

MANAGEMENT OF ALLERGIC RHINITIS

Antihistamines and Decongestants

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ANTIHISTAMINES

Background

Histamine plays a significant pathogenic role in the development of many of the signs and symptoms of allergic rhinitis. Mast cells and basophils are the predominant cellular sources of histamine. In a sensitized host, these cells release preformed granules of histamine in response to antigen-induced cross-linking of IgE. Once released, histamine binds to specific histamine type I (H_1) receptors on nerve endings, smooth muscles, and glandular cells, and acts to dilate blood vessels, increase vessel permeability, and stimulate parasympathetic nerve endings and reflexes. Collectively, these actions cause local irritation, inflammation, and edema formation.^{24, 45} Intranasal administration of histamine reproduces the symptoms of allergic rhinitis, including sneezing, nasal pruritus and congestion, and rhinorrhea.⁹ Consequently, antihistamines are effective against many of the symptoms of allergic rhinitis.^{3, 38}

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Mechanism of Action

First- and second-generation antihistamines exert major clinical effects by competitively and reversibly inhibiting the binding of histamine to H_1 receptor sites. Blockade of H_1 receptors on postcapillary venule smooth muscle, glandular cells, and nerve endings causes decreased local irritation, vascular permeability, cellular exudation, and edema formation.³⁷ Consequently, in individuals with allergic rhinitis, antihistamines are clinically effective against symptoms of rhinorrhea, pruritus, and sneezing. In experimental models, second-generation antihistamines also exhibit a range of anti-inflammatory activities. These include down-regulation of adhesion molecule expression, inhibition of eosinophil migration and activation, blockade of mast cell and basophil mediator release, and up-regulation of β -adrenoceptor function. It is not known, however, whether these effects contribute to the clinical efficacy of these drugs in the treatment of allergic rhinitis. There is no evidence for tachyphylaxis with antihistamines.

Types

Early or first-generation antihistamines are lipophilic molecules, which can easily cross the blood-brain barrier and induce pharmacologic actions in the central nervous system (CNS). The major limitation of the use of first-generation antihistamines is sedation. Other limitations include the induction of anticholinergic, antimuscarinic, and antiadrenergic effects.^{10, 31, 34, 37} First-generation antihistamines are placed into different classes based on their chemical structure. Representative first-generation antihistamines include diphenhydramine, triprolidine, chlorpheniramine, brompheniramine, and hydroxyzine³⁷; and are available in oral formulations and are sold over the counter.

Second-generation antihistamines are lipophobic, have a large molecular size, and possess an electrostatic charge. Because of their physiochemical properties, they generally do not cross the blood-brain barrier, and therefore exhibit negligible CNS effects. One of the primary advantages of second-generation antihistamines is that they are nonsedating or significantly hyposedating. They also have a long duration of action and are amenable to once- or twice-daily dosaging. Other advantages of second-generation antihistamines include preferential binding to peripheral H_1 receptors and minimal anticholinergic, antimuscarinic, and antiadrenergic effects.^{8, 10, 11, 31, 34, 37} Second-generation antihistamines also are grouped into different classes, based on their chemical structure. Currently marketed second-generation antihistamines include loratadine, cetirizine, and fexofenadine. All of these medications are available in oral formulations and require a prescription. Two second-generation antihistamines, terfenadine and astemizole, were withdrawn from the market owing to their association with cardiac dysrhythmias.⁴⁷ Dosages and frequencies of administration of second-generation antihistamines

Table 1. FORMULATIONS AND DOSAGES OF CURRENTLY MARKETING SECOND-GENERATION ANTIHISTAMINES

Drug	Formulation	Recommended Dosage
Azelastine	Nasal solution 0.1% (0.137 µg/spray)	Adult: 2 sprays per nostril bid
Cetirizine	Tablets (10 mg)	Adult: 10 mg qd
	Syrup (5 mg/5 mL)	Pediatric (6–12 y): 5–10 mg qd
		Pediatric (2–5 y): 2.5–5 mg qd
Fexofenadine*	Tablets (60 mg)	Adult: 60 mg bid or 180 mg qd
Loratadine*	Tablets (10 mg)	Adult: 10 mg qd
	Rapidly Disintegrating Tablets (10 mg)	
	Syrup (5 mg/5 mL)	Pediatric (6–12 y): 10 mg qd

*Available in fixed-dose combination with pseudoephedrine hydrochloride.

are summarized in Table 1. Other second-generation antihistamines are currently being developed and tested.

Azelastine is the only antihistamine currently marketed for intranasal use.²⁰ It is formulated in a 0.1% aqueous solution in a metered-spray delivery device. Azelastine is systemically bioavailable, can cross the blood-brain barrier, and, in some individuals, can cause CNS side effects. The most commonly reported adverse effects are bitter taste and somnolence. The major advantages of this agent are its rapid onset of action, which occurs approximately 15 to 30 minutes following administration, and a possible effect on nasal congestion. The recommended dosage of azelastine in adults and children over 12 years of age is two sprays to each nostril twice daily. Each spray delivers a mean dose of 137 µg of the drug.

Pharmacokinetics

The pharmacokinetic profiles of antihistamines are summarized in Table 2.^{3, 11, 13} In general, oral antihistamines are readily absorbed, with

Table 2. PHARMACOKINETICS OF ORAL SECOND-GENERATION ANTIHISTAMINES

	Terfenadine	Astemizole	Loratadine	Cetirizine	Fexofenadine
T _{max}	2.5 h*	1 h	1.4–1.6 h	1 h	2 h
Half-life	3.5 h*	20 h†	8.4 h*	9 h	12–14 h
Absorption	↓ with food	↓ with food	No food effect	No food effect	↓ with food
Onset of action	1–2 h	1–5 d	1–2 h	1–2 h	1–2 h
First-pass hepatic metabolism (P450)	Extensive CYP3A4	Extensive CYP3A4	Extensive CYP3A4 CYP2D6	Limited	Limited
Active metabolites	Carboxylate	Hydroxylated	Descarboethoxy	None	None
Elimination	60% fecal; 40% renal	Primarily fecal	50% fecal; 50% renal	30% fecal; 70% renal	80% fecal; 11% renal

*Refers to active metabolite.

†Refers to parent drug and metabolite.

↓ = decreased

peak serum concentrations reached within 2 to 3 hours following administration. Antihistamines vary widely in their onset of activity, with topical preparations (e.g., azelastine) acting within 15 to 30 minutes and oral agents (e.g., astemizole) acting within several days. With the exception of cetirizine and fexofenadine, all oral first- and second-generation antihistamines are metabolized by way of the hepatic cytochrome P450 system. Two alternative pathways, a predominant one involving the cytochrome P450 CYP3A4 hepatic enzyme system and a less dominant one involving the P450 CYP2D6 isoenzyme system, metabolize loratadine. Some oral antihistamines, including loratadine, astemizole, and hydroxyzine, are converted to clinically relevant, active metabolites. Antihistamines are eliminated by way of the renal and fecal or biliary routes, and clearance rates are variable, ranging from 2 hours to 10 days. The pharmacokinetic profiles of some oral antihistamines may be altered with age, food, concomitant use of ketoconazole or erythromycin, or renal or hepatic dysfunction.

The duration of bioactivity is longer than the serum half-lives of antihistamines.^{11, 13, 37} For example, peak suppressive effects of antihistamines on histamine- or antigen-induced wheal and flare reactions usually occur 5 to 7 hours following administration of an oral dose. Suppressive effects of many antihistamines, including hydroxyzine and cetirizine, can persist for at least 24 to 36 hours, even after serum concentrations of the parent compound have declined below their lowest limit of detection. This is most likely owing to the presence of active metabolites and high tissue concentrations of active drugs. Astemizole is unique because this agent binds to peripheral H₁ receptors with more affinity than do other antihistamines.³⁰ As a result, serum and tissue levels of astemizole can persist for days to weeks, and suppression of skin test responsiveness can persist for at least 6 weeks following the administration of a single dose.

Clinical Efficacy

Antihistamines are clinically efficacious for controlling symptoms of allergic rhinitis that are attributed to the early-phase reaction.^{3, 10, 15, 33, 40} These include rhinorrhea, pruritus, and sneezing. They are less efficacious in controlling nasal congestion, which is related to the late-phase reaction. Antihistamines are more effective when they are occupying the H₁ receptor before histamine is released. Consequently, the maximum benefit from antihistamines is achieved with prophylactic treatment before exposure to allergen. In general, all first-generation antihistamines demonstrate a comparable degree of clinical efficacy, and the efficacy of second-generation antihistamines is equal or superior to that of first-generation agents. Antihistamines are generally equally or slightly more efficacious than topical sodium cromoglycate, and are less efficacious than topical corticosteroids. Efficacy may be improved by affecting con-

gestion by the combination of an antihistamine with a decongestant or a topical corticosteroid.¹¹

Adverse Effects

Adverse effects of antihistamines are summarized in the box below. Antihistamines have been reported to cause four types of CNS effects: stimulatory, neuropsychiatric, peripheral, and depressive, including sedation or performance impairment.^{31, 34} An advantage of second-generation antihistamines over first-generation agents is that the former have a more favorable adverse effect profile, especially with regard to sedation and performance impairment. For example, first-generation antihistamines have been reported to impair reaction times, visual-motor coordination, and learning, even in the absence of sedation. Additionally, these agents have been associated with decreased work productivity, impaired academic performance, and an increased risk of occupational and automobile accidents. These effects can occur in the absence of any subjective complaints, and may be potentiated by the concomitant use of alcohol,

Box 1. Adverse Effects of Antihistamines

- Central Nervous System*
 - Stimulation
 - Neuropsychiatric
 - Peripheral
 - Depressive (includes sedation and cognitive impairment)
- Cardiac†
 - Prolongation of QT interval
 - Ventricular arrhythmias
- Anticholinergic*
 - Dry mouth and eyes
 - Urinary retention
 - Impotence
 - Worsening of glaucoma
- Others
 - Weight gain
 - Rashes
 - Photosensitivity
 - Hypersensitivity reactions
 - Blood disorders
 - Hepatic dysfunction

*Less common with second-generation agents.

†Associated with astemizole and terfenadine only.

sedatives, hypnotics, and antidepressants.^{12, 31, 34, 43} In contrast, most of the second-generation antihistamines, including terfenadine, astemizole, loratadine, and fexofenadine, have been classified as nonsedating because the incidence of sedation and impaired CNS function associated with recommended doses of these agents is similar to that seen with placebo.¹⁹ At higher than recommended dosages and in certain individuals using standard dosages, however, sedation or CNS dysfunction may occur. Standard dosages of nonsedating antihistamines have not been shown to potentiate the CNS effects of alcohol or other drugs. Cetirizine, the newest second-generation antihistamine, has been classified as hyposedating because the incidence of sedation associated with recommended dosages of this agent is less than that seen with first-generation antihistamines but greater than that seen with placebo.¹¹

Two of the nonsedating antihistamines, terfenadine and astemizole, rarely can produce serious cardiovascular effects if used at higher than recommended dosages.⁴⁷ Elevated tissue levels of these agents can cause prolongation of the QT interval, which may predispose to the development of torsades de pointes or other ventricular arrhythmias, cardiac arrest, sudden near death, or death. Risk factors for the development of these cardiovascular effects include overdosage, hepatic dysfunction, hypocalcemia, hypokalemia, congenital QT syndrome, or the use of concomitant medications that interfere with the metabolism of these agents by the cytochrome P450 isoenzyme system. Such medications include azole antifungals, some macrolides, and ciprofloxacin.²⁹ Because of their association with rare cardiac effects, terfenadine and astemizole have been withdrawn from the market. The other nonsedating antihistamines, including cetirizine, fexofenadine, and loratadine, have not been shown to be associated with QT interval changes, rhythm disturbances, or other cardiac effects.^{11, 47}

Other adverse effects can occur with antihistamines.^{8, 11, 33} Anticholinergic effects have been associated with first-generation antihistamines. The most common anticholinergic effects include dry mouth, dry eyes, and urinary retention. Less common anticholinergic effects include tachycardia, impotence, worsening of glaucoma, headache, somnolence, coma, seizures, dyskinesia, and behavioral changes. Astemizole and azelastine have been associated with appetite stimulation and weight gain. Other rare adverse effects include rashes, photosensitivity, hypersensitivity reactions, blood disorders, and hepatic dysfunction. Previous concerns about the potential adverse effects of antihistamines in patients with asthma have not been substantiated. In fact, some of the second-generation antihistamines have been shown to possess some mild anti-asthma effects.^{7, 14, 28}

Special Populations

Recommendations for the use of second-generation antihistamines in special populations are summarized in Table 3. Allergic rhinitis is

Table 3. SPECIAL CONSIDERATIONS FOR DOSING OF ORAL SECOND-GENERATION ANTIHISTAMINES

Agent	Usual Adult Dosing	Pediatric Dosing (<12 y)	Adult Dosing With Renal Dysfunction	Adult Dosing With Hepatic Dysfunction	Pregnancy Category
Cetirizine	10 mg qd	6–12 y: 5–10 mg qd 2–5 y: 2.5–5 mg	5 mg qd	5 mg qd	B
Fexofenadine	60 mg bid or 180 mg qd	None	No change	60 mg qd	C
Loratadine	10 mg qd	6–12 y: 5–10 mg qd	10 mg qod	10 mg qod	B

one of the most common causes of nasal symptoms during pregnancy. Symptoms of allergic rhinitis may worsen, improve, or stay the same during pregnancy. First- and second-generation antihistamines have not been incriminated as human teratogens. First-generation antihistamines, however, are favored over their second-generation counterparts, based on their longevity and record of safety. All first- and second-generation antihistamines are category B (i.e., no evidence of risk in humans) or category C (i.e., risk cannot be ruled out).²¹ Because adequate and well-controlled human studies are lacking, antihistamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Allergic rhinitis affects approximately 10% of school-aged children and 20% to 30% of adolescents. In these populations, inadequate symptom control may contribute to learning difficulties and cause poor academic performance. These effects can be compounded by the use of first-generation antihistamines, which increase daytime drowsiness and decrease cognition, thereby impeding learning. Second-generation antihistamines are preferred over first-generation agents because they provide adequate symptom relief without inducing significant CNS effects. Two second-generation antihistamines are currently available for treating children younger than 12 years of age.¹¹ Cetirizine is approved for use in children 2 years of age and older, and loratadine is approved for use in children 6 years of age and older. These medications are available in a syrup formulation, and their pediatric dosages are summarized in Table 3.

Allergic rhinitis is an uncommon cause of rhinitis in individuals over 65 years of age. More common causes of rhinitis in this population include cholinergic hyperreactivity, α -adrenergic hyperactivity, and sinusitis. Certain adverse effects of antihistamines may be more common or of greater concern in the elderly.^{11, 33, 35} For example, this population is more sensitive to the potentially sedative and cognitive effects of first-generation antihistamines. They also are at greater risk for complications resulting from drug-induced functional impairment, such as fractures and subdural hematomas caused by falling. Additionally, the anticholinergic effects of first-generation antihistamines may complicate prostate hypertrophy, cause bladder disturbances, or cause problems with visual

accommodation. Advancing age may alter the pharmacokinetic profile and pharmacodynamic effects of antihistamines. Finally, the risk of adverse drug interactions with antihistamines is increased because many geriatric patients have concomitant diseases for which they are taking various medications. In general, second-generation antihistamines are preferred over first-generation agents because they are less likely to cause sedation, cognitive dysfunction, and unwanted anticholinergic effects in this population.

As discussed previously, certain adverse effects of second-generation antihistamines may be increased by the concomitant use of other medications or underlying hepatic or renal dysfunction. For example, the risk of developing QT interval prolongation was increased when terfenadine or astemizole was used in combination with macrolide antibiotics or oral imidazole antifungal agents. The concomitant use of other second-generation antihistamines, including loratadine, cetirizine, and fexofenadine, with these agents does not cause QT interval prolongation.⁴⁷ As summarized in Table 3, dosage schedules for oral second-generation antihistamines should be modified in patients with liver disease. Additionally, dosage schedules for cetirizine and loratadine should be modified in patients with renal impairment.¹¹

Selecting an Antihistamine

The Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology, Palatine, IL, recently published guidelines on the diagnosis and management of rhinitis. These guidelines review the considerations in selecting an antihistamine for the treatment of allergic rhinitis.¹¹ As with any medication, the choice of an antihistamine should be considered in the context of an individual patient's needs and response to a given agent regarding the benefit obtained versus the risk of adverse effects. Second-generation antihistamines have fewer sedative and anticholinergic effects than first-generation antihistamines,^{12, 31, 34, 43} which is an important consideration for any patient, but particularly for pediatric and geriatric patients. Cost also may be a consideration. First-generation antihistamines are less expensive than second-generation agents; however, this must be balanced against the greater risk of adverse effects and costs associated with poor work or school productivity in a sedated patient. Adherence also may be another consideration. Patient adherence may be enhanced by the use of second-generation antihistamines because most of these agents are administered once daily.

First- and second-generation antihistamines are ineffective at relieving nasal congestion, and a topical or oral decongestant may need to be added.^{11, 33} Many combination antihistamine-decongestant formulations are available. The major advantage of these combination agents is their convenience. Disadvantages are intolerance of the fixed dose of decongestant in certain patients and an inability to titrate each agent independently.

Patients should be educated about the appropriate use of antihistamines. For optimal results, antihistamines should be administered prophylactically (2 to 5 hours before allergen exposure) or on a regular basis if needed chronically. Although antihistamines are effective on an as-needed basis, these agents work best when they are administered in a maintenance fashion.

DECONGESTANTS

Mechanisms

Nasal congestion occurs when there is increased resistance to air flow in the nose. The resistance to air flow can be fixed (e.g., polyp) or dynamic (e.g., the nasal cycle). In allergic rhinitis, congestion develops secondary to engorgement of the cavernous venous sinusoids in the nasal turbinates, which leads to tissue swelling, reduced internal nasal diameter, and increased resistance to air flow. Secretions also may contribute to the increased resistance to air flow. The nasal vasculature is affected by a number of mediators that cause nasal dilation, such as histamine, bradykinin, prostaglandins, leukotrienes, and platelet-activating factor.²³ Neuropeptides—substance P and calcitonin gene-related peptide—also are capable of inducing nasal dilation and contributing to congestion.⁴⁶

The venous sinusoids are controlled primarily by sympathetic innervation and, to a lesser extent, by parasympathetic innervation.¹⁶ Postcapillary venules are capacitance vessels that, when dilated, accommodate large volumes of blood. Increased blood volume secondarily increases the volume of the nasal mucosa, leading to congestion.

Pharmacology

Decongestants contain sympathomimetic agents (i.e., drugs that mimic the actions of the neural transmitter, norepinephrine, and bind to and activate two types of adrenergic receptors, α_1 and α_2).¹⁷ The α_1 -adrenergic receptors densely populate postcapillary venules. When stimulated, this receptor subtype activates phospholipase C by way of the G-protein, which cleaves phosphatidylinositol-bisphosphate into the second messengers, inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 and DAG then mobilize calcium from stores and initiate the phosphorylation of key enzymes to produce vasoconstriction. Thus, activation of α_1 -receptors causes vasoconstriction that reduces the volume of blood in the mucosa and the mucosa volume, leading to decreased nasal congestion.

The α_2 -adrenergic receptors tend to be concentrated on precapillary arterioles, and, when activated, induce constriction of the smooth muscle of the vessel by an increased reflux of calcium ions. Vasoconstriction

then diminishes blood flow into the capillary bed of the nasal mucosa, which reduces the extracellular fluid that is associated with congestion and rhinorrhea.

Decongestants can produce their effects by two broad mechanisms.³² Direct-acting sympathomimetic drugs activate adrenergic receptors resulting in vasoconstriction. Depending on the molecular structure of the particular adrenergic agonist, either or both subtypes of adrenergic receptors could be activated equally or they could be activated selectively. For example, phenylephrine (PE) selectively activates α_1 -adrenergic receptors, whereas oxymetazoline selectively activates α_2 -adrenergic receptors. Tetrahydrozoline activates both receptor subtypes. Indirect acting sympathomimetic agents function by being taken up into the prejunctional nerve terminal where they displace norepinephrine from storage vesicles. The dispensed norepinephrine then is released from the sympathetic nerve terminal to postjunctional-adrenergic receptors, producing vasoconstriction. Some indirect acting agents also may increase norepinephrine concentrations in the neural effector junction by blocking its reuptake into nerve terminals. Many indirect acting sympathomimetic agents also bind directly to adrenergic receptors so their overall effect is equal to the sum of their direct and indirect actions. Examples of sympathomimetic agents with indirect or mixed mechanisms of action are pseudoephedrine (PDE) and phenylpropanolamine (PPA). There is a possible decrease in total protein and lysozyme with the use of oxymetazoline, which is reflected by a decrease in secretions.⁵

Types

Oral decongestants are PDE, PPA, and PE (Table 4). Their efficacy in allergic rhinitis has been demonstrated in several controlled studies.^{1,2} The dosage for PDE is 1 mg/kg four times a day in children under the age of 6; 30 mg four times a day in children 6 to 12 years old; and 60 mg four times a day or 120 mg extended release twice a day in patients older than 12 years. These pills are available in 30-mg, 60-mg, 120-mg, and 240-mg tablets, and as 15 mg/5 mL and 30 mg/5 mL liquid.

Table 4. TYPES OF DECONGESTANTS

Oal	Formulation	Dosage (mg)	T _{max} (h)	Half-Life (h)
Pseudoephedrine	Tablet	60	1.6	5.5
Phenylpropanolamine	Solution	50	1.47	4.0
Phenylephrine	Solution	1	1.25	2.5
Topical				
Phenylephrine				
Oxymetazoline				
Naphthazoline				
Tetrahydrozoline				
Zylometazoline				

Topical agents used as nasal sprays and drops include PE, oxymetazoline, xylometazoline, and naphthazoline. Oxymetazoline is a long-acting topical agent, dosed twice a day and approved for children as young as 6 years old.

Side Effects

Oral decongestants cause generalized constriction of blood vessels, and increased arterial pressure is always of concern.²⁶ Most available oral agents, however, cause blood pressure elevations in normal persons only at doses that significantly exceed the recommended dose. The primary side effects of oral decongestants (Box 2) are nervousness, irritability, tachycardia, palpitations, headache, and insomnia. They also may interfere with urinary flow in men and may increase blood pressure in some hypertensive patients. Other possible adverse effects are reflex bradycardia, mydriasis (with effects on glaucoma), and effects on endocrine and other regulators of metabolic function. PDE is considered to be the oral decongestant of choice for use during pregnancy. Recent case-controlled studies, however, associated first-trimester PDE (and other decongestant) use with an increased risk of gastroschisis.^{42, 44} Prolonged use of oral decongestants may lead to withdrawal symptoms of headache and fatigue when the drug is stopped.

Topical agents used as nasal sprays act rapidly, usually within minutes, and therapeutic doses have no systemic side effects. Rebound hyperemia (rhinitis medicamentosa) or chemical rhinitis, however, is a frequent side effect especially in patients who use the drugs over an extended period of time. The mechanism for rhinitis medicamentosa is not clear. Receptor desensitization also may occur.^{26, 27} Long-acting topical nasal decongestants may be used safely for longer than the recommended 3- to 5-day periods without adverse effects if used once nightly.⁴⁸ The administration of topical decongestants may cause ciliary loss and subsequent sinusitis in certain patients.²²

Pharmacokinetics of Oral Decongestants

Only three drugs are commonly used as oral decongestants: PPA, PDE, and PE. These are chiral drugs that exist as stereoisomers. Each

Box 2. Side Effects of Decongestants

- Headache
- Tachycardia
- Arrhythmias
- Hypertension
- Palpitations
- Nervousness
- Excitability
- Nausea
- Vomiting
- Difficult urination

enantiome can reflect significant enantioselective differences with regard to pharmacokinetic and pharmacodynamic effects. PPA and PDE are absorbed readily and are not substantially metabolized, whereas PE, with a bioavailability of only approximately 38%, is subject to gut wall and liver metabolism and is believed to be absorbed erratically. Concentrations are reached within 30 minutes to 2 hours after administration. All three drugs are distributed extensively into extravascular sites. Elimination of PPA and PDE is predominantly renal. Half-lives are short, approximately 2.5 hours for PE, 4 hours for PPA, and 6 hours for PDE. Elimination of PPA and PDE may be rapid in children.³⁶ Reduced metabolism of PE occurs with concurrent administration of monoamine oxidase inhibitors. No direct relationship between nasal decongestant effect and plasma concentrations has been established for any of the agents.¹⁸

Selecting a Decongestant

Chronic nasal stuffiness has been noted to respond to treatment with PDE, PPA, and PE, compared with placebo in reducing nasal airway resistance. Forty milligrams of PPA and 60 mg of PDE decreased nasal airway resistance as measured by rhinomanometry. PDE and PPA do not undergo clinically important first-pass metabolism, as does PE.

There are differences in formulation. Slow release formulation alters performance. Slow release decreases the peak concentration. This difference may not be clinically relevant.¹⁸

Combinations of antihistamines and decongestants represent a convenient way of counteracting all the symptoms of allergic rhinitis on a short-term basis, but have no effect on the underlying pathophysiology. It is difficult to vary the dose of each component separately when they are used in combinations. There are various proprietary combinations, including formulations with the newer non-sedating antihistamines. The clinical trials have shown that the combination drugs are more effective than the individual components alone.^{4, 25, 41}

Mucosal congestion also may affect adjacent structures, such as the eustachian tubes. One study showed significantly improved eustachian tube function in subjects who used the antihistamine decongestant combination in an experimental challenge setting.³⁹

The sedative effects of antihistamines are believed to be neutralized by the excitatory effects of the α -adrenergic decongestants. There are, however, no objective data from studies on skilled performance to substantiate this opinion. Similarly, there are no data that compare the effects on performance of a combined preparation with a non-sedating antihistamine.

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