Antihistamine Therapy in Allergic Rhinitis

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Allergic rhinitis is a common disorder that is associated with a high incidence of morbidity and considerable costs. The symptoms of allergic rhinitis are primarily dependent upon the tissue effects of histamine.

Antihistamines are the mainstay of therapy for allergic rhinitis. Recently, a second generation of antihistamines has become available. These agents lack the adverse effect of sedation, which is commonly associated with older antihistamines. Current practice of antihistamine therapy in allergic rhinitis often involves random selection among the various agents. Based upon the available clinical trials, chlorpheniramine appears to be the most reasonable initial antihistaminic agent. A nonsedating antihistamine should be used initially if a patient is involved in activities where drowsiness is dangerous. In this comprehensive review of allergic rhinitis and its treatment, the current as well as future options in antihistamine pharmacotherapy are emphasized.
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Allergic rhinitis is a common condition afflicting somewhere between 15 and 30 million people in the United States.[1–3] The prevalence of disease among adolescents is estimated to be 20% to 30%. Two thirds of the adult allergic rhinitis patients are under 30 years of age.[4–6] Consequently, considerable costs are incurred in days lost from school and work. It is estimated that between 1 and 2 million days are lost from school and that 3.5 million work days are lost yearly.[4] Annual financial costs have been estimated at $154 million in lost wages and greater than one-half billion dollars paid in physician fees and medications for symptomatic relief.[7]

Allergic rhinitis is an antibody-mediated inflammatory disease of nasal mucous membranes. It is classified as seasonal or perennial depending on timing and duration of symptoms.[4] The characteristic symptoms include paroxysms of sneezing, nasal pruritus and congestion, and mucus secretion often resulting in postnasal drainage.[1] *Seasonal allergic rhinitis* is most common in young people, often associated with watery eyes and itching of ears and throat, and may be most bothersome upon rising in the morning. The time of year in which symptoms are worst is defined by the period of exposure to those agents to which a patient is sensitive. Allergens in seasonal allergic rhinitis consist of pollens from nonflowering plants such as trees, grasses, and weeds. These pollens generally create symptoms in early spring, late spring through early summer, and fall, respectively. Also, mold spores may generate symptoms in areas with high humidity from early spring through the first frost.[4] Ragweed pollen is the most common allergen in the East and Midwest, being involved in approximately 75% of patients with seasonal allergic rhinitis. The symptom pattern in *perennial allergic rhinitis* has no distinct seasonal variation and can be either intermittent or continuous. The inciting allergens are typically components of house dust such as insect debris, animal danders, mold, and such fibers as feathers from pillows.[4] Common physical findings seen with allergic rhinitis and particular laboratory diagnostic procedures such as immunoglobulin E (IgE) levels, allergen skin tests, allergen-specific serum IgE antibodies, nasal smear examination for eosinophils, and nasal provocation testing are described elsewhere.[1,2,7]

Nasal allergy begins with the deposition of particulate matter on nasal mucosa, diffusion of water-soluble antigens, and the specific activation of mature B cells to produce specific antibody of the IgE subclass.[2] The disease process involves both immediate and late-phase reactions. The classic immediate hypersensitivity reaction is initiated upon allergen exposure and the subsequent release of histamine and other mediators of inflammation.[1,2,6,8] Symptoms of the immediate reaction typi-

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TABLE 1. DIRECT AND INDIRECT ACTIONS OF HISTAMINE IN ALLERGIC RHINITIS

	Direct	Indirect
Sneezing		H_1
Pruritus		H_1
Secretion		H_1
Congestion		
Increased capillary vasodilation	H_2	H_1
Increased capillary permeability	H_1	

cally abate within 30 to 60 minutes. The late-phase reaction of allergic rhinitis may occur between 4 and 24 hours after the initial mast cell degranulation. It is the consequence of an inflammatory cellular infiltration that is largely dependent on the chemotactic factors released during the immediate hypersensitivity reaction.[9,10] The initial influx of inflammatory cells results in a second increase in allergic mediators.[1,8] Nasal obstruction is the main clinical manifestation.[6,9] It is hypothesized that the late-phase reaction contributes to chronic rhinitis as well as nasal hypersensitivity.[6] Complications of chronic rhinitis include sinusitis, otitis, chronic mouth breathing, and preoccupation with nasal symptoms resulting in frequent physician visits.[11] Such patients may become habitual users of topical nasal decongestants and are then subject to the condition known as rhinitis medicamentosa. This condition is a result of vascular rebound after the effect of the vasoconstricting medication wears off,[4,5,7] and leads to soreness of the nasal mucosa and exacerbation of nasal congestion.

The mediators of inflammation in allergic rhinitis include histamine, leukotrienes C_4D_4 and E_4, prostaglandin D_2, kinins and tosyl-L-arginine methyl ester esterase.[2,7] Histamine is considered to be the mediator most responsible for symptoms and signs of allergic rhinitis. The effects of the other mediators are described elsewhere.[6] The tissue effects of histamine are dependent on histamine interaction with receptors, which are classically divided into H_1 and H_2 subtypes. Recently, an H_3 receptor has also been described as regulating histamine's own synthesis and release from nerve, lung, and skin tissues.[12] The majority of histamine effects in allergic disease are H_1 mediated. Histamine acts through H_1 and H_2 receptor subtypes both directly and indirectly, producing symptoms of allergic rhinitis as outlined in Table 1.[1,11,13,14]

The indirect actions of histamine in nasal allergy are reflex mediated.[8,11,13] The probable neural pathway is through parasympathetic fibers along branches of the trigeminal nerve, nerve of the pterygoid canal (vidian), and the greater petrosal nerve (branch of cranial nerve VII). The afferent limb consists of subepithelial receptors that, when stimulated by histamine, convey sensations such as pruritis and pain. The efferent limb mediates motor control for sneezing as well as mucus secretion and capillary vasodilation. H_1 receptor-mediated vasodilation is immediate and not sustained, while the H_2-mediated response develops more slowly and is sustained.[15]

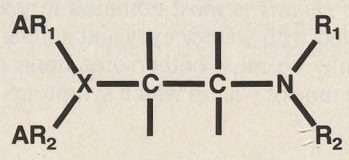
The three treatment options in the management of allergic rhinitis are allergen avoidance, drug treatment of symptoms, and immunotherapy. Antihistamines are considered to be effective in 70% to 95% of patients with allergic rhinitis.[16–18] H_1 antagonists, however, are considerably less effective in relieving nasal congestion because of the prolonged vasodilatory effect mediated by H_2 receptors as described above.

H_1 ANTIHISTAMINES

Histamine antagonism was first discovered in 1937 by Bovet and Staub, who used certain agents to inhibit histamine-induced smooth-muscle contraction and anaphylaxis. One of the first clinically useful antihistamines, pyrilamine maleate, was described by Bovet in 1944, who received the Nobel Prize for the development of antihistamines in 1957.[15,19] Now called H_1 antihistamines, they relieve those symptoms of allergic disease that are histamine-related by means of competitive inhibition. There may, however, be other clinically significant actions such as anticholinergic, antiserotonergic, and α-adrenergic antagonism.[20] In addition to allergic rhinitis, H_1 antihistamine therapy may be used in treating other hypersensitivity phenomena such as urticaria-angioedema and other pruritic skin eruptions. Additionally, various H_1 antihistamines are useful as sedative and antiemetic agents.

Classifications of H_1 Antihistamines

Several classification systems of H_1 antihistamines exist. Historically, antihistamines have been classified into six categories according to the substitution groups linked via the **X** to the ethylamine structure shown below.



The nature of the linkage atom declares the chemical class as found in Table 2.

Specific structural formulae of the classical H_1 antihistamines are found elsewhere.[15,16] These antihistamines can be associated with significant central nervous system

TABLE 2. CLASSICAL H_1 ANTAGONISTS ACCORDING TO LINKAGE ATOM

Linkage Atom	Chemical Class
O	Ethanolamine
N	Ethylenediamine
C	Alkylamine
N in phenothiazine ring	Phenothiazine
N in piperazine ring	Piperazine
N in piperidine ring	Piperidine

(CNS) side effects such as sedation. To avoid sedation, a second generation of antihistamines, termed the nonsedating antihistamines, has been developed. It should be noted that some authorities use a miscellaneous category which includes various agents that may be categorized as classical,[21] or agents that are included in both classical and nonsedating categories.[1,2] Examples of classical and nonsedating agents are found in Table 3. Some of the nonsedating agents can be categorized into one of the classical chemical classes as shown with some of the half-lives.[22–24] The costs are those estimated from the published average wholesale price for the usual dose of drug for one day of treatment.[25]

TABLE 3. CLASSIFICATION OF H_1 RECEPTOR HISTAMINE ANTAGONISTS

Chemical Class	Examples	Half-life	Cost($)*
Classical			
Ethanolamines	Diphenhydramine	3–9 h	.24
	Clemastine		1.06
	Carbinoxamine		
Ethylenediamines	Tripelennamine		.15
	Pyrilamine		
Alkylamines	Chlorpheniramine	14–25 h	.07
	Brompheniramine	25 h	.06
	Triprolidine	2 h	.12
Piperazines	Hydroxyzine	20 h	.17
	Cyclizine		
	Meclizine		
Phenothiazines	Promethazine	10–14 h	.03
	Methdilazine		
	Trimeprazine		
Piperidines	Cyproheptadine		.12
	Azatadine		.98
	Diphenylpyraline		.53
Nonsedating			
Piperidines	Terfenadine	4.5 h	1.09
	Astemizole	7–20 days	1.09
	Loratidine	9–12 h	
Piperazine	Cetirizine	9 h	
Others	Acrivastine		
	Azelastine		
	Mequitazine		
	Temelastine		

Estimated average wholesale price for 1 day of treatment

Terfenadine was the first nonsedating agent discovered and the first to be marketed in the United States. Ironically, terfenadine was discovered in the search for a new agent with antipsychotic properties[26]; after being found to be devoid of CNS activity, and because of its piperidine ring structure on a substituted alkylamine, it was tested and found to have significant antihistaminic properties. Since then, many new nonsedating H_1 antihistamines have been developed.

The distinction between classical and nonsedating agents is based upon both objective and subjective evaluation of potential CNS and anticholinergic side effects. The major objective factors used to discern CNS effects are reduced sleep latency (greater sleepiness) and performance impairment. The multiple sleep latency test is used as a measure of daytime sleepiness and alertness.[27] Specifically, it measures the time before electroencephalographic (EEG) signs of sleep appear in a patient under standardized conditions. Performance tests are used under the assumption that specific impairments are related to CNS effects.[27,28] Examples of performance tests include reaction time, arithmetical exercises, visual-motor coordination, digit-symbol substitution, and critical flicker fusion (the threshold for fusion of a flickering light). Using criteria just described, potential CNS and anticholinergic effects have been investigated in normal human subjects. Studies have shown that the nonsedating agents terfenadine, astemizole, and cetirizine are devoid of such side effects compared with various classical antihistamines.[26–37]

The lack of CNS effects may be due to an agent's relative selectivity for H_1 receptors over those sites involved with sedation, or an agent's relative exclusion from the central compartment because of lipophobicity. In vitro studies have shown that terfenadine and astemizole are quite receptor-selective.[26,28,31,33,35] Cetirizine appears to be the most highly selective in that it failed to affect any receptor sites other than H_1 receptors in ex vivo studies.[38] Exclusion from the CNS also appears to be important in explaining the lack of central effects. Terfenadine appears to have equal affinity to peripheral and central H_1 receptors,[39,40] yet when administered systemically, it does not occupy cerebral receptors. For example, in in-vivo receptor binding studies, the intraperitoneal injection of terfenadine and chlorpheniramine revealed that the former did not block brain receptors whereas the latter did.[39] In ex vivo studies, the occupation of central H_1 receptors after intraperitoneal injections of dexchlorpheniramine, hydroxyzine, terfenadine, and cetirizine was compared.[38] At doses of 10 mg/kg, the two classical agents occupied a majority of central H_1 receptors (>80%), whereas both nonsedating agents failed to do so (<25%). At doses of 30 mg/kg, however, terfenadine and cetirizine occupied 70% and 34%, respectively, of central

H_1 receptors after intraperitoneal administration. Therefore, these nonsedating agents are relatively, not absolutely, excluded from the central compartment. Further, at high doses, terfenadine appears twice as likely to cross the blood-brain barrier than does cetirizine.

Adverse Effects of H_1 Antihistamines

Classical Agents

The use of classical H_1 antihistamines is commonly limited by dose-related side effects. The most clinically significant side effect is sedation. Sedative effects tend to coincide with peak levels[20,22] and usually manifest as difficulty in concentration, memory lapses, lack of initiative, fatigue, and drowsiness.[27] The mechanism for sedation is unknown. Possible explanations include central H_1 receptor blockade,[28,31] occupation of central nonhistamine sites, and inhibition of histamine-N-methyltransferase,[28] the most important enzyme for metabolism of histamine. Other nonspecific CNS effects can be dizziness, tinnitus, incoordination,[16,31] and potentiation of alcohol or other CNS depressants such as diazepam.[27] Although some patients become tolerant to the CNS side effects including sedation within days, many have to discontinue taking classical agents because of impairment in their performance.

Other relatively common adverse effects include gastrointestinal complaints such as anorexia, nausea, vomiting, abdominal discomfort, constipation, and diarrhea.[15,16,21,31] These conditions, however, may be overcome by concomitant administration with meals or milk.[15,41] Peripheral and central anticholinergic effects are also possible. Peripheral effects include dry mucous membranes, tachycardia, diplopia, urinary retention, impotence, aggravation of narrow-angle glaucoma, and headache.[16,21] Central anticholinergic effects include somnolence, coma, seizures, and delirium.[43] Overdose may result in what has been termed *atropine psychosis*, characterized by fever, diplopia, and psychotic features. Rare but potential adverse reactions from H_1 antihistamines include dyspnea, dyskinesia, and drug allergy, particularly contact dermatitis caused by topical agents.[18] Also, several cases of extrapyramidal reactions have been described after long-term use of classical agents.[41–43] Finally, though controversial, there appears to be a subset of asthmatic children in whom the administration of antihistamines without concurrent bronchodilator treatment exacerbates asthma symptoms.[41]

Nonsedating Agents

In contrast to classical H_1 antihistamines, the nonsedating agents are associated with few adverse effects. Both terfenadine and astemizole have been shown not to potentiate the CNS effects of alcohol or diazepam.[31,35] It should be noted that astemizole use is associated with increased appetite and weight gain.[35]

The use of nonsedating agents also appears to be quite safe. The toxicity of terfenadine is considerably lower than other commonly used antihistamines. Specifically, the median lethal dose for terfenadine in rats and mice is approximately 33 times that found with chlorpheniramine. There are no known long-term adverse effects, as terfenadine has been used in several animal models for periods of up to 2 years. Further, terfenadine does not appear to affect fertility in rats, and neither teratogenic effects nor evidence of mutagenic or carcinogenic potential has been observed in animal models.[44]

Clinical Pharmacology of H_1 Antihistamines

Classical Agents

Clinical effects typically occur within 30 minutes, and peak serum levels are attained between 1 and 3 hours following oral ingestion. Maximal antihistaminic activity, however, often occurs after the peak serum levels are reached. Elimination half-lives are known for many of the H_1 antagonists and are listed in Table 3. In children, the corresponding half-lives are shorter. These drugs are largely metabolized by the liver and eliminated by renal and fecal excretion. They are widely distributed in the body, and though protonated at physiologic pH, readily cross the blood-brain barrier and placenta because of their lipophilicity.[22–24,45,46]

Nonsedating Agents

As a group, the nonsedating agents possess more prolonged antihistaminic effects than classical agents. This property may be partly explained by different binding characteristics. For example, at low concentrations, terfenadine acts as a competitive antagonist, similar to classical agents, in that it causes parallel shifts of dose-response curves. At high concentrations, however, terfenadine acts as a noncompetitive antagonist. Further, it was found that terfenadine binds more slowly than classical agents, but, once bound, it is not easily displaced and dissociates very slowly.[39,47] Astemizole is interesting in that it has an extremely long elimination half-life. Astemizole also has a slow onset of action with a steady state reached in 1 to 2 weeks.[35] Therefore, it is suggested that a loading dose be given during the first week of treatment.[22] Because of decreased bioavailability with concomitant food ingestion, astemizole should be taken on an empty stomach.[35] Cetirizine is unique in that it is primarily excreted unchanged in the urine.[22,24] The elimination of cetirizine has been shown to be significantly prolonged in elderly patients and patients with mild to moderate renal

insufficiency. The disposition of cetirizine, however, was found to be independent of age but dependent on renal function.[48]

Clinical Trials Involving H_1 Antihistamines

H_1 antagonists remain the most used treatment in management of allergic rhinitis. Ironically, however, there are very few well-controlled clinical trials that compare various agents from different classes with each other and with placebo in symptom relief and side effects. The following discussion will summarize the findings of clinical trials involving classical and nonsedating H_1 antagonists in the treatment of allergic rhinitis.

Classical Agents

The first double-blinded, placebo-controlled study involving classical antihistamines evaluated the efficacy and side effects of brompheniramine, chlorpheniramine, and placebo in patients with perennial allergic rhinitis.[49] Unlike the modern double-blinded investigations in which agents are administered for fixed periods, the patients were instructed to switch to a different agent after 1 to 2 days of no symptom relief. The two active agents, both being alkylamines, were equally effective and superior to placebo in treating perennial allergic rhinitis. A second early study compared daily hydroxyzine and placebo in seasonal allergic rhinitis.[50] Hydroxyzine was found to be significantly more effective than placebo ($P < .05$), while drowsiness and dry mouth were noted as significant side effects. This study led to the first comparison of two active agents with each other and placebo.[51] Both hydroxyzine and chlorpheniramine were found to be significantly superior to placebo in relieving sneezing and itchy nose ($P < .05$). Overall, a trend toward a therapeutic advantage with hydroxyzine was observed. There were two other important findings: (1) nearly all the subjects developed tolerance to side effects after a 7- to 10-day treatment period; and (2) efficacy correlated well with reduction of histamine-induced wheal size, thereby lending credence to the skin test as an accurate bioassay of antihistamine effect.

The first comparative study involving more than two active agents used the wheal reduction model.[52] One agent from five of the classical classes was used to compare the efficacy and side effects in a double-blind study. It was found that hydroxyzine was superior to chlorpheniramine, tripelennamine, promethazine, and diphenhydramine in suppressing the degree and duration of a wheal response. Hydroxyzine was also associated with the most side effects, though only slightly more so than the side effects attributed to the least effective agent.

A clinical trial similar in design to the wheal-reduction study just described investigated the relative efficacy and side effects of one classical H_1 antihistamine from each of the six classes and placebo in 11 patients with perennial allergic rhinitis during a seven-way crossover trial.[53] Each of the active agents and placebo were given for 2-week periods. Similar to other antihistamine studies, patients were given diary sheets to record their daily side effects and symptom severity. The patients were evaluated every 2 weeks with respect to diary sheets, nasal examination, and determination of nasal patency via nasal peak inspiratory flow rates. It was found that hydroxyzine and chlorpheniramine were the most efficacious in terms of overall symptom relief for perennial allergic rhinitis. Nasal peak inspiratory flow and nasal examination scores did not show any significant difference between any of the antihistamines and placebo. This finding is consistent with the notion that H_2-mediated mechanisms contribute more to nasal patency than do H_1-mediated mechanisms. Chlorpheniramine treatment resulted in the fewest side effects as well as the most desirable balance between efficacy and side effects. Two weaknesses of the study were the small number of subjects and the single-blinded study design.

In another study, an antihistamine pack containing one classical H_1 antagonist from five of the classes was evaluated to determine patient preferences and incidence of side effects in 782 patients (30% younger than 11 years old) with allergic rhinitis.[54] The protocol did not include a placebo or an agent from the piperidine class. The agents were administered for 2-week periods in a fixed order. Significant patient preferences were found for the agents as follows: chlorpheniramine (27%), diphenhydramine (22%), tripelennamine (20%), hydroxyzine (16%), and trimeprazine (14%). Complaints of side effects for each antihistamine, in increasing order of frequency, occurred with trimeprazine, chlorphenirmine, hydroxyzine, diphenhydramine, and tripelannamine. Following completion of the trial, patients were given prescriptions for the antihistamine of their choice based upon the above findings. Fewer than 1% of the subjects were not able to find a suitable agent. The patients were then followed for up to 5 years to assess what percentage of patients remained on their antihistamine of first choice. It was found that 78%, 71%, and 57% remained compliant on the initial agent for 1-, 3-, and 5-year periods, respectively. Unfortunately, placebo was not included, and the fixed order administration may have instilled a bias toward particular agents over others. Even so, the study revealed the merits of an antihistamine pack in determining patient preference.

Nonsedating Agents

Most of the early clinical experience with nonsedating H_1 antagonists has been with terfenadine. Several years ago, English investigators compared the efficacy and side effects of terfenadine, chlorpheniramine, and placebo in two study populations of 132 and 60 patients. The larger

study found that both active agents were equally effective; however, chlorpheniramine was associated with significantly more sedation than either terfenadine or placebo ($P < .01$).[55] The smaller study revealed no significant differences between active agents and placebo in efficacy or side effects although trends were similar to the findings in the larger study.[56]

German investigators evaluated prophylactic terfenadine in two small studies of 25 and 15 patients with seasonal allergic rhinitis for periods of 6 and 3 months, respectively.[57,58] The second study also included five patients who received clemastine, a classical H_1 antagonist. Of the 40 patients who received terfenadine, only one experienced an "allergic rhinitis attack" compared with two of the five clemastine-treated patients. The authors also attempted to correlate reductions of serum IgE levels with H_1 antagonist use. Reductions in IgE levels were associated with antihistamine use; however, they were either statistically insignificant[57] or were found to be dependent on the ambient pollen concentration.[58]

A multicenter Italian investigation compared terfenadine, dexchlorpheniramine, and placebo in 119 patients with allergic rhinitis.[59] It was found that the active agents were significantly more efficacious than placebo ($P < .01$), though not significantly different from each other. Further, dexchlorpheniramine was associated with significantly more sleepiness than either terfenadine or placebo ($P < .001$).

Terfenadine, dexchlorpheniramine, and placebo were also compared in a multicenter investigation in France.[60] A total of 312 patients with seasonal allergic rhinitis rated symptom relief on a spectrum from excellent response to exacerbation. Eleven predominant symptoms were ranked in order of importance according to their frequency on presentation in the patient population (1 = most important, 11 = least important). The two antihistamines were of equivalent efficacy, and significantly better than placebo ($P < .001$). However, terfenadine was considered by patients as "excellent" to "very good" in symptom relief for symptoms ranked 1, 2, 4, 5, 6, 7, and 8. Symptom 3 (nasal obstruction) received a ranking of "good." In contrast, only symptoms ranked 5 and 8 (nose itching and throat itching, respectively) received "excellent" to "very good" marks with dexchlorpheniramine. Further, dexchlorpheniramine induced significantly more sleepiness than terfenadine ($P < .01$) and placebo ($P < .05$), whereas there was no significant difference between terfenadine and placebo.

Terfenadine was compared with dexchlorpheniramine in 42 patients with grass pollen seasonal allergic rhinitis in The Netherlands.[61] Both agents performed nearly equally in keeping symptoms at a mild level. Dexchlorpheniramine, however, was associated with a significantly increased score for tiredness in contrast to terfenadine.

In a multicenter Canadian study, dexchlorpheniramine and terfenadine were investigated in 174 patients with seasonal allergic rhinitis in a parallel manner.[62] In contrast to other studies, dexchlorpheniramine was found to be significantly superior to terfenadine in efficacy ($P < .005$); however, dexchlorpheniramine was associated with significantly more somnolence ($P < .002$), and more overall side effects ($P < .05$).

An early investigation in the United States compared chlorpheniramine and placebo with various dosages of terfenadine in separate studies over three pollen seasons.[63,64] In general, when administered for more than 3 days, terfenadine was indistinguishable in efficacy from chlorpheniramine, though both agents were superior to placebo. Chlorpheniramine use was associated with a higher incidence of sedation than both terfenadine and placebo. It is interesting that in terfenadine doses of up to five times the standard, reports of sedation were not significantly different from that reported in the placebo-treated patients. Finally, it was determined that the efficacy of large doses of terfenadine (200 mg three times daily) could not be distinguished from either standard doses of terfenadine (60 mg twice daily) or chlorpheniramine (4 mg three times daily).

Another more recent multicenter double-blind parallel study compared terfenadine, chlorpheniramine, and placebo in 345 patients over a 7-day period during the 1982 spring pollen season.[65] Terfenadine was significantly superior to placebo ($P < .05$) and comparable to chlorpheniramine in the relief of allergic rhinitis symptoms. Chlorpheniramine was associated with significantly more side effects than either placebo or terfenadine ($P < .01$). The differences in side effects between terfenadine and placebo, however, were statistically insignificant. Finally, in one of the few published controlled trials of antihistamine use in children, it was found that terfenadine suspension was a safe and effective option in treating seasonal allergy rhinitis.[66]

Astemizole is the second nonsedating agent now available commercially in the United States. It has been found to be significantly superior to placebo ($P < .001$) in relieving symptoms of allergic rhinitis.[67] Studies comparing astemizole and terfenadine in adult patients have shown astemizole to be either superior to or equal to terfenadine in efficacy.[68] The CNS effects of astemizole range from 6.9% to 18.6% compared with placebo rates of 7.2% to 10.7%.[67,68] It has been noted that although patients may notice some sedation from astemizole, it is still considered a nonsedating agent when compared with classical agents.[68] Other nonsedating agents are now being investigated in controlled trials. Reports indicate that loratidine,[69–73] acrivastine,[74,75] azelastine,[76] and temelastine[77] are similar to terfenadine in being effective

for relieving symptoms as well as being associated with few or no central effects.

OTHER PHARMACOTHERAPEUTIC OPTIONS IN ALLERGIC RHINITIS

As mentioned above, the three approaches in management of allergic rhinitis are allergen avoidance, symptomatic pharmacotherapy, and immunotherapy. Though H_1 antagonists remain the mainstay of medications used, other approaches include α-adrenergic sympathomimetics, anticholinergics, cromolyn sodium, and corticosteroids.

α-Adrenergic agents include topical preparations such as the short-acting phenylephrine and the long-acting oxymetazoline[1]; and oral agents such as phenylpropanolamine and pseudoephedrine.[2] These agents increase nasal patency by shrinking swollen turbinates and therefore are effective in relieving nasal congestion. As mentioned earlier, prolonged use of topical preparations may lead to rhinitis medicamentosa and thus these preparations should not be used for more than a few days.[1] In contrast, the oral preparations may be used to reduce the occurrence of rebound congestion and mucosal irritation.[17]

Anticholinergic agents such as topical atropine may be used to block hypersecretion. The treatment, however, is often complicated by centrally mediated adverse effects such as dry mouth and tachycardia. Ipratropium is a quaternary analog of atropine that is purported to be devoid of atropine side effects.[78] It is approved by the Food and Drug Administration for treatment of bronchospasm and chronic bronchitis but remains investigational for rhinitis.[11]

Cromolyn sodium suppresses symptoms of allergic rhinitis by preventing mast cell degranulation. It is most effective therefore when given prophylactically.[13,79] It should be noted that patients may not notice improvement for 2 to 4 weeks after initiation of treatment.[1] Topical cromolyn is more effective on allergic eye symptoms than nasal symptoms because of the inability of cromolyn to block reflex-mediated actions that occur in the nose but not in the eye.[13] Cromolyn may be an alternative for those patients who cannot tolerate the adverse effects of classical antihistamines. It is usually ineffective, however, in patients who are refractory to antihistamines.[78]

Topical corticosteroids usually are very effective agents for treatment of allergic rhinitis.[78,80] They are more effective than cromolyn sodium for relief of nasal symptoms, especially nasal congestion.[80] The older agents such as dexamethasone are associated with some adrenal suppression as a result of partial absorption and subsequent systemic effects. The newer agents such as beclomethasone dipropionate, flunisolide, and fluocortin butylester, however, show no evidence of adrenal suppression, even if swallowed, and are therefore useful in chronic allergic rhinitis.[78,81] The particular advantage of topical corticosteroids is that when given within the proper pretreatment period, they may prevent both the immediate as well as the late-phase hypersensitivity reaction.[6,78] Mechanisms of corticosteroid-induced suppression of the immediate reaction include inhibition of inflammatory mediator release, reduction in epithelial mediator cells, decreased epithelial and endothelial permeability, and decreased glandular response to cholinergic stimuli.[13,78,80] The corticosteroid-induced abatement of the late-phase reaction is mediated by suppression of neutrophil chemotaxis[6] as well as due to inhibiting the release of chemotactic factors of the immediate reaction. Because the long-term effects are unknown, topical corticosteroids should be used at the lowest effective dose and preferably used only intermittently on properly selected patients.[80] Occasionally, management of severe acute allergic rhinitis may require systemic therapy with an orally administered corticosteroid. If used for a short period of time, this treatment is safe as well as highly effective.

Inhalant allergen immunotherapy is also effective in treating well-documented allergic rhinitis.[1] The mechanisms of immunotherapy involve (1) an increase in serum IgG-blocking antibodies, (2) an increase of IgG- and IgA-blocking antibodies in nasal secretions, (3) a blunting of seasonal increases in IgE levels, (4) a reduced basophil reactivity, (5) a reduced lymphocyte responsiveness to antigens, and (6) and increase in specific suppressor T cells.[1,7,82]

CLINICAL APPROACH TO ANTIHISTAMINE THERAPY

When properly used, antihistamine therapy is highly effective in specifically reducing the sneezing, rhinorrhea, and itching of eyes, nose, and throat of patients with allergic rhinitis. The following considerations are important for optimal antihistamine therapy: (1) Before initiation of therapy, the common reasons for treatment failure (adverse effects and lack of efficacy) must be understood so that, if possible, they may be avoided; (2) a reasonable approach toward selecting antihistamines should be used; (3) the contraindications of antihistamines must be considered; and (4) concomitant use of antihistamines with other pharmacotherapeutic options may be necessary.

There are several ways to help minimize or avoid the adverse effects associated with classical agents. First, patients should be encouraged to remain compliant during initial treatment, as many will become tolerant to sedative

effects. Second, classical agents with long half-lives, such as chlorpheniramine and hydroxyzine, need not be administered three or four times daily. Instead, such agents should be administered once every appropriate half-life.[23,24,45] Third, classical agents can be administered initially only at bedtime, and then a morning dose added if clinically indicated.[20] To ensure optimum opportunity for efficacy, incorrect self-administration practices can be avoided through proper patient education. Specifically, patients should be aware that antihistamines must be administered either prophylactically (3 to 5 hours before anticipated allergen exposure) or on a regular basis if needed chronically.

For routine management of allergic rhinitis, a rational first choice for H_1 antagonist therapy is the inexpensive, over-the-counter agent chlorpheniramine. This recommendation is based on the potency of chlorpheniramine, similar to hydroxyzine, and its relatively low incidence of side effects.[53,54,83] For those patients who absolutely do not tolerate the CNS effects of a particular classical agent, three options are available: (1) try a classical agent from a different chemical class, (2) use a nonsedating antihistamine, and (3) use a nonsedating agent in the morning and continue taking the classical agent in the evening.[83] A nonsedating agent should be prescribed initially and exclusively, however, for those patients who are involved in activities where drowsiness may be risky. Of the nonsedating agents, terfenadine is preferred over astemizole in acute allergic rhinitis because of the delayed onset of action of the latter. Because of its prolonged effect, however, astemizole is considered to be the most useful nonsedating agent in the prophylactic and long-term therapy of patients with either chronic or recurrent symptoms.[68]

Particular attention should be paid to antihistamine choice in patients with known organ system pathology, eg, hepatic and renal disease, which are associated with prolonged elimination half-lives of diphenhydramine and chlorpheniramine, respectively.[23] In general, all antihistamines should be used with caution in patients with hepatic or renal dysfunction.

Finally, combined therapy utilizing H_1 antagonists with other pharmacotherapeutic options may be indicated. For example, the concomitant use of either oral or topical H_2 antagonists,[22,84,85] cromolyn sodium,[79] intranasal anticholinergics, topical steroids,[8,22,80] or oral sympathomimetics[17,86] may offer synergistic assistance in the control of symptoms of allergic rhinitis.

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