

REVIEW

Drug-induced rhinitis

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Summary

Background Rhinitis is characterized by inflammation of the mucous membranes lining the nose and can be divided into two categories, allergic and non-allergic. Drug-induced is a type of non-allergic rhinitis.

Objective A review of the literature was conducted. Very little is known about this topic and there are no publications to date solely devoted to drug-induced rhinitis.

Methods A PubMed and Medline search was conducted using a combination of the keywords; drug, medication, rhinitis, congestion, rhinorrhea, sneezing, pruritus, vasomotor, reflex, neurogenic, allergic and non-allergic. Medications that were found in the search were then cross-referenced with the physicians desk reference and Epocrates. The final literature search was conducted in August 2009.

Results Three categories of drug-induced rhinitis exist based on the mechanism of action. These include local inflammatory, neurogenic and idiopathic types. Rhinitis medicamentosa, a form of drug-induced rhinitis, has unique characteristics.

Conclusion When possible, the offending medication should be discontinued or substituted. Although there are no established treatment recommendations for drug-induced rhinitis other than avoidance, clinical experience suggests that it would be reasonable to initiate use of an intranasal corticosteroid spray to treat symptomatically. The addition of an intranasal antihistamine in combination with use of an intranasal corticosteroid may be considered as step-up therapy if the intranasal corticosteroid alone is not effective.

Keywords allergic and non-allergic, congestion, drug, medication, neurogenic, pruritus, reflex, rhinitis, rhinorrhea, sneezing, vasomotor

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Introduction

Rhinitis is characterized by inflammation of the mucous membranes lining the nose and is associated with nasal congestion, rhinorrhea, sneezing, itching of the nose and/or post-nasal drip. This upper airway disease can be divided into two categories, allergic and non-allergic.

While allergen exposure is a common cause of rhinitis, 50% of individuals do not demonstrate allergic sensitivity, thus other causes need to be considered [1]. Individuals with allergic rhinitis (AR) may have coexisting non-allergic triggers with so-called mixed rhinitis.

Non-AR usually presents after age 20 and is more often associated with the female gender, heightened sensitivity to irritants, perennial symptoms and in 33%, nasal eosinophilia [2]. Even though allergic sensitivity demon-

strated either by skin testing or by measuring serum-specific IgE can contribute significantly to nasal symptoms, coexisting non-AR also needs to be looked into and identified [3].

Classification

Non-AR is classified into subtypes including infectious, non-allergic rhinitis with eosinophilia syndrome (NARES), perennial non-allergic rhinitis, vasomotor, atrophic, hormonal, exercise, reflex (gustatory), drug-induced and idiopathic [4–7]. Drug induced has been grouped into the larger category of non-allergic non-infectious perennial rhinitis along with NARES and idiopathic rhinitis.

Drug-induced rhinitis may be further classified into three subtypes;

- (1) local inflammatory type
- (2) neurogenic type
- (3) idiopathic (unknown) type

The local inflammatory type is secondary to inflammation that occurs after ingestion of a drug. Drugs that exhibit their effect via neural stimulation cause the neurogenic type and the third type is reserved for drugs where there is little or no information available about the underlying mechanism [8, 9].

Rhinitis medicamentosa is a term used specifically to refer to a condition, which occurs with persistent overuse of topical nasal decongestants. A different mechanism underlines the congestion caused by these medications. Histology of the sinus mucosa reveals ciliary loss, epithelial cell denudation, inflammatory cell infiltration and oedema [10]. The nasal mucosa can become beefy-red and inflamed with areas of punctate bleeding and scant mucus [11].

These findings are in contrast to drug-induced rhinitis where different pathophysiologic mechanisms are involved and the nasal mucous membrane is often normal.

Local inflammatory type

Aspirin and the non-steroidal anti-inflammatory drugs (NSAIDs) are examples of drugs that induce an acute inflammatory response in the nose. A syndrome associated with NSAIDs use is known as aspirin exacerbated asthma (AEA), and the triad of nasal polyposis, asthma and aspirin or other NSAIDs sensitivity characterizes this condition [12]. There are a variety of pathogenic mechanisms proposed to explain how aspirin and other NSAIDs induce an inflammatory response. However, it is widely accepted that the principle mechanism involved is the inhibition of cyclooxygenase-1 (COX-1). COX-1 along with the enzyme lipooxygenase is involved in

arachidonic acid metabolism. Inhibition of COX-1 shifts the metabolism of arachidonic acid to the lipooxygenase pathway, resulting in a decrease in available prostaglandin E_2 (PGE_2). The decrease in PGE_2 results in an increase in cysteinyl leukotriene production by the lipooxygenase pathway involving the enzyme 5-lipooxygenase (5-LO). Leukotrienes C_4 , D_4 and E_4 (LTC_4 , D_4 , E_4) are all products of this pathway and are collectively known as cysteinyl leukotrienes, however, it is LTC_4 that is thought to be the chief cysteinyl leukotriene responsible in the pathogenesis of AEA [13]. LTC_4 synthase is the enzyme responsible for the production of LTC_4 , and an allele of the LTC_4 synthase gene (allele C) has been identified in individuals with aspirin sensitivity. There is a much higher incidence of allele C expression in individuals who have AEA [14].

Neurogenic type

Alpha and β -adrenergic antagonists including clonidine, guanethidine and methyl dopa are examples of drugs that induce rhinitis through a neurogenic mechanism. These medications are sympatholytic and serve to down-regulate sympathetic tone. Sympathetic, parasympathetic and sensory fibres innervate the airways [15] and are concentrated in nasal blood vessels, mucosa, and to a lesser extent secretory glands. Disruption of sympathetic and parasympathetic tone in the nasal mucosa may result in symptoms of congestion and rhinorrhea, however, the decreased sympathetic tone affecting the nasal blood vessels is predominantly responsible for the nasal congestion that follows the administration of sympatholytics [16].

Adrenergic sympathetic neuron fibres contain norepinephrine and neuropeptide-Y (NPY). NPY is also involved independently in the modulation of postganglionic cholinergic responses by acting directly on NPY-2 receptors in the nasal mucosa [17]. Decreased sympathetic tone caused by sympatholytic drugs results in the down regulation of the sympathetic nervous system in the nose and blunting of the effects of norepinephrine and NPY primarily causing nasal congestion and rhinorrhea [18] Fig 1.

Phosphodiesterase-5 inhibitors, such as sildenafil, tadalafil and vardenafil, are also implicated in drug-induced rhinitis. There have been two case reports in the literature describing epistaxis after their use. The postulated mechanism is that the turbinates of the nose contain erectile tissue. Nasal stuffiness occurs during sexual activities (honeymoon rhinitis) and the administration of this group of medications aggravates this phenomenon [19, 20].

Management

Diagnosis

A careful medical history and physical examination is imperative to correctly diagnose drug-induced rhinitis.

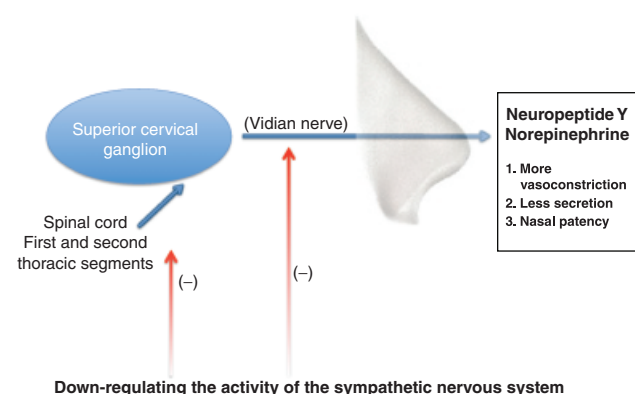


Fig. 1. Pathway of neurogenic type drug-induced rhinitis.

Although drug-induced rhinitis may occur in conjunction with allergic and non-AR, it is important to recognize medications that may contribute to this disease.

With rhinitis medicamentosa, the nasal examination can reveal a characteristic beefy red mucosa, whereas in drug-induced rhinitis, there are usually no specific physical findings visible in the examination of the nares. Patients will have non-specific symptoms common to most forms of non-AR including but not limited to nasal congestion, anterior rhinorrhea and post-nasal drip. In non-AR nasal pruritus and sneezing are less common than in the allergic variety and hence are usually not present (Tables 1 and 2).

Treatment

The first step in the treatment of drug-induced rhinitis is discontinuation of the offending medication. If symptoms persist despite stopping the drug or if there are no reasonable alternatives for the causative agent, then it may be necessary to empirically initiate treatment to alleviate symptoms.

Although there are no established treatment recommendations for drug-induced rhinitis other than avoidance, clinical experience suggests that it would be reasonable to initiate use of an intranasal corticosteroid spray to treat symptomatically. An intranasal corticosteroid spray may be started at one spray in each nostril once a day and can be increased up to two sprays in each nostril twice daily after several days if the patient is still symptomatic. The patient should continue to use the intranasal corticosteroid at the effective dose until they are well for 7 days and then can attempt to taper the dose to least amount of medication that still controls symptoms.

The addition of an intranasal antihistamine in combination with use of an intranasal corticosteroid may be considered as step-up therapy if the intranasal corticosteroid alone is not effective. Intranasal antihistamines can be helpful but should be considered as adjunctive medications when used alongside an intranasal corticosteroid. Some data suggest that the combination of intranasal fluticasone and azelastine provides improvement in symptoms of nasal congestion in patients with AR and it may be reasonable to initiate combination therapy in patients with drug-induced rhinitis in an attempt to control symptoms [21]. This approach may be particularly helpful in patients with hypertension, in whom use of oral decongestants may exacerbate their hypertension. The use of oral non-sedating antihistamines may be considered, but clinical experience suggests that these agents are in general, less effective than intranasal corticosteroids and/or intranasal antihistamines in drug-induced rhinitis.

Patients with rhinitis medicamentosa should receive an intranasal corticosteroids and be advised to discontinue the topical decongestant as soon as possible [5].

Table 1. Medications associated with drug-induced rhinitis [1, 3, 11]

I. Mechanism – local inflammatory type
Aspirin
NSAIDs
II. Mechanism – neurogenic type
Centrally acting sympatholytics
Clonidine (α_2 -agonist, anti-hypertensive (anti-HTN))
Guanfacine (α_2 -agonist, anti-HTN)
Methyldopa (α_2 -agonist, anti-HTN)
Moxonidine (imidazoline receptor agonist, anti-HTN)
Rescinnamine (ACE inhibitor, anti-HTN)
Reserpine (vesicular monoamine transport inhibitor anti-psychotic/HTN)
Rilmenidine (imidazoline receptor agonist, anti-HTN)
Ganglion blocking sympatholytics
Mecamylamine (α_3 , β_4 nicotinic receptor inhibitor, anti-HTN)
Trimethaphan (ganglion type receptor inhibitor, anti-HTN)
Peripherally acting sympatholytics
Prazosin (α_1 -antagonist, anti-HTN)
Guanethidine (magnesium-ATPase inhibitor, anti-HTN)
Indoramin (α_1 -antagonist, anti-HTN)
Doxazosin (α blocker, anti-HTN)
Phentolamine (α_1 -antagonist, anti-HTN)
Vasodilators – Phosphodiesterase type-5 inhibitors
Sildenafil
Tadalafil
Vardenafil
III. Mechanism – Idiopathic (Unknown) Type
Antihypertensives:
Amiloride
Angiotensin-converting enzyme inhibitors
Oral β -Blockers
Calcium channel blockers
Intraocular or ophthalmic preparations of β -blockers [18]
Chlorothiazide
Hydralazine
Hydrochlorothiazide
Hormones
Exogenous estrogens
Oral contraceptives
Psychotropics
Chlordiazepoxide–amitriptyline
Chlorpromazine
Risperidone
Thioridazine
Miscellaneous
Gabapentin

Table 2. Decongestants causing rhinitis medicamentosa

Sympathomimetics
Amphetamine
Benzedrine
Ephedrine
Phenylephrine
Phenylpropanolamine
Imidazolines
Naphazoline
Oxymetazoline
Xylometazoline

Occasionally, a short course of systemic corticosteroids for 5–7 days may be needed to wean patients off topical nasal decongestants [1]. In the local inflammatory type of drug-induced rhinitis, aspirin or NSAID desensitization should be considered if the need for these medications is clinically indicated.

Conclusions

Drug-induced rhinitis is a clinical condition that may be seen in individuals taking commonly prescribed medications. It is a condition that often impairs quality of life and leads to persistent symptoms. Although certain drugs that cause this syndrome are known to mediate rhinitis via a neuronal pathway, there are many drugs where the mechanism is unknown. Drug-induced rhinitis may coexist along with allergic and other non-allergic subtypes. A thorough history and physical examination is vital for diagnosis and physicians along with patients should be aware that medications could be causing rhinitis. When it is possible, the offending medication should be discontinued or substituted. When that is not possible a trial of an intranasal corticosteroids and/or intranasal antihistamine should be initiated to reduce symptoms. Despite many prescription warnings and manufacturer labels listing certain medications as causing rhinitis, drug-induced rhinitis still often goes undiagnosed. If there is greater awareness and familiarity with this phenomenon, proper diagnosis and treatment can be provided to those who suffer from this form of rhinitis.

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