Pharmacologic rationale for treating allergic and nonallergic rhinitis

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Allergic rhinitis (AR) and perennial nonallergic rhinitis (PNAR) represent conditions affecting millions of individuals across the world. Although the diagnosis of AR might be presumptively based on the types of symptoms and the history of allergen triggers, confirmation requires documentation of specific IgE reactivity. In contrast, PNAR is a condition with similar symptomatology but in which the patient has no identifiable specific allergic sensitivities. This review presents the diverse options of currently available pharmacologic agents for the treatment of AR and PNAR, including intranasal corticosteroids, H1-antihistamines, decongestants, cromolyn sodium, antileukotrienes, anticholinergics, capsaicin, anti-IgE, and intranasal saline. Furthermore, appropriate stepped-up, stepped-down pharmacotherapeutic algorithms are described for the various forms of rhinitis. (J Allergy Clin Immunol 2006;118:985-96.)

Key words: Allergic rhinitis, nonallergic rhinitis, nonallergic rhinitis with eosinophilia syndrome, perennial nonallergic rhinitis, pharmacotherapy, H1-antihistamines, intranasal corticosteroids, antileukotrienes, capsaicin, cromolyn sodium

Abbreviations used
AR: Allergic rhinitis
INS: Intranasal corticosteroid
NARES: Nonallergic rhinitis with eosinophilia syndrome
OTC: Over the counter
PNAR: Perennial nonallergic rhinitis
VMR: Vasomotor rhinitis

Rhinitis, an extremely common rhinopathy, is characterized by the presence of nasal pruritus, sneezing, rhinorrhea, and nasal congestion. However, these symptoms do not always reflect an underlying pathologic process. For example, up to 95% of healthy adults sneeze and blow their nose up to 4 times in a given day. In addition, nasal cycling, which results in temporary unilateral nasal congestion, as well as exposure to cold air, which promotes rhinorrhea, are 2 examples of normal physiologic mechanisms that sometimes could be misinterpreted as being abnormal. Therefore the magnitude and persistence of the symptoms is an important parameter.

Rhinopathies can be classified as being structural, infectious, allergic, or nonallergic (Fig 1). The latter category is the most heterogeneous and includes drug- and hormonal-induced rhinitis, irritative-toxic rhinitis, and perennial nonallergic rhinitis (PNAR). This article will focus on allergic rhinitis (AR) and PNAR.

EPIDEMIOLOGY

The epidemiology of specific forms of rhinitis can be difficult to study because of the differences in classification and diagnostic assessments. AR has been reported to affect approximately 17% of the general population in the United States, and in selected pediatric populations might be present in up to 42%. Less information is available on the demographics of nonallergic rhinitis in the general population. However, in an attempt to define the prevalence of various forms of rhinitis, the National Rhinitis Classification Task Force retrospectively analyzed 975 patients with rhinitis from a variety of allergy practices. They determined...
that in the surveyed cohort, 43% of patients had "pure" AR, 23% had "pure" nonallergic rhinitis, and 34% had mixed rhinitis. Thus 57% of the patients with rhinitis had nonallergic rhinitis either alone or of mixed form.

CLASSIFICATION AND DIAGNOSIS OF AR

AR, an inflammatory condition of the nasal mucosa mediated by an IgE-associated response to indoor and outdoor environmental allergens, has traditionally been classified as being seasonal or perennial, depending on whether an individual is sensitized to cyclic pollens or year-round allergens, such as dust mites, pets, cockroaches, and molds. This classification scheme has proved to be artificial and often inconsistent because, depending on the locale, allergic sensitization to multiple seasonal allergens can result in year-round disease, and conversely, allergic sensitization to perennial allergens, such as animal dander, can result in symptoms during only a limited period of time.

Although clinical research and regulatory agencies continue to use this nomenclature, recent global guidelines for classification and treatment of AR, as set forth by the Allergic Rhinitis and Its Impact on Asthma workshop, have proposed that allergic nasal disease be defined as being intermittent or persistent and mild or moderate-severe. Intermittent rhinitis is defined on the basis of symptoms that are present for less than 4 days per week or less than 4 weeks in duration. If symptoms are present for more than 4 days per week and are present for more than 4 weeks, AR is defined as being persistent. Mild symptoms do not affect sleep, interfere with work or school, or impair daily activities, sports, and leisure and, although present, are not considered troublesome. Conversely, moderate-severe symptoms can result in impairment or disturbances of any or all of these activities or aspects of life. Although the duration categories of intermittent and persistent appear to be a practical system, further refinement of the severity categories would be valuable. In addition, development of a validated method for assessing rhinitis control would be useful to monitor the often variable course of a patient’s disease.

The diagnosis of AR can be made presumptively based on the types of symptoms and the history of allergen triggers. Confirmation requires documentation of specific IgE reactivity through determination of allergen sensitivity by using skin prick testing or in vitro specific IgE determination. These procedures can help detect specific allergic sensitivities and provide information for directing environmental control interventions.

CLASSIFICATION AND DIAGNOSIS OF PNAR

PNAR is a condition in which the patient has no identifiable specific allergic sensitivities. Although it is controversial how to best subdivide PNAR, one previous approach has been to do so based on the presence or absence of nasal eosinophilia. Individuals with nasal eosinophilia and with no IgE sensitivity have traditionally
been classified as having nonallergic rhinitis with eosinophilia syndrome (NARES). Although the reported number of eosinophils required to make a diagnosis of NARES varies, it is generally accepted that nasal scrapings from the nasal turbinate demonstrating 5 to 25 eosinophils per high-power field are compatible with such a diagnosis.6

Individuals with PNAR who lack nasal eosinophilia can be classified as having vasomotor rhinitis (VMR), which some clinicians have termed idopathic rhinitis. VMR is characterized by the presence of chronic symptoms for 9 or more months each year.7 It can be differentiated from AR by the relative later age of onset, frequent lack of atopic comorbidities, nature of triggering factors, and type of symptoms. Precipitants include climate changes and nonspecific olfactory irritants, such as perfumes and tobacco smoke. Nasal obstruction and rhinorrhea are hallmark features of VMR and are more commonly seen than sneezing or itching.8 A study by Togias9 found that patients with VMR were more likely than patients with AR to report headaches, nasal pressure, and posterior rhinorrhea and less likely to be affected by sneezing, nasal pruritus, and conjunctival symptoms.

The exact pathophysiology of PNAR remains elusive. Some groups have found that affected individuals have infiltrating mast cells10 and IgE-positive cells in the nasal mucosa11 similar in quantity to their counterparts with AR. In fact, approximately two thirds of individuals with PNAR might respond to nasal allergen challenges with cat, dog, grass, and dust mite allergens.12 Thus it has been hypothesized that the underlying pathophysiology of PNAR might involve a local allergic process.13,14 Consistent with this possibility has been the finding that B cells residing in the nasal mucosa are able to undergo switching to IgE in the context of a local immune response to allergen, a process that was only thought to occur in lymphoid tissue.15

In contrast, other groups have noted a lack of cellular inflammation in the nasal mucosa, as evidenced by the absence of infiltrating eosinophils, mast cells, and T cells in biopsy specimens.16,17 Some of the discrepancies between these various findings might be explained by the fact that individuals with inflammatory changes did not have nasal smears done to rule out NARES, which could possibly account for the observed inflammation. Eosinophils, through production and release of their toxic and proinflammatory products, such as superoxide radicals, major basic protein, and eosinophilic cationic protein, could presumably interfere with normal nasal functioning and lead to pathologic rhinitis.18

Increasing evidence points toward the importance of nasal neurovascular mechanisms in the pathogenesis of noneosinophilic PNAR. Neurovascular homeostasis is maintained by a balance of sympathetic and parasympathetic tone in the upper airways.19 The former pathway controls the release of norepinephrine and neuropeptide Y, which favor a state of nasal patency.20 In contrast, parasympathetic fibers release acetylcholine and, among other neuropeptides, vasoactive intestinal peptide. These are thought to induce nasal congestion and mucus secretion. In VMR there might be a state of relative hyperreactivity of the parasympathetic nervous system and hyporesponsiveness of the sympathetic nervous system, perhaps as a result of being exposed to irritants or noxious stimuli, such as cold dry air21 or, alternatively, histamine and methacholine.22

Others groups have hypothesized that the neurogenic imbalance responsible for inducing VMR might be due to overactivity of C-fibers contained in the nasal mucosa. C-fibers define the nonadrenergic noncholinergic system, an abnormally heightened tone of which can promote release of substance P, calcitonin gene-related protein, and neurokinins A and K, which can lead to nasal congestion and overproduction of nasal secretions.19

OVERVIEW OF PHARMACOLOGIC TREATMENT

With mild intermittent AR, suggested initial pharmacologic therapy consists of an oral H1-blocker, an intranasal H1-blocker, and/or an oral or intranasal decongestant, the last on a strictly short-term or intermittent basis. A leukotriene modifier is also a consideration. If intermittent disease is moderate or severe, initial treatment with an intranasal corticosteroid (INS) is usually preferred to the aforementioned agents. Persistent mild AR is treated in the same manner as moderate or severe intermittent AR. If symptoms are persistent and moderate or severe, INSs should be the first class of medication used. With all grades of severity, appropriate follow-up should take place in a reasonable amount of time, and therapy should be stepped up or stepped down, as indicated. A pharmacologic treatment algorithm for AR is presented in Fig 2.

Treatment of PNAR has historically depended on the presence of nasal eosinophilia that, if present, predicted a likely beneficial response to INSs. In contrast, treatment of noneosinophilic nonallergic rhinitis has usually targeted those specific nasal symptoms proving most bothersome. Thus empiric treatment with decongestants, oral antihistamines, INSs, intranasal saline irrigation, intranasal ipratropium bromide, and other agents with anticholinergic properties was often undertaken with varying degrees of success. A stepped-up, stepped-down approach based on progress monitoring is also appropriate for PNAR treatment management. A proposed pharmacologic treatment algorithm for PNAR is presented in Fig 3.

INSs
Role of INSs in the treatment of AR

INSs improve all nasal symptoms of AR, including nasal congestion, rhinorrhea, itching, and sneezing. They generally do so to a greater extent than any other currently available pharmacologic agent.5 The comprehensive clinical effects of INSs are based on a broad mechanism of action. As glucocorticoids diffuse across the cell membrane, they bind to specific intracellular receptors, forming a complex that is then transported into the nucleus, where it binds to glucocorticoid response elements.23 As a result, transcription of glucocorticoid response element associated
genes is either downregulated or, less frequently, upregulated. This leads to a reduction of the nasal mucosa inflammatory cells and their associated cytokines.

Currently available INSs include beclomethasone, budesonide, flunisolide propionate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. All these are delivered in aqueous preparations and have shown efficacy in both seasonal and perennial AR in a large number of well-controlled studies. Although INSs might vary with regard to their sensory attributes (eg, perceived discomfort, taste, or smell) and thus patient acceptance and adherence, there do not appear to be any clear, clinically relevant differences in efficacy between them.

Among the reported side effects are nasal burning and stinging, dryness, and epistaxis. These can occur in 5% to 10% of patients, with the only exception being flunisolide, which, because of its excipients, appears to cause a higher incidence of nasal discomfort. Nasal mucosal atrophy does not occur with chronic INS use, in contrast to local skin atrophy, which occurs with dermatologic high-potency corticosteroids. This is evidenced by the findings of 2 separate year-long studies with fluticasone and mometasone. Local candidiasis, sometimes seen with inhaled corticosteroids, is extremely rare with INSs.

In terms of systemic side effects, laboratory evaluations of the hypothalamic-pituitary-adrenal axis by multiple means have shown minimal to no hypothalamic-pituitary-adrenal axis suppression with recommended doses of INS. Osteocalcin, a marker of bone turnover, and eosinophilia were both unaffected by intranasal budesonide, mometasone, and triamcinolone, suggesting that the systemic glucocorticoid burden was clinically insignificant. These results appear to be confirmed by a recent case-control study showing no increased likelihood of bone fractures among octogenarians using INSs, regardless of the dose used. Nevertheless, some concerns have been raised about the effects of INSs on linear growth in children. Intra-nasal beclomethasone caused a small but significant reduction in linear growth in at least one study with twice-daily dosing. In contrast, no growth delay was observed in children treated over the course of 1 year with mometasone, fluticasone, or budesonide. However, a continuing clinical concern is that no studies have examined linear growth in children receiving a combination of an intranasal and an inhaled corticosteroid, a common clinical scenario.

INSs are the single most effective class of medications for AR and are thus recommended as first-line therapy by both national and international taskforces for those with moderate-severe or persistent rhinitis. They are superior to antihistamines and leukotriene antagonists and, with limited information, probably equivalent or even superior to combinations of antihistamines and...
leukotrienes. For the most part, the addition of an anti-
histamine to an INS does not appear to confer additional
clinical benefits over the use of an INS alone.45,46 In a
European seasonal AR study, nasal fluticasone was com-
pared with placebo and various pharmacologic com-
binations: fluticasone plus cetirizine, fluticasone plus
montelukast, and cetirizine plus montelukast. Fluticasone
monotherapy was not inferior to the other 3 active treatment
groups in reducing individual nasal symptoms except for
nasal pruritus, where addition of cetirizine conferred an
additional benefit. In terms of nasal congestion, only those
treatment arms containing the nasal steroid were superior
to placebo in relieving nasal congestion.43

Role of INSs in the treatment of PNAR

Of the currently available INS preparations in the
United States, only fluticasone has the US Food and
Drug Administration indication for the treatment of non-
allergic rhinitis regardless of the presence of nasal eosin-
ophilia.47 In a large study of patients with PNAR, admin-
istration of fluticasone at the lower dose, 200 μg once daily, was as effective as at the higher dose, 400 μg once daily, in achieving symptom reduction.48 In a separate study in patients with VMR, fluticasone, 200 μg once daily, was significantly superior to placebo in reducing symptoms of nasal obstruction and decreasing inferior turbinate hypertrophy, as assessed by means of computed tomographic (CT) scanning.49 However, the evidence for benefit of INSs in PNAR is inconsistent. In a different study mometasone, 200 μg once daily, was not significantly more effective than placebo in reducing overall rhinitis symptoms in a cohort of individuals with
PNAR during a 6-week treatment period.50

H1-ANTIHISTAMINES
Role of oral antihistamines in the treatment of AR

Although many chemical mediators can induce one or
more symptoms of AR, histamine remains the quintes-
sential mediator of allergic nasal disease, especially during
the early-phase response. Acting at the H1-receptors,
histamine can induce most of the allergic symptoms (eg,
sneezing; itching of the nose, throat, and palate; and
rhinorrhea) through stimulation of the sensory nerves,
increase in vascular permeability, and mucus production.
H1-antihistamines antagonize the H1-receptor on smooth
muscle cells, nerve endings, and glandular cells, leading to
a reduction in all of the above symptoms. However, they
only have a mild effect on nasal congestion.51 Tolerance to
the beneficial effects of H1-antihistamines has not been
shown to occur.52 H1-antihistamines also appear to have
supplementary functions, such as inhibition of mediator
release from mast cells and basophils.53 Furthermore,
some of the currently available nonsedating antihistamines
appear to exert additional anti-inflammatory properties, such
as inhibition of TNF-α–induced release of the chemokines
IL-8 (fexofenadine)54 and RANTES (desloratadine),55
as well as a reduction in intercellular adhesion molecule 1 ex-
pression on cultured keratinocytes (cetirizine).56 It is unclear
whether these properties are clinically relevant.
Several older or first-generation oral H1-antihistamines are available as over-the-counter (OTC) formulations (diphenhydramine, clemastine, tripelennamine, pyrilamine, brompheniramine, chlorpheniramine, and triprolidine) or as prescription drugs (hydroxyzine, promethazine, and cyproheptadine). These preparations have poor selectivity for the H1-receptor and, as such, inhibit muscarinic receptors, which might result in various degrees of mucous membrane drying, vision blurring, constipation, urinary retention, and tachycardia.

Sedation is a major adverse effect of the older H1-antihistamines. It occurs because they cross the blood-brain barrier and affect the H1-receptors in the central nervous system. The term sedation has been used to include both drowsiness and a global reduction in intellectual and motor performance.\(^{57}\) Sedating H1-antihistamines have been linked to air\(^{58}\) and industrial\(^{59}\) accidents, as well as significant loss of productivity at school and work.\(^{60}\) A single 50-mg dose of diphenhydramine led to a degree of diminished driving performance, as assessed in a driving simulator, greater than that seen from the ingestion of ethanol leading to an estimated blood alcohol level of 0.1%.\(^{61}\) Similar to the effects of ethanol intake, a discrepancy often exists between self-perception of sedation and objective measures of drowsiness and performance.\(^{62}\)

Even though dosing for first-generation H1-antihistamines is often undertaken several times a day, the terminal elimination of first-generation antihistamine half-life varies from 9.2 to 27.9 hours,\(^{53}\) leading to potential day-time deficits, even when administered only at bedtime. One study suggested that tolerance can develop to the sedating properties of diphenhydramine.\(^{64}\) It also appears that many individuals with chronic urticaria are able to function reasonably normally on high doses of various sedating antihistamines when taken on a daily basis (Kaplan A, personal communication). Unresolved and requiring further study is the extent to which tolerance to sedation really occurs and whether this might be a class effect.

Second-generation oral H1-antihistamines currently available in the United States include the OTC preparation loratadine and the prescription drugs cetirizine, desloratadine, and fexofenadine. In contrast to the older first-generation antihistamines, for which studies showing clinical efficacy are very limited,\(^{65}\) effectiveness for cetirizine, desloratadine, fexofenadine, and loratadine have been established in a variety of well-designed, double-blind, placebo-controlled studies. These studies have also helped to establish onset of action, peak effect, and duration of action. Such information is lacking with first-generation antihistamines so that current dosing suggestions for agents belonging to this category are based, at best, on the individual antihistamine’s ability to suppress the cutaneous wheal-and-flare response after allergen or histamine introduction into the skin.\(^{53}\)

Second-generation oral H1-antihistamines have better H1-receptor selectivity and thus less anticholinergic and antiserotonergic side effects. All these agents, with the exception of fexofenadine, have the potential to cross the blood-brain barrier and bind to central H1-receptors, resulting in sedation. This process has been observed in individuals using loratadine and desloratadine at higher than recommended doses.\(^{66,67}\) For the second-generation oral agents available in the United States, cetirizine is the only one labeled to cause an increased incidence of sedation at its recommended dose in persons older than 12 years (11% to 14% vs 6% receiving placebo).\(^{68}\)

Because of variations in their metabolic profiles, certain antihistamines can either interact with specific drugs or foodstuffs, altering their plasma concentrations. For example, coadministration of the antifungal ketoconazole with either fexofenadine or desloratadine can increase the plasma concentrations of these antihistamines by 135% and 40%, respectively.\(^{69,70}\) Grapefruit juice, when administered in large quantities (1.2 L), has the potential to decrease plasma levels of fexofenadine, putatively through saturation of organic anion-transporting peptide carriers. The clinical significance of these findings is questionable. Individuals also have significant variations in their ability to break down a specific drug or metabolite through the cytochrome P-450 or N-acetyltransferase pathway, among others. Desloratadine is metabolized slowly by approximately 6% of the general population and 17% of African Americans,\(^{71}\) resulting in increased plasma levels, which, in turn, could increase dose-related adverse effects, such as sedation. However, sedation was not noted to be more frequent in a large cohort taking desloratadine compared with placebo,\(^{72}\) so that further studies are required to better characterize the real-life significance of these findings.

A few studies have directly compared the clinical effect of different second-generation antihistamines. Although fexofenadine once daily was not inferior to cetirizine once daily in reducing the total symptom score over a 2-week period in 2 separate studies,\(^{72,73}\) some short-term environmental exposure unit studies suggested that cetirizine was more effective than fexofenadine in reducing seasonal AR symptoms during both the 5- to 12-hour\(^{74}\) and 21- to 24-hour postdose period.\(^{75}\) In a 2-week study looking at both objective and subjective criteria, desloratadine at 5 mg and fexofenadine at 180 mg were equivalent in their ability to improve both peak nasal inspiratory flow and nasal symptoms in 49 patients with seasonal AR.\(^{76}\)

Despite the frequent finding of therapeutic equivalency between various second-generation antihistamines in clinical trials, individual patients sometimes perceive differences in efficacy among agents of this class. A recent issue has been posed by loratadine, which, because of its OTC status, has become the preferred treatment of allergies by many insurance companies. This special positioning of loratadine, which appears to be less effective than other nonsedating antihistamines,\(^{51,77,78}\) results in higher copayments or non-coverage for other second-generation antihistamines.

**Role of oral antihistamines in the treatment of PNAR**

Although there is no clear established role for antihistamines in the treatment of PNAR, patients who have sneezing as a predominant symptom might respond favorably to oral antihistamines.\(^5\) Also, a single placebo-
Role of intranasal antihistamines in the treatment of AR and PNAR

Currently, azelastine is the only intranasal antihistamine available commercially in the United States, although intranasal olopatadine might become marketed in the near future. Azelastine appears to have a range of anti-inflammatory properties in addition to its H1-receptor effect. These include interference with the vasoactive neuromodulator substance P, inhibition of production of the leukotrienes B4 and C4, and possibly decrease of nuclear factor κB, a transcription factor for multiple proinflammatory substances. The clinical relevance of these effects is unclear.

Dose-ranging trials have shown a therapeutic onset of action within 3 hours after initial dosing and persistence of efficacy over a 12-hour interval. The most common side effects at the recommended dose of 2 sprays per nostril twice a day are bitter taste (19.7% vs 0.6% placebo) and sedation (11.5 vs 5.4% placebo). Azelastine and olopatadine have demonstrated efficacy in seasonal rhinitis, and in recent studies azelastine appears to be slightly superior to cetirizine, desloratadine, and fexofenadine in its ability to reduce total nasal symptom scores, including nasal congestion. An older study, however, did not find that azelastine was superior to cetirizine in seasonal AR.

In the 2 pivotal studies that established a role for intranasal azelastine in the treatment of nonallergic, non–eosinophilic chronic rhinitis, all nasal symptoms, including nasal congestion, were reduced compared with those after placebo. No studies comparing azelastine with other pharmacologic agents have been performed in VMR.

ROLE OF DECONGESTANTS IN THE TREATMENT OF AR AND PNAR

 Vasconstrictors exist in both intranasal and oral form. Topically applied vasconstrictor sympathomimetic agents belong to the catecholamines (eg, phenylephrine) or amidazoline family (eg, oxymetazoline), whereas oral vasoconstricting agents are primarily catecholamines (pseudoephedrine and phenylephrine). These agents exert their effects through the α1- and α2-adrenergic receptors present on nasal capacitance vessels responsible for mucosal swelling and associated nasal congestion. The reduction in blood flow to the nasal vasculature after administration leads to increased nasal patency in 5 to 10 minutes when applied topically or 30 minutes when administered orally. Nasal decongestion can last up to 8 to 12 hours with intranasal preparations and 24 hours with extended-release oral decongestants. Traditionally, it has been thought that pseudoephedrine cannot ameliorate symptoms of rhinitis other than nasal congestion. However, a recent study comparing once-daily pseudoephedrine with montelukast showed a reduction in rhinitis symptoms other than nasal congestion in both groups. These additional effects might possibly be due to the halo effect, in which improvement in one particular symptom, such as nasal congestion, leads to a more global sense of well-being and thus less perceived severity of other nasal symptoms.

Overall, monotherapy with vasoconstrictors has a limited role in the treatment of AR unless nasal congestion presents as the sole or most bothersome symptom. However, when oral decongestants are combined with an antihistamine, all cardinal symptoms of AR are targeted.

The adverse affects of topical nasal decongestants include nasal burning, stinging, dryness, and, less commonly, mucosal ulceration. Tolerance and rebound congestion can occur when these agents are used for longer than 1 week and can culminate in rhinitis medicamentosa. Adverse affects of oral decongestants include central nervous system stimulation, such as insomnia (which might occur in a significant portion of individuals), nervousness, anxiety, and tremors, as well as tachycardia, palpitations, and increases in blood pressure.

Decongestants can be used in the treatment of PNAR for symptomatic improvement. When administered topically, intermittent dosing is required for the abovementioned reasons.

ROLE OF CROMOLYN SODIUM AND NEDOCROMIL SODIUM IN THE TREATMENT OF AR AND PNAR

Cromolyn inhibits the degranulation of sensitized mast cells, thereby blocking the release of inflammatory mediators. It does not interfere with either the binding of IgE to the high-affinity IgE receptor or with binding of the allergen to its specific IgE. In allergen challenge studies of individuals with AR, cromolyn sodium has proved effective in reducing both the early- and late-phase allergic reaction. Cromolyn is indicated for both seasonal and perennial AR. The onset of relief appears during the first week of treatment, and symptoms often continue to improve as the medication is dosed over the subsequent weeks. The 4% intranasal solution is recommended for adults and children age 2 years and older. The frequency of dosing might lead to adherence problems given the need to initially instill the solution 4 times daily to obtain a beneficial result. However, once symptoms are under control, a less frequent dosing regimen might suffice for adequate symptom control. Topical adverse effects, such as sneezing, nasal irritation, and unpleasant taste, are uncommon, and cromolyn is poorly absorbed systemically and therefore has an excellent safety record. Tolerance to the clinical effects of cromolyn has not been described.

The conclusions derived from several older studies about the role of cromolyn in the treatment of PNAR are inconclusive. Given the limited role of histamine in the genesis of symptomatology of patients with PNAR, the role of cromolyn would be expected to be modest.
One study revealed no symptom improvement in a group of adults with NARES after a 2-month-long treatment with 4% cromolyn solution. In contrast, another group found that 2% disodium cromoglycate was preferred over placebo by a majority of individuals with VMR.

ROLE OF ANTLLEUKOTRIENES IN THE TREATMENT OF AR

Cysteinyl leukotrienes are potent lipid mediators derived from the enzymatic action on nuclear membrane phospholipids. Initially studied in the lower airway inflammation of asthma, these inflammatory molecules also appear to play a role in the upper airways, as evidenced by the appearance of high concentrations of leukotriene C4 in nasal secretions of atopic individuals after allergen challenge. Furthermore, nasal challenge with leukotriene D4 in healthy human subjects can significantly increase nasal mucosal blood flow and nasal airway resistance. Leukotrienes do not appear to stimulate the sensory nerves present in the nasal mucosa and thus probably do not contribute significantly to nasal itching or sneezing.

Although blockage of the leukotriene pathway could be accomplished by means of either inhibition of synthesis through the 5-lipoxygenase inhibitor zileuton or by receptor blockade of the cysteinyl leukotriene 1 receptor with zafirlukast or montelukast, only montelukast is US Food and Drug Administration approved for treatment of AR, in which it has shown clinical efficacy in both seasonal and perennial AR. One of the leukotriene inhibitors, montelukast, results in few side effects, has a pregnancy B category, and is approved in children as young as 6 months.

Montelukast, with very limited comparator data, does not appear to be more effective than nonsedating antihistamines and is less effective than INSs in the treatment of AR. In a pediatric perennial AR study, montelukast was inferior to cetirizine in improving nasal and throat itching symptoms, equivalent in reduction of nasal congestion, and superior in terms of night sleep quality. A recent meta-analysis of 11 published studies on the clinical effects of leukotriene receptor antagonists concluded that these agents only had limited effectiveness in the treatment of AR, reducing mean daily rhinitis symptom scores (in absolute terms) 5% more than placebo (95% CI, 3% to 7%). In comparison with the leukotriene antagonists, antihistamines provided 2% (95% CI, 0% to 4%) greater improvement in symptom scores, and INSs provided 12% (95% CI, 5% to 18%) greater improvement in symptom scores. At this time, no published studies have shown a role for leukotriene modifiers in the treatment of PNAR.

ROLE OF IPRATROPIUM BROMIDE IN THE TREATMENT OF AR AND PNAR

Ipratropium bromide is an intranasally administered antimuscarinic agent that inhibits parasympathetic function within the nasal mucosa, thus controlling the secretory output from serous and seromucous glands. Because of its low systemic absorption, it is relatively free of the side effects usually accompanying the administration of oral compounds with anticholinergic properties, unless administered at higher than recommended doses.

Ipratropium has an onset of action within 15 to 30 minutes. Because of its pharmacokinetic profile, the recommended 24-hour dose ranges from 120 to 320 μg administered in 3 to 6 daily applications. Tolerance to the therapeutic effects of ipratropium has not been described. Side effects are usually limited to local irritation, dryness, and epistaxis, which occur in a dose-dependent manner.

Ipratropium has shown efficacy in perennial AR and various forms of nonallergic rhinitis, including infectious rhinitis, gustatory rhinitis, and VMR in both children and adults. Although ipratropium bromide is primarily effective at controlling watery anterior nasal discharge, several of the above-referenced studies found that it might improve nasal symptoms other than rhinorrhea. However, given ipratropium’s mechanism of action, these findings might be representative of the halo effect (discussed earlier) rather than reflect a true physiologic cause and effect. Ipratropium should primarily be used in the management of isolated anterior rhinorrhea. It has not proved particularly effective in the management of postnasal drip. It might also be prescribed as an adjunct for the treatment of rhinorrhea not fully controlled by other pharmacologic agents.

ROLE OF CAPSAICIN IN THE TREATMENT OF PNAR

Local application of capsaicin, a pungent compound present in red-hot peppers, can induce nasal burning, rhinorrhea, and nasal congestion through stimulation of the nasal C-fibers. With repeated application of capsaicin, C-fibers are thought to become depleted of neuropeptides, leading to reduced nasal hyperreactivity.

Several studies have shown symptomatic improvement in patients with VMR treated with capsaicin. A published practical therapeutic approach has suggested induction of local anesthesia, followed by 5 hourly applications of capsaicin. This treatment plan has shown similar efficacy with intermittent treatment over 2 weeks. Although some investigators estimate that improvement after a single treatment course might last for more than 1 year, more research is required to better define the role and long-term effects of capsaicin therapy. Capsaicin is not currently available in the United States as a standardized preparation.

ROLE OF OMALIZUMAB (ANTI-IgE) IN THE TREATMENT OF AR

Omalizumab is one of the more exciting recent developments in the treatment of atopic diseases. It is probably only the first of several mAbs aimed at modulating allergic inflammation. Omalizumab is a humanized mAb that binds to the constant region of the IgE molecule at its IgE binding sites.
receptor-binding portion, thereby effectively hindering IgE’s interaction with the high-affinity IgE receptor present on mast cells, basophils, and dendritic cells. Anti-IgE binds to circulating, but not cell-bound, IgE, forming stable and long-lived anti-IgE–IgE complexes. After initial appropriate dosing, free IgE concentrations decrease in a rapid dose-dependent fashion by 97% to 99%. Omalizumab has been shown to be effective for AR in both allergen challenge studies and clinical trials. Multiple randomized, double-blind, placebo-controlled studies have shown efficacy of omalizumab in seasonal and perennial AR. It remains to be determined how omalizumab compares with other treatment modalities. However, given its cost, the application of omalizumab in the treatment of AR in the absence of other atopic diseases will likely be restricted to a narrowly defined set of circumstances. No published studies have shown a role for omalizumab in the treatment of PNAR.

ROLE OF NASAL SALINE IRRIGATION

For many years, nasal saline irrigation has been used as an adjunct treatment for various forms of rhinitis, despite the lack of good clinical trial data. In the process of douching, several ounces of isotonic or hypertonic saline are introduced into the nose and nasopharynx by using a variety of devices, such as a bulb syringe, Neti Pot, squeezable plastic bottle with nasal adaptor, or a pulse irrigator combined with a nasal adaptor. The goal is to remove mucus, enhance ciliary clearance and sinus ostial patency, and, perhaps, to remove pollen and other allergenic or irritant material from the nasal and nasopharyngeal mucosa. Limited data suggest that although hypertonic saline is generally more irritating, it might stimulate ciliary transport to a greater degree than isotonic saline, as evidenced by its ability to improve mucociliary transit times of saccharin.

In a pediatric study of 44 children with seasonal allergic rhinoconjunctivitis, those rinsing with nasal hypertonic saline 3 times daily during the 7-week peak pollen season had a lower weekly mean rhinoconjunctivitis score during all weeks, although only in a statistically significant manner during weeks 6 and 7, than the control group. In addition, rinsers had a markedly reduced need for oral antihistamines during 5 of the 7 weeks.

In a separate prospective study of 211 individuals with sinonasal disease, including AR, “aging rhinitis,” atrophic rhinitis, postnasal drip, and chronic rhinosinusitis, 3 to 6 weeks of hypertonic saline irrigation led to statistically significant improvement in 23 of 30 symptoms by using a nasal disease-specific symptom questionnaire.

EFFICACY OF COMBINATION THERAPY IN AR

Few studies have assessed the value of using combination therapy, even though in clinical practice, satisfactory control of symptoms is frequently not achieved unless individual pharmacologic agents are used together. The following is a brief summary of selected studies comparing treatment regimens not including an INS (see INS section for combination therapy including an INS). In seasonal AR trials the combinations of loratadine plus pseudoephedrine and fexofenadine plus pseudoephedrine were more effective in reducing symptoms than monotherapy with the individual agents. In a group of adults with seasonal AR, a combination of fexofenadine and pseudoephedrine was compared with a combination of loratadine and montelukast. Both treatment arms improved symptoms, rhinoconjunctivitis quality-of-life questionnaire scores, and nasal obstruction in seasonal AR to a similar degree. When montelukast was added to loratadine in patients 15 years or older with seasonal AR, the combination was superior to either agent alone in reducing daytime nasal symptoms in patients. Similarly, treatment of adults with seasonal AR by using a combination of montelukast and cetirizine was found to be preferable to treatment with both individual agents alone. However, another study suggested that symptoms of seasonal AR were not better controlled with the combination of montelukast and loratadine than with once-daily fexofenadine.

CONCLUSIONS

AR and PNAR represent conditions affecting millions of individuals in industrialized nations. Unlike AR, the pathophysiology underlying PNAR is not fully understood, probably in part because of the heterogeneity of conditions comprising this category. Although a large number of different pharmacologic agents have shown clinical efficacy and safety for the treatment of AR, there are fewer well-designed, double-blind, placebo-controlled trials providing evidence for the treatment options of PNAR. As understanding of the pathologic processes underlying PNAR increases, so will the ability to find compounds that interfere with specific biologic pathways.

REFERENCES


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