticosteroids should be used to speed recovery.

Key words: Rhinitis medicamentosa. Congestion. Decongestants. Sympathomimetic amines. Imidazolines

Resumen. La rinitis medicamentosa (RM) es una enfermedad originada por un uso abusivo de descongestivos nasales. El término "rinitis medicamentosa", también denominada rinitis química o de rebote, se utiliza también para describir la congestión nasal adversa que se desarrolla tras el uso de otros medicamentos que no son descongestivos tópicos. Estos medicamentos incluyen antagonistas de los receptores ß-adrenérgicos orales, antipsicóticos, anticonceptivos orales y antihipertensores. Sin embargo, existen diferencias entre el mecanismo de congestión causado por los descongestivos nasales tópicos y el causado por los medicamentos orales.

Se han realizado muy pocos estudios prospectivos sobre la RM, y la mayor parte de la información conocida sobre esta enfermedad procede de la observación clínica y de estudios histológicos. Los cambios histológicos correspondientes a la RM son pérdida nasociliar, metaplasia de células escamosas, edema epitelial, denudación de células epiteliales, hiperplasia de células caliciformes, aumento del receptor del factor de crecimiento epidérmico e infiltración de células inflamatorias. No se ha determinado de forma concluyente la dosis acumulada de descongestivos nasales ni el período de tiempo necesario para el inicio de la RM, por lo que estos medicamentos sólo deben utilizarse durante un período de tiempo lo más corto posible. Es preciso establecer criterios validados para un mejor diagnóstico de la enfermedad. La interrupción del descongestivo nasal es el tratamiento de primera línea para la RM. En caso necesario, deben administrarse glucocorticoesteroides intranasales para acelerar la recuperación.

Palabras clave: Rinitis medicamentosa. Congestión. Descongestivos. Aminas simpaticomiméticas. Imidazolinas

Introduction

This review, based on literature searches in MEDLINE and the bibliographies of relevant articles, addresses the most current information on the pathophysiology, diagnosis, and treatment of rhinitis medicamentosa (RM). RM is "… a drug-induced, nonallergic form of rhinitis in which the nasal mucosa is induced or aggravated by the excessive or improper use of topical decongestants" [1].

Since the first nasal vasoconstrictor was isolated in 1887 from ma-huang, a herb containing ephedrine, these medications have been used in the nose as inhalants, oils, sprays, and drops [2]. Fox [3] originally described the effects of chronic usage of topical decongestants in 1931. "Rebound congestion" was first mentioned by Feinberg [4] in 1944 when subjects developed nasal congestion after using privine hydrochloride, after which Lake [5] coined the term rhinitis medicamentosa in 1946. Very few

prospective studies of RM have been performed, and most of the knowledge about the condition comes from case reports and histologic studies [6, 7].

The term RM, also called rebound or chemical rhinitis, is also used to describe the adverse nasal congestion that develops after using medications other than topical decongestants. Such medications include oral ß-adrenoceptor antagonists, phosphodiesterase type 5 inhibitors, antipsychotics, oral contraceptives, and antihypertensives (see Table 1) [1, 8-11]. Since a different mechanism may underlie the congestion caused by topical nasal decongestants compared with other oral medications, a term other than RM is preferred to describe rhinitis associated with oral medications, such as "drug-induced rhinitis."

The first criteria for the diagnosis of RM were proposed in 1952 and included "…(1) history of prolonged nasal medication, (2) constant nasal obstruction, and (3) poor shrinkage of nasal mucous membranes on examination" [12]. Many criteria have been used since that time to characterize RM, even though validated criteria do not yet exist. In addition, the results of studies designed to identify the timing of its onset are inconclusive. For example, several studies demonstrate that rebound congestion does not develop with up to 8 weeks of topical decongestant use [13, 14], while others have suggested that the onset of RM occurs after the use of topical sympathomimetics for 3 to 10 days [1, 15]. Discontinuation of oxymetazoline is recommended after 3 days of use [16]. This is supported by a study that shows increased nasal airway resistance after 3 days of daily or intermittent oxymetazoline [17]. However, several smaller studies by Graf and Juto [18-20] showed that rebound congestion does not begin until after 10 days of use in healthy volunteers. In addition, the congestion continues to worsen from day 10 to day 30. Those authors also found that doubling the dose of oxymetazoline in 9 healthy volunteers for 30 days does not increase rebound congestion [18]. However, since that was a small study, further work needs to be done to determine whether increased dosages of decongestants worsen RM.

Presentation

RM is characterized by nasal congestion without rhinorrhea, postnasal drip, or sneezing that begins after using a nasal decongestant for more than 3 days [21]. Nasal decongestants are used to relieve congestion in patients with allergic rhinitis, nonallergic rhinitis, acute or chronic sinusitis, nasal polyposis, rhinitis secondary to pregnancy, or rhinitis due to nasal septal deviation or obstruction [1, 15]. They are also frequently used by individuals with viral upper respiratory tract infections, 25% to 50% of whom may develop RM [1].

RM occurs at a similar rate in men and women but is more common in young and middle-aged adults [1, 22]. The incidence reported in otolaryngology clinics ranges from 1% to 7% [1, 23, 24]. Out of 500 consecutive patients

Table 1. Medications Associated With Drug-Induced Rhinitis*

– Antihypertensives:
  • Amiloride
  • Angiotensin-converting enzyme inhibitors
  • ß-blockers
  • Doxazosin
  • Chlorothiazide
  • Clonidine
  • Guanethidine
  • Hydralazine
  • Hydrochlorothiazide
  • Methyldopa
  • Phentolamine
  • Prazosin
  • Reserpine

– Phosphodiesterase type 5 inhibitors:
  • Sildenafil
  • Tadalafil
  • Vardenafil

– Hormones:
  • Exogenous estrogens
  • Oral contraceptives

– Pain relievers:
  • Aspirin
  • NSAIDs

– Psychotropics:
  • Chlordiazepoxide-amitriptyline
  • Chlorpromazine
  • Risperidone
  • Thioridazine

– Miscellaneous:
  • Cocaine
  • Gabapentin

* NSAID indicates nonsteroidal antiinflammatory drug. Table based on previously published data [11, 69, 70].

with nasal congestion in an allergy clinic, 9% had RM [1, 25]. In a survey of 119 allergists, 6.7% of the patient population was reported to have RM [26].

The appearance of the nasal mucosa does not distinguish RM from infectious or allergic rhinitis. The nasal mucosa can be "beefy-red" with areas of punctate bleeding and minimal mucus [1, 12, 27], or edematous with a profuse, stringy, mucoid discharge [23]. The mucosa may be pale and edematous or even atrophic and crusted following continued use of nasal decongestants [28]. Subjects with RM may snore, have insomnia from rebound congestion, and mouth-breathe, resulting in dry mouth and sore throat [8, 10].

The pathologic changes caused by nasal decongestants can alter normal nasal physiologic functions such as filtration of particulates and the regulation of temperature and humidity [23]. RM may also predispose to chronic sinusitis, otitis media, nasal polyposis, or atrophic rhinitis

[22, 23]. Psychological dependence and an abstinence syndrome consisting of headaches, restlessness, and anxiety following discontinuation of nasal decongestants have been reported, leading some authors to use the word "addiction" when describing this syndrome [26, 29]. A case report described a subject with RM who carried 4 gallons of phenylephrine aboard a wartime ship [30], allegedly because of an addiction to this medication. In addition, neonatal respiratory distress syndrome has been associated with the use of topical phenylephrine [31].

Physiology of Nasal Congestion

The nasal mucosa is composed of both resistance and capacitance blood vessels. The resistance vessels, comprising small arteries, arterioles, and arteriovenous anastomoses, drain into the capacitance vessels, which are made up of venous sinusoids [32]. The venous sinusoids are richly innervated with sympathetic fibers and when stimulated these nerves release norepinephrine, which binds to prejunctional α_2 and postjunctional α_1 and α_2 receptors. This leads to reduced nasal congestion by decreasing blood flow and increasing sinus emptying in the capacitance vessels [32-36].

Other nerves such as parasympathetic, sensory C-fibers, and nonadrenergic noncholinergic (NANC) peptidergic nerves also contribute to nasal congestion [32]. Parasympathetic nerves release both acetylcholine, which increases nasal secretions, and vasoactive intestinal peptide (VIP), which causes vasodilation. Sensory C fibers contain substance P, neurokinin A, and calcitonin gene-related peptide, all of which downregulate intrinsic sympathetic vasoconstriction. Stimulation of NANC nerves causes rhinorrhea, sneezing, and congestion.

Local mediators also affect nasal congestion by inducing changes in nasal resistance and capacitance vessels. Mast cells, eosinophils, and basophils contribute to nasal congestion by the release of histamine, tryptase, kinins, prostaglandins, and leukotrienes [32]. Exudation of plasma, which contains albumin, immunoglobulins, and factors involved in the kinin, complement, coagulation, and fibrinolytic systems, occurs through the fenestrations of the superficial capillaries [32]. Goblet cells, which are increased in RM, are not under autonomic control, but rather, can cause congestion by releasing mucin after stimulation from proteases, arachidonic acid metabolites, histamine, neurotransmitters, cytokines, or nucleotide triphosphates [32].

Mechanism of Action of Nasal Decongestants

There are 2 classes of nasal decongestants: sympathomimetic amines and imidazolines. Sympathomimetic amines include caffeine, benzedrine, amphetamine, mescaline, phenylpropanolamine (no longer used in the USA), pseudoephedrine, phenylephrine,

Table 2. Decongestants Causing Rhinitis Medicamentosa

– Nasal decongestants:
  – Sympathomimetic:
    • Amphetamine
    • Benzedrine
    • Caffeine
    • Ephedrine
    • Mescaline
    • Phenylephrine
    • Phenylpropanolamine (no longer available in the USA)
    • Pseudoephedrine

– Imidazolines:
  • Clonidine
  • Naphazoline
  • Oxymetazoline
  • Xylometazoline

and ephedrine (see Table 2) [1, 33]. Nasal imidazolines include oxymetazoline, naphazoline, xylometazoline, and clonidine.

Sympathomimetic amines mimic the actions of the sympathetic nervous system through the presynaptic release of norepinephrine in sympathetic nerves. Norepinephrine then binds postsynaptically to α-receptors and results in vasoconstriction. They are also mild ß-receptor agonists and cause rebound vasodilation after the α-effect has waned. They have no effect on blood flow [1].

The imidazolines are primarily α_2-agonists that act postsynaptically on sympathetic nerves and cause vasoconstriction [1]. They also lower the production of endogenous norepinephrine via a negative feedback mechanism, thus decreasing blood flow and decongesting the nose.

Pathophysiology of RM

The pathophysiology of RM is unknown. There are various hypotheses as to why it exists. It may be secondary to the decreased production of endogenous sympathetic norepinephrine through a negative feedback mechanism [1]. With prolonged use or following discontinuation, the sympathetic nerves may be unable to maintain vasoconstriction because norepinephrine release is suppressed.

In a human study by Cauna et al [37], plasma cells were found surrounding degenerating autonomic and sensory nerve endings in the nasal mucosa. In rabbits treated with either oxymetazoline or phenylephrine, acute purulent maxillary sinusitis developed in 13.3% of the former group and in 33.3% of the latter group [38]. In that study, histology of the sinus mucosa revealed ciliary loss, epithelial cell denudation, inflammatory cell infiltration, and edema.

Benzalkonium chloride (BKC), a quaternary ammonium compound used as a preservative to prevent bacterial contamination in many nasal sprays [1], may increase the risk of developing RM by inducing mucosal swelling [39-43]. Therefore, Graf [1] recommends using BKC-free nasal decongestants, even though there is no evidence of worsening congestion in subjects who use nasal glucocorticosteroids containing BKC [44-46].

Histology of RM

Many different changes have been found in histologic studies of RM (see Table 3). Disruption of nasociliary function, proposed as early as 1934, was confirmed in an uncontrolled study in rabbits treated either with 1% ephedrine with sodium sulfathiazole or naphazoline 4 times a day [47]. The rabbits were found to have ciliary loss beginning at day 5, epithelial cell damage of the nasal mucosa in the first week, and edema in the second week. Edema of the subepithelial layer was followed by fibrosis and hypertrophy during the third week. Further cellular damage with accompanying edema and mucus production occurred during the third and fourth week. Total cellular disorganization was noted in the fifth week, and the epithelial cells changed from ciliated columnar to nonciliated, stratified squamous cells by the eighth week. Blood vessels were initially dilated but later became sclerotic and constricted.

Talaat et al [48] used electron microscopy in a rabbit model to compare normal nasal mucosa with mucosa treated with 1% ephedrine for 2 and 3 weeks. The rabbits treated with ephedrine for 2 weeks developed abnormal microtubules lacking the normal 9+2 structure; instead, the microtubules adhered together in homogeneous "club-like" groups. Edema caused the epithelial cells to separate. Desmosomes, which connect cells in the basal cell layer near the basal lamina, were decreased. The subepithelial layer was also edematous and contained irregularly arranged collagen fibrils. After 3 weeks of medication, a marked decrease in the number of cilia on the epithelial surface was noted. Edema was again present in the epithelium. Vascular dilation and congestion was present

Table 3. Pathologic Changes Associated With Rhinitis Medicamentosa

– Nasociliary loss and changes in nasociliary structure
– Squamous cell metaplasia
– Increased mucus production
– Epithelial cells can change from ciliated columnar to nonciliated, stratified squamous
– Epithelial cell denudation
– Increase in intercellular widening, vascularity, fibrosis, edema of the epithelial cell layer
– Goblet cell hyperplasia
– Increase in epidermal growth factor receptor in the epithelial cell layer
– Increase in lymphocytes, fibroblasts, and plasma cells

in the tunica venules with increased openings in the endothelial cell junctions. The basement membrane was also thickened.

In another study, RM was induced in guinea pigs by instilling 2 drops of 0.05% naphthazoline nitrate into their nostrils 3 times a day [50]. The animals were sacrificed at 2, 4, 6, 8, 12, and 16 weeks, and specimens divided into 2 groups, 1 for histopathology using light microscopy and the other for histochemical studies. The number of goblet cells was found to increase until week 6, after which time the number decreased. Increased numbers of lymphocytes, plasma cells, and fibroblasts, squamous metaplasia, increased vascularity, glandular hyperplasia, and edema were seen during the study. An increase in the enzyme cholinesterase was found throughout the entire study in cholinergic nerve fibers around the glands, suggesting a decreased parasympathetic response. Histochemical studies also revealed increased activity of the enzymes succinic dehydrogenase, alpha esterase, alkaline phosphatase, and acid phosphatase.

Suh et al [51] evaluated the effect of phenylephrine and oxymetazoline on 90 healthy rabbits by light and electron microscopy. The rabbits were divided into 3 groups: topical phenylephrine, oxymetazoline, or saline administered for 1 week, 2 weeks, or 4 weeks. After 2 weeks of phenylephrine or oxymetazoline, animals had mucociliary loss, mucosal cell infiltration, primarily of lymphocytes, and subepithelial edema. The ciliary loss at the epithelial surface increased at 4 weeks in both the phenylephrine and oxymetazoline groups compared to controls. In addition, mitochondrial and endoplasmic vacuolization and cytoplasmic vesicles were discovered in the nasal decongestant groups after 2 and 4 weeks. Acute purulent maxillary sinusitis only occurred in the phenylephrine group at 4 weeks.

Results in human studies have been inconclusive. For example, xylometazoline has been reported not to affect nasal ciliary function [52]. Petruson and Hannson [52, 53] used electron microscopy and posterior rhinomanometry to study 20 healthy subjects after 6 weeks of xylometazoline (1 mg/mL), 0.15 mL, 3 times daily. The nasal mucosa showed no morphological changes in the intercellular spaces, basement membrane, or tunica propria after 6 weeks of treatment. Five subjects developed a viral upper respiratory infection during the trial. These subjects also did not display decreased mucociliary transport or reactive congestion after treatment. Another study showed no development of rebound congestion in normal subjects after using xylometazoline for 3 weeks, but RM did develop in subjects with nonallergic rhinitis [15].

Lin et al [49] used electron microscopy and immuno-histochemistry to compare the nasal mucosa in control subjects and individuals with chronic hypertrophic rhinitis or RM. Subjects with RM had the most prominent goblet cell hyperplasia and the highest levels of epidermal growth factor receptor in the basal layers of the hyperplastic epithelium. The epidermal growth factor receptor is important in epithelial cell differentiation and cell

proliferation. It is seen in malignancy and hypersecretory airway disease but is rarely expressed in normal nasal tissue [49].

In a study by Graf and Juto [20], no rebound congestion was observed in 8 healthy volunteers after 10 days of oxymetazoline use. However, subjects were found to have significant rebound swelling after 30 days of use. Other studies by Graf and Juto [19, 54] have shown an increase in histamine sensitivity and subjective nasal congestion symptom scores in healthy volunteers. The changes began on day 10 of oxymetazoline treatment and continued through day 30.

In a study involving 30 human subjects diagnosed with RM secondary to naphazoline, destruction of the nasal cilia and epithelial cell mitochondria was demonstrated [55]. In addition, the nasal epithelium was swollen secondary to arteriolar dilation, mononuclear infiltration, and glandular secretion and hyperplasia. Nasal mucus clearance using saccharin was also prolonged in this group. Human studies suggest that nasal decongestants are more likely to cause RM in subjects with previous nasal congestion, and rebound congestion may develop in healthy subjects after 10 days of use [15, 19, 20, 52, 54].

Treatment of RM

The first goal in the treatment of RM is the immediate discontinuation of the nasal decongestant. It has been suggested that the nasal decongestant should continue to be used in 1 nostril as much as needed until the congestion is relieved in the opposite nostril [2]. However, this practice has never been confirmed in a randomized trial.

Abrupt cessation of the decongestant may result in rebound swelling and congestion. Several treatments have been used for this problem. Nasal cromolyn, sedatives/hypnotics, and saline nasal spray have been suggested in several review papers, but no prospective trials could be found to support their use [1,26,56,57]. Oral adenosine triphosphate, nasal dexamethasone drops, and nasal triamcinolone drops were used in a Chinese case series of RM with 100%, 89%, and 100% cure rates, respectively [55].

An oral antihistamine/decongestant combination (the specific antihistamine/decongestant was not described in the study) along with intranasal dexamethasone has also been recommended [2]. In that study, 22 subjects used an oral antihistamine/decongestant for 4 weeks in combination with tapering doses of intranasal dexamethasone. All subjects stopped their nasal decongestant within 2 weeks of treatment. Only 1 case series could be found where oral corticosteroids were used [59]. In that study, combination treatment with topical and oral corticosteroids after discontinuing the nasal decongestant improved nasal congestion in all 20 subjects.

Some studies have suggested beneficial effects of corticosteroid injections. Mabry [59] recommended injecting triamcinolone acetonide 20 mg into the anterior turbinates to reduce interstitial edema in RM, but no clinical trials or case reports were provided to support this recommendation. Mowat [60] reported a decrease in nasal congestion in 3 subjects with RM after injecting 2 mL of 2.5% aqueous prednisolone 25mg/mL into the inferior turbinates. Despite these case reports, injected glucocorticosteroids are not recommended for routine treatment of RM because of the inherent risks of administrating them into the nasal cavity and the discomfort associated with their administration. No randomized controlled trials are available to prove the usefulness of glucocorticosteroid injections, oral glucocorticosteroids, or oral antihistamines.

Nasal glucocorticosteroids have been shown in case reports, animal models, and randomized controlled trials to be beneficial in the treatment of RM. Intranasal glucocorticosteroids were first reported to be beneficial in a case study of 4 subjects [61]. Those subjects were given 2 sprays of dexamethasone sodium phosphate in each nostril 3 times daily for 5 days. All 4 subjects were able to discontinue their nasal decongestants. In another case series, 10 subjects with RM were able to stop their nasal decongestants and showed improvement in objectively measured congestion after 6 weeks of treatment with budesonide 400 μg daily [58].

Elwany [62] induced RM in 20 guinea pigs with 0.05% naphazoline nitrite insufflated 3 times a day for 8 weeks to determine the effects of fluticasone propionate aqueous nasal spray 50 μg/day. Five animals were sacrificed to confirm RM by light and electron microscopy. The 15 remaining guinea pigs were treated with fluticasone propionate aqueous nasal spray (50 μg) once a day for 2 weeks. The animals treated in this manner were found by light and electron microscopy to have reduced interstitial edema.

In a study by Tas et al [63], RM was experimentally induced in 24 guinea pigs with oxymetazoline 0.05% 3 times a day for 8 weeks. Six of the 24 guinea pigs were sacrificed to confirm the development of RM by light and electron microscopy. The remaining 18 animals were divided into 3 groups and received either 0.05% aqueous mometasone furoate (50 μg) twice a day for 14 days, saline solution 0.9% twice a day for 14 days, or no treatment. By the end of the 2 weeks, light and electron microscopy revealed that the respiratory mucosa of the mometasone furoate group showed decreased edema, congestion, and inflammatory cell infiltrates. In contrast, the groups that received saline or no treatment had persistent edema, inflammation, and fibrosis.

In a study by Baldwin [2], 22 patients who had been using a nasal decongestant for at least a month were treated with an unspecified oral decongestant-antihistamine and intranasal dexamethasone for 1 month. The subjects were diagnosed with RM by the investigator, who determined that the subjects' nasal congestion was primarily due to the decongestant. No objective or histologic studies were done to document RM. Dexamethasone 0.084 mg was administered as an aerosol for 4 weeks in decreasing amounts. Patients used 2 puffs in each nostril 4 times a day during the first week, 3 times

a day during the second week, twice a day during the third week, and once a day during the fourth week. All subjects were able to discontinue their nasal decongestants within 2 weeks and at 6 months remained free of nasal decongestant use.

In a randomized, double-blind study, 20 human subjects with RM for at least 2 years were randomized to receive either fluticasone propionate nasal spray 200 μg/day or placebo aqueous nasal spray [64, 65]. Subjects stopped their decongestant and administered 2 puffs of the fluticasone propionate 50 μg or placebo nasal spray into each nostril every morning for 14 days. Measurements of the subjects' nasal mucosa, minimal cross-sectional area, and peak nasal inspiratory air flow were documented by rhinostereometry, acoustic rhinometry, and a Youlten meter on days 0, 7, and 14 of the study. Both the fluticasone propionate and the placebo group reported a decrease in nasal congestion; however, the onset of relief occurred on day 4 in the fluticasone group versus day 7 in the control group. Nasal mucosal swelling decreased in both groups after 7 and 14 days of treatment, but the reduction was significantly greater with fluticasone propionate. The fluticasone propionate group also had a reduction in edema and an increase in nasal sensitivity to histamine after 14 days of treatment. The control group, however, continued to have interstitial edema and no changes in histamine sensitivity.

Twenty patients with chronic nasal congestion secondary to perennial allergic rhinitis were randomized in a double-blind, placebo-controlled trial to study the effect of budesonide (32 μg/spray) aqueous nasal spray on RM [66]. For the first week of the trial, subjects did not use any nasal sprays. During the second through fourth weeks, all patients used 2 sprays of 0.05% oxymetazoline twice a day. At the beginning of the fourth week, subjects used 2 sprays of either saline or budesonide (32 μg/spray) aqueous nasal spray in each nostril once a day. During the fifth week, patients stopped the oxymetazoline and continued either the saline or the budesonide nasal spray. In the sixth week, subjects ceased all nasal sprays. Acoustic rhinometry showed a significant increase in nasal volume after the addition of budesonide to oxymetazoline in week 4. This increase in nasal volume was not found in the placebo group. Both the budesonide and placebo group had a decrease in nasal volume and minimal cross sectional area 24 hours after the cessation of oxymetazoline in week 5. However, a statistically significant increase in nasal volume and minimal cross sectional area was shown at the end of week 5 in the budesonide group, while a decrease in nasal volume and minimal cross sectional area persisted in the placebo group. This was further supported by the placebo group, in which an increase in congestion was seen during weeks 5 and 6 after the cessation of oxymetazoline. The subjects in the budesonide group reported less congestion than the placebo group during weeks 5 and 6, and no increase in congestion after stopping budesonide in week 6.

Nasal corticosteroids have been shown to decrease nasal edema, inflammation, and congestion associated with RM in both animal models and several small, randomized, controlled human trials [2, 59-64, 66, 67]. However, none of the trials had sufficient power and it is questionable in all the studies whether the subjects actually had RM [2, 64-66]. Nasal congestion in subjects with presumed RM may not only be caused by the implicated nasal decongestant but may instead be caused or worsened by a concomitant condition such as allergic rhinitis, nonallergic rhinitis, or other nasal pathology.

It is impossible to confirm a cause for rebound congestion in subjects with presumed RM, as no standard accepted definition exists. Validated criteria for this condition are necessary using both histologic and clinical features. Adequately powered studies using nasal glucocorticosteroids are necessary once a validated definition for RM has been developed.

Further Research

In order to make an accurate diagnosis of RM and improve research into the condition, validated criteria using clinical and pathologic characteristics are necessary. Diagnostic criteria will aid in distinguishing RM from other nasal diseases such as allergic rhinitis, nonallergic rhinitis, and viral upper respiratory infections. In many subjects, RM occurs after they begin using nasal decongestants to treat one of these other nasal conditions. It is difficult to determine if the rebound congestion is secondary to the initial nasal condition, RM, or both.

Animal studies showed lymphocytic infiltrates on histologic evaluation [51, 52] Therefore, cytokines may be involved in the development of RM and research to study their role may help to generate a better understanding of this disease. No studies have been performed to see if other mediators of congestion such as histamine, tryptase, kinins, prostaglandins, leukotrienes, and neuropeptides contribute to rebound congestion. Another area of possible research should address the factors that increase the number of goblet cells and control the release of mucin by those cells.

Since nasal glucocorticosteroids appear to be beneficial in the treatment of RM, the question arises whether the combination of nasal glucocorticosteroids and decongestants can be used safely together in the treatment of allergic and nonallergic rhinitis. Many subjects with chronic rhinitis continue to have persistent nasal congestion despite adequate doses of nasal glucocorticosteroids. The addition of a nasal decongestant may benefit this patient population.

References

1. Graf P. Rhinitis medicamentosa: a review of causes and treatment. Treat Respir Med. 2005; 4:21-9.
2. Baldwin RL. Rhinitis medicamentosa (an approach to treatment). J Med Assoc State Ala. 1975; 47:33-5.

3. Fox N. Chronic effect of epinephrine and ephedrine on the nasal mucosa. Arch Otolaryngol. 1931; 30:73-6.

4. Feinberg SM, Friedlaender S. Nasal congestion from frequent use of privine hydrochloride. JAMA. 1945; 128:1095-6.

5. Lake CF. Rhinitis medicamentosa. Proc Staff Meet Mayo Clin. 1946; 21:367-71.

6. Walsh TE, Cannon PR. The problem of intranasal medication. Ann Otol Rhinol Laryngol. 1938; 47:579-607.

7. Fitzhugh WM. Neosynephrine hydrochloride in otolaryngology. Arch Otolaryngol. 1936; 24:425-34.

8. Graf P. Rhinitis medicamentosa: aspects of pathophysiology and treatment. Allergy. 1997; 52:28-34.

9. Blue JA. Rhinitis medicamentosa. Ann Allergy. 1968; 26:425-9.

10. Gorenberg D. Rhinitis medicamentosa. West J Med. 1979; 131:313-4.

11. Basu A, Ryder RE. New treatment options for erectile dysfunction in patients with diabetes mellitus. Drugs. 2004; 64:2667-88.

12. Walker JS. Rhinitis medicamentosa. J Allergy. 1952; 23:183-6.

13. Watanabe H, Foo TH, Djazaeri B, Duncombe P, Mackay IS, Durham SR. Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis. Rhinology. 2003; 41:167-74.

14. Yoo JK, Seikaly H, Calhoun KH. Extended use of topical nasal decongestants. Laryngoscope. 1997; 107:40-3.

15. Akerlund A, Bende M. Sustained Use of Xylometazoline Nose Drops Aggravates Vasomotor Rhinitis. American J of Rhinology. 1991; 5:157-60.

16. Bralow L. Vicks Sinex. 58th ed. Montvale, NJ: Thomson PDR; 2004.

17. Morris S, Eccles R, Martez SJ, Riker DK, Witek TJ. An evaluation of nasal response following different treatment regimes of oxymetazoline with reference to rebound congestion. Am J Rhinol. 1997; 11:109-15.

18. Graf P, Juto JE. Sustained use of xylometazoline nasal spray shortens the decongestive response and induces rebound swelling. Rhinology. 1995; 33:14-7.

19. Graf P, Juto JE. Correlation between objective nasal mucosal swelling and estimated stuffiness during long-term use of vasoconstrictors. J Otorhinolaryngol Relat Spec. 1994; 56:334-9.

20. Graf P, Juto JE. Decongestion effect and rebound swelling of the nasal mucosa during 4-week use of oxymetazoline. ORL J Otorhinolaryngol Relat Spec. 1994; 56:157-60.

21. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, Li JT, Bernstein IL, Berger W, Spector S, Schuller D. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol. 1998; 81:478-518.

22. Toohill RJ, Lehman RH, Grossman TW, Belson TP. Rhinitis medicamentosa. Laryngoscope. 1981; 91:1614-21.

23. Black MJ, Remsen KA. Rhinitis medicamentosa. Can Med Assoc J. 1980; 122:881-4.

24. Stride RO. Nasal decongestant therapy. Br J Clin Pract. 1967; 21:541.

25. Feinberg A, Feinberg S. The "nose drop nose" due to oxymetazoline (Afrin) and other topical vasoconstrictors. IMJ III Med J. 1971; 140:50-2.

26. Fleece L, Mizes JS, Jolly PA, Baldwin RL. Rhinitis medicamentosa. Conceptualization, incidence, and treatment. Ala J Med Sci. 1984; 21:205-8.

27. Kully BM. The use and abuse of nasal vasoconstrictor medications. JAMA. 1945; 127:307-10.

28. Scadding GK. Rhinitis medicamentosa. Clin Exp Allergy. 1995; 25:391-4.

29. Snow SS, Logan TP, Hollender MH. Nasal spray addiction and psychosis: a case report. Br J Psychiatry. 1980; 136:297-9.

30. Pearson MM, Little RB. The addictive process in unusual addictions: a further elaboration of etiology. Am J Psychiatry. 1969; 125:1166-71.

31. Osguthorpe JD, Reed S. Neonatal respiratory distress from rhinitis medicamentosa. Laryngoscope. 1987; 97:829-31.

32. Howarth PH. Allergic and Nonallergic Rhinitis. In Atkinson N, editor. Middleton's Allergy Principles and Practice. 6th ed. Phildelphia: Mosby; 2003.

33. Hall LJ, Jackson RT. Effects of alpha and beta adrenergic agonists on nasal blood flow. Ann Otol Rhinol Laryngol. 1968; 77:1120-30.

34. Malm L. Stimulation of sympathetic nerve fibres to the nose in cats. Acta Otolaryngol. 1973; 75:519-26.

35. Eccles R, Wilson H. The autonomic innervation of the nasal blood vessels of the cat. J Physiol. 1974; 238:549-60.

36. Proctor DF, Adams GK. Physiology and Pharmacology of Nasal Function and Mucus Secretion. Pharmacology & Therapeutics. Part B; General & systematic pharmacology. 1976; 2:493-509.

37. Cauna N, Cauna D. Association of nerve fibers and plasma cells in abnormal human nasal respiratory mucosa. Ann Otol Rhinol Laryngol. 1974; 83:347-59.

38. Min YG, Kim HS, Suh SH, Jeon SY, Son YI, Yoon S. Paranasal sinusitis after long-term use of topical nasal decongestants. Acta Otolaryngol. 1996; 116:465-71.

39. Graf P, Hallen H. Effect on the nasal mucosa of long-term treatment with oxymetazoline, benzalkonium chloride, and placebo nasal sprays. Laryngoscope. 1996; 106:605-9.

40. Graf P, Hallen H, Juto JE. Benzalkonium chloride in a decongestant nasal spray aggravates rhinitis medicamentosa in healthy volunteers. Clin Exp Allergy. 1995; 25:395-400.

41. Graf P. Benzalkonium chloride as a preservative in nasal solutions: re-examining the data. Respir Med. 2001; 95:728-33.

42. Graf P. Adverse effects of benzalkonium chloride on the nasal mucosa: allergic rhinitis and rhinitis medicamentosa. Clin Ther. 1999; 21:1749-55.

43. Graf P, Enerdal J, Hallen H. Ten days' use of oxymetazoline nasal spray with or without benzalkonium chloride in patients with vasomotor rhinitis. Arch Otolaryngol Head Neck Surg. 1999; 125:1128-32.

44. Marple B, Roland P, Benninger M. Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. Otolaryngol Head Neck Surg. 2004; 130:131-41.

45. Scadding GK. Adverse effects of benzalkonium chloride on the nasal mucosa: allergic rhinitis and rhinitis medicamentosa. Clin Ther. 2000; 22:893-5.

46. Bernstein IL. Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? A cautionary note based on compromised mucociliary transport. J Allergy Clin Immunol. 2000; 105:39-44.

47. Ryan RE. Vasomotor rhinitis medicamentosa viewed histologically. Proc Staff Meet Mayo Clin. 1947; 22.

48. Talaat M, Belal A, Aziz T, Mandour M, Maher A. Rhinitis medicamentosa: electron microscopic study. J Laryngol Otol. 1981; 95:125-31.

49. Lin CY, Cheng PH, Fang SY. Mucosal changes in rhinitis medicamentosa. Ann Otol Rhinol Laryngol. 2004; 113:147-51.
50. Elwany SS, Stephanos WM. Rhinitis medicamentosa. An experimental histopathological and histochemical study. J Otorhinolaryngol Relat Spec. 1983; 45:187-94.
51. Suh SH, Chon KM, Min YG, Jeong CH, Hong SH. Effects of topical nasal decongestants on histology of nasal respiratory mucosa in rabbits. Acta Otolaryngol. 1995; 115:664-71.
52. Petruson B, Hansson HA. Function and structure of the nasal mucosa after 6 weeks' use of nose-drops. Acta Otolaryngol. 1982; 94:563-9.
53. Petruson B. Treatment with xylometazoline (Otrivin) nosedrops over a six-week period. Rhinology. 1981; 19:167-72.
54. Graf P, Juto JE. Histamine sensitivity in the nasal mucosa during four-week use of oxymetazoline. Rhinology. 1994; 32:123-6.
55. Wang JQ, Bu GX. Studies of rhinitis medicamentosa. Chin Med J (Engl). 1991; 104:60-3.
56. Chodirker WB. Rhinitis medicamentosa. Can Med Assoc J. 1981; 124:370, 2.
57. May M, West JW. The "stuffy" nose. Otolaryngol Clin North Am. 1973; 6:655.
58. Graf P, Hallen H, Juto JE. The pathophysiology and treatment of rhinitis medicamentosa. Clin Otolaryngol. 1995; 20:224-9.
59. Mabry RL. Rhinitis medicamentosa: the forgotten factor in nasal obstruction. South Med J. 1982; 75:817-9.
60. Mowat GG. Submucosal injections of hydrocortisone for allergic rhinitis and rhinitis medicamentosa. J Laryngol Otol. 1961; 75:283-7.
61. Stephens AL, Jr., Boggs PB. Intranasal dexamethasone: an adjunct in the treatment of chemical rhinitis. Ann Allergy. 1968; 26:612-3.
62. Elwany S, Abdel-Salaam S. Treatment of rhinitis medicamentosa with fluticasone propionate—an experimental study. Eur Arch Otorhinolaryngol. 2001; 258:116-9.
63. Tas A, Yagiz R, Yalcin O, Uzun C, Huseyinova G, Adali MK, Karasalihoglu AR. Use of mometasone furoate aqueous nasal spray in the treatment of rhinitis medicamentosa: An experimental study. Otolaryngol Head Neck Surg. 2005; 132:608-12.
64. Hallen H, Enerdal J, Graf P. Fluticasone propionate nasal spray is more effective and has a faster onset of action than placebo in treatment of rhinitis medicamentosa. Clin Exp Allergy. 1997; 27:552-8.
65. Graf PM, Hallen H. Changes in nasal reactivity in patients with rhinitis medicamentosa after treatment with fluticasone propionate and placebo nasal spray. J Otorhinolaryngol Relat Spec. 1998; 60:334-8.
66. Ferguson BJ, Paramaesvaran S, Rubinstein E. A study of the effect of nasal steroid sprays in perennial allergic rhinitis patients with rhinitis medicamentosa. Otolaryngol Head Neck Surg. 2001; 125:253-60.
67. Graf PM, Hallen H. One year follow-up of patients with rhinitis medicamentosa after vasoconstrictor withdrawal. Am J Rhinol. 1997; 11:67-72.

John T. Ramey

Division of Allergy & Clinical Immunology
University of South Florida & James A. Haley VA Medical Center
13000 Bruce B. Downs Blvd. (111D), Tampa
FL 33612, USA
Fax: (+1) 813-910-4041
E-mail: jtramey@yahoo.com