Natural Treatment of Perennial Allergic Rhinitis

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Abstract
Perennial allergic rhinitis is an IgE-mediated inflammatory disorder of the nasal mucosa characterized by paroxysms of sneezing, nasal congestion, pruritis, and rhinorrhea. The condition may be caused by certain environmental agents, food sensitivities, structural abnormalities, metabolic conditions, or synthetic drugs. Recent health impairment outcome studies on allergic rhinitis sufferers reveal a measurable decline in physical and mental health status and the inability to perform daily activities. Antihistamines, decongestants, anticholinergic agents, and corticosteroid drug therapy, alone or in combination, are typically used in the treatment of allergic rhinitis. Reported adverse side effects include sedation, impaired learning/memory, and cardiac arrhythmias. Therapeutic strategies should seek to decrease the morbidity already associated with this condition. *Urtica dioica*, bromelain, quercetin, N-acetylcysteine, and vitamin C are safe, natural therapies that may be used as primary therapy or in conjunction with conventional methods.
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Introduction

Allergic rhinitis is the most common allergic disorder in the United States, affecting 10-20 percent of the population.[1,2] The condition is characterized by continuous or periodic nasal congestion, rhinorrhea, sneezing, pruritis of the conjunctiva, nasal mucosa and oropharynx, allergic shiners, lacrimation, and fatigue. Predisposing factors are a positive family history of similar symptoms and a personal history of collateral allergy manifested as eczematous dermatitis, urticaria, and/or asthma. Clinical presentation may include nasal polyps, pale and boggy (sometimes reddened or excoriated) nasal passages, congested and edematous conjunctiva, injected pharynx, and swelling of the turbinates and membranes of the ear. Often, there is a temporal relationship between an allergen exposure and an acute episode of allergic rhinitis. Environmental agents that can cause this condition are dust mites, feathers, animal dander, mold, pollen, grass, and fungus spores. Many people with allergic rhinitis are also allergic to certain foods and may experience symptoms as a result of eating allergy-triggering substances in such foods as eggs, nuts, fish, shellfish, dairy products, or wheat.[3] In the absence of nonspecific stimuli in the history, structural abnormalities of the nasopharynx, exposure to irritants,

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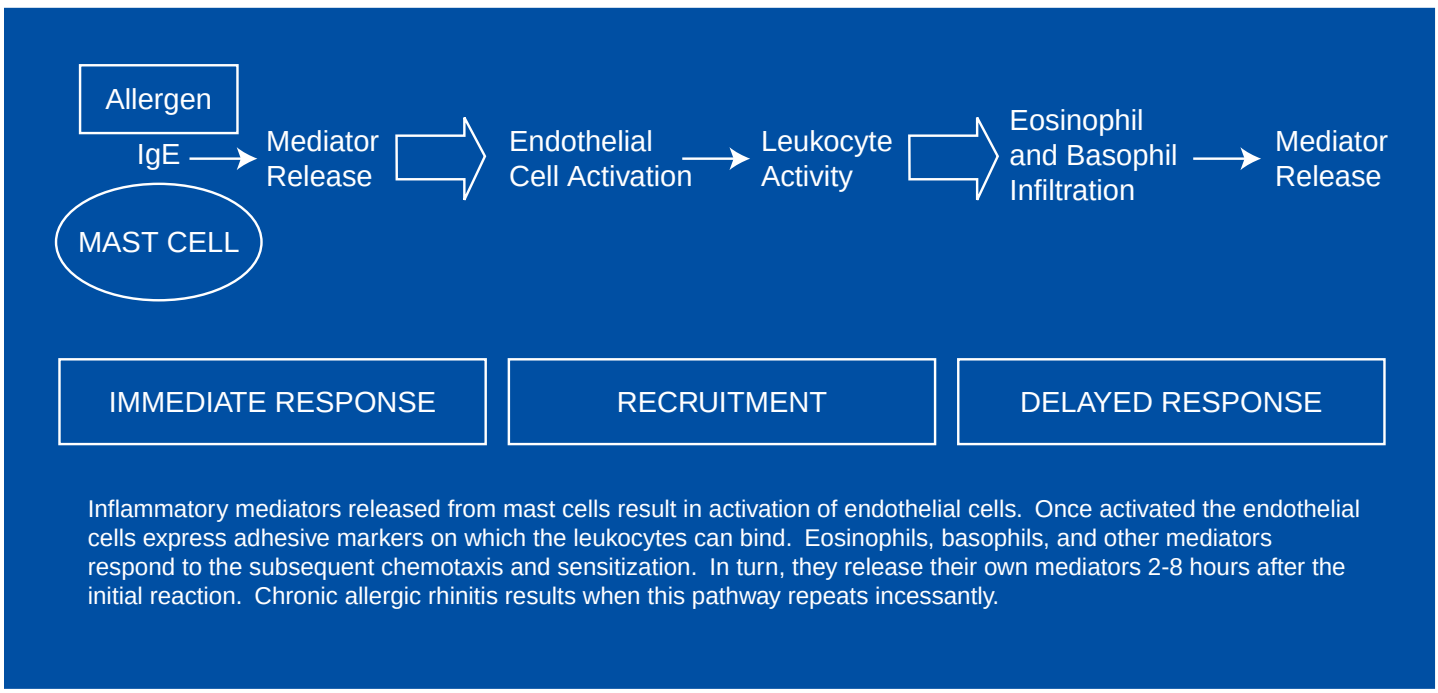
upper respiratory infection, pregnancy with prominent nasal mucosal edema, prolonged use of alpha-adrenergic agents, or use of rauwolfia, beta-adrenergic antagonists, or estrogens should be excluded.

Pathophysiology

Most cases of allergic rhinitis are due to an indeterminate, yet specific, allergen-reagin reaction in the nasal mucosa. The immediate-response phase consists of an allergen binding to the IgE component of the mast cell. This initial pathophysiological event results in recruitment of numerous chemoattractants and inflammatory mediators, which signal eosinophil, basophil, neutrophil, and monocyte infiltration.[4] Usually 2-8 hours after exposure to the antigen (delayed-response phase), there is intense infiltration of tissues with inflammatory mediators as well as tissue destruction in the form of mucosal epithelial cell damage, as there exists a perpetual mediator response (Figure 1). This late or delayed inflammation is associated with an increased sensitivity to the allergen after repeated exposures and a hyper-responsiveness to irritants or certain pharmacologic agents.

While mast cells are widely distributed throughout the human body, they are found in high concentrations in the blood vessels of the sub-epithelial connective tissue of the respiratory tract and conjunctiva. Mast cell degranulation accounts for approximately one-half the symptoms of allergic rhinitis. Histamine, the principal inflammatory mediator in allergic rhinitis, is released by mast cells in the immediate-response phase and by basophils in the delayed-response phase. Histamine binding to H1-receptors has several consequences; it increases vasodilation, capillary permeability, and smooth muscle contraction, manifesting as rapid fluid leakage into the tissues of the nose as well as swollen, secretory nasal linings.[2]

Figure 1: The allergen-reagin reaction begins when the allergen binds to the mast cell.



Inflammatory mediators released from mast cells result in activation of endothelial cells. Once activated the endothelial cells express adhesive markers on which the leukocytes can bind. Eosinophils, basophils, and other mediators respond to the subsequent chemotaxis and sensitization. In turn, they release their own mediators 2-8 hours after the initial reaction. Chronic allergic rhinitis results when this pathway repeats incessantly.

Discussion

Antihistamines comprise the largest group of drugs on the market. Their effect is based on the blockade of H_1 histamine receptors located on the nasal vasculature and nerve endings.[5] Structural differences between the various drugs account for the differences in the potential side effects. The first-generation antihistamines contain ethylamine moieties that make them highly lipophilic and readily able to cross the blood-brain barrier.[5] This characteristic partly explains the numerous adverse effects associated with sedating antihistamines, including dizziness, tinnitus, cardiac arrhythmias, gastrointestinal distress, lassitude, incoordination, blurred vision, diplopia, euphoria, and tremors. In fact, it has been reported the first-generation antihistamines cause discernible drowsiness in 25 percent of adults.[6] Even in the absence of sedation, they can substantially impair thought processes and the ability to drive or operate machinery.

The piperazine- or piperidine-like structures of the second-generation antihistamines do not cross the blood-brain barrier and have not been found to cause significant sedation, fatigue, or anticholinergic effects. However, astemizole and terfenadine can cause torsades de pointes (a potentially fatal cardiac arrhythmia) if given concurrently with macrolides (erythromycin and troleandomycin), imidazole antifungals (ketoconazole and itraconazole), or to a person with liver disease. Drug interactions are also suspected with certain antidepressants and HIV-specific protease inhibitors.[6]

Topical decongestants reduce airflow resistance by attenuating the blood volume in the nasal mucosa. While selective in their action, these drugs are not effective for long-term use (defined as greater than one week) because of the risk of rebound hyperemia, receptor desensitization, mucosal damage, or ultimately, rhinitis medicamentosa, an excruciatingly painful condition of the nasal passages.[6] Oral decongestants are likely to create more adverse systemic effects, including cardiac arrhythmias, hypertension, and CNS disturbances. They are contraindicated in individuals with heart disease, hyperthyroidism, glaucoma, or diabetes mellitus.

Anticholinergic agents control the vasodilation and secretion of serous glands in the nasal mucosa. Reportedly, these drugs can affect visual perception, reaction time, coordination and memory. In fact, the U.S. Food and Drug Administration ruled in 1985 that anticholinergics were not suitable (i.e., safe and effective) for over-the-counter distribution.[6]

Intranasal corticosteroid treatment has local side effects, including nasal irritation and bleeding and septal perforation. Their mechanisms of action involve modification of gene expression, formation of cell-regulatory proteins, and inhibition of inflammatory mediators.

A recent study by Marshall et al reveals a significant impairment in verbal learning, decision-making speed, and psychomotor speed in those who suffer from allergies. The end result is either frequent absenteeism from work or substantial decreases in productivity at work.[7] A nationwide study using the SF-36 and RQLQ questionnaires revealed rhinitis patients are tormented by repeated nose blowing, have a disrupted sleep pattern, are fatigued, and have a reduced ability to concentrate.[8] Taking drugs (prescription or over-the-counter) that further decrease the quality of life already imposed by allergic rhinitis should be avoided. Fortunately, there are certain nutrients and botanical medicines that can provide primary therapy or be used in combination with conventional methods.

Figure 2: *Urtica dioca (*Stinging Nettle)

Botanical and Nutritional Therapies for Allergic Rhinitis

Urtica Dioica (Stinging Nettle)

Histamine, serotonin (5-hydroxytryptamine), and acetylcholine are concentrated in the fresh stinging hairs on the leaves of nettle species.[9,10] Urtica also contains glucoquinones and chlorophyll. While there is no known botanical substance whose mechanism is inherently the same as that of antihistamines for treating allergic rhinitis, the recent development of biomechanical preservation by freeze-drying allows *Urtica dioica* to work in similar ways to its allopathic antihistamine counterparts.

A randomized, double-blind study using 300 mg freeze-dried *Urtica dioica* in the treatment of allergic rhinitis found 69 patients who completed the study rated it higher than placebo in global assessments: 58 percent rated it effective in relieving their symptoms and 48 percent found it to be equally or more effective than their previous medicine.[11]

Since antihistamines are used in allergic rhinitis to antagonize histamine, acetylcholine, and serotonin, it appears contradictory that a plant containing these mediators is used to treat allergic rhinitis. However, histamine also acts as an autocoid (a local hormone) to modulate the immune response.[12] Subcutaneous and intravenous injections of histamine have been used effectively to treat numerous allergic conditions including headaches, migraine, cluster headache associated with vasomotor rhinitis, penicillin reaction, allergic arthritis, and cold urticaria with associated anaphylaxis.[13] It has been shown that an acute allergic response did not correlate with high plasma values of histamine, but low plasma histamine was linked to a severe reaction during inhalation of the antigen.[14]

A dose of 300 mg/day of freeze-dried *Urtica dioica* is recommended for the treatment of allergic rhinitis.[11] Side effects are rare, typically allergic and gastric in nature, the latter due to ingesting the medication on an empty stomach.

Bromelain

Bromelain, a glycoprotein with one oligosaccharide moiety and one reactive sulfhydryl group for each molecule, is a proteolytic enzyme derived from the stem of the pineapple plant (*Ananas comosus*). The optimal activity of this enzyme is between pH 5.0 and 8.0. Bromelain has been found to be an effective mucolytic agent in respiratory tract diseases.[15] Bromelain's pharmacological activity is via several mechanisms (Table 1).

Tissue damage stimulates the kinin, complement, fibrinolytic, and clotting systems. The role of fibrin in the promotion of the inflammatory response is to form a matrix that sequesters the area of inflammation, resulting in nutritive circulatory repression, inadequate tissue drainage, and subsequent edema. The kinin system cascade concomitantly generates

Table 1: Bromelain: Mechanisms of Action.

- Induction of proteolytic activity at inflammatory sites
- Activation of fibrinolysis activity via the plasminogen-plasmin system
- Depletion of kininogen
- Inhibition of pro-inflammatory prostaglandin biosynthesis and initiation of prostaglandin E1 accumulation (which inhibits the release of polymorphonuclear leukocyte lysosomal enzymes). [16-18]

kinins (e.g., bradykinin and kallidin) which function to increase vascular permeability; this produces edema and pain. Bromelain counteracts the fibrin and kinin pathways by stimulating plasmin production. This results in depolymerization of fibrin, thereby preventing fibrin-clogged venous stasis and localized edema.[16,17]

Plasmin has been shown to block the mobilization of endogenous arachidonic acid by phospholipases, thereby reducing platelet aggregation and possibly other prostaglandin-mediated phenomena.[19] Bromelain has also been shown to reduce plasma kininogen, resulting in inhibition in the production of kinins. The depletion of kininogen and the activation of plasmin are essentially the pharmacological effects thought to reduce the edema and inflammation associated with allergic rhinitis.[17,19]

The therapeutic dose for allergic rhinitis ranges from 400-500 mg three times daily of an 1800-2000 m.c.u. potency bromelain.[19] Some authorities believe that, due to bromelain's documented effect as a digestive enzyme post-pancreatectomy, healing adjunct for gastric ulcers, and prophylactic agent for enterotoxin-induced diarrhea, bromelain should be taken on an empty stomach.[19] However, existing literature does not compare the efficacy of bromelain when administered either with or between meals. Bromelain demonstrates very low toxicity with an LD_{50} greater than 10 g/kg.[19] Allergic reactions may occur in those who are sensitive to pineapple. Nausea, vomiting, diarrhea, menorrhagia, and metrorrhagia are unlikely side effects.

Quercetin

Quercetin is a flavonoid aglycone of rutin and is found in a wide variety of vegetables and herbs. Quercetin inhibits inflammatory processes attributed to activated neutrophils due to membrane stabilization, potent antioxidant effects and inhibition of the enzyme hyaluronidase (which prevents the breakdown of collagen matrix). Membrane stabilization results in prevention of mast cell and basophil degranulation and decreased inflammation by inhibition of neutrophil lysosomal enzyme secretion and leukotriene production.[20,21]

In a Japanese study of mast cells from nasal mucosa of individuals with perennial allergic rhinitis, quercetin significantly inhibited antigen-stimulated histamine release. Quercetin's effect was almost twice that of sodium cromoglycate at the same concentration.[22]

The recommended dosage for allergic rhinitis ranges from 250-600 mg, three times daily, five to ten minutes before meals.[23,24] Quercetin's efficacy may be enhanced when bromelain is taken concomitantly.[17]

N-Acetylcysteine

N-acetylcysteine (NAC) is a natural, sulfur-containing amino acid derivative that detoxifies as well as protects cells and cellular components against oxidative stress. NAC has been documented as an effective mucolytic agent in individuals with chronic bronchitis, cystic fibrosis, asthma, sinusitis, and pneumonia. A dosage of 200 mg twice daily was found to decrease symptoms of chronic bronchitis.[25] NAC helps reduce the viscosity of mucus so it may be more easily expectorated,[26] accomplishing this by converting the disulfide bonds of the mucoproteins into sulfhydryl bonds and cleaving the mucoproteins into smaller molecules.

While specific research on the use of NAC for allergic rhinitis has not been conducted, because of its affinity for mucus membranes, both as an antioxidant and mucolytic, it may have application as part of a treatment protocol for allergic rhinitis. Recommended therapeutic dosages range from 500 mg to 2 gm daily.

Vitamin C

Vitamin C has been found to exert a number of effects on histamine. It appears to prevent the secretion of histamine by white blood cells and increase its detoxification.[27] Histamine levels were found to increase exponentially as ascorbic acid levels in the plasma decreased.[28]

In a study of the effectiveness of intranasal vitamin C, 48 subjects received either ascorbic acid solution (n=27) or placebo (n=21) sprayed into the nose three times daily. After two weeks 74 percent of subjects treated with ascorbate solution were found to have decreased nasal secretions, blockage, and edema. Improvement was seen in only 24 percent of placebo treated patients. The pH of the secretions in the allergic rhinitis sufferers appeared to be more alkaline, over 7.0, with normal nasal secretions tending be in the range of 5.5-7.0. The pH of nasal secretion was found to be within normal ranges after administration of vitamin C; patients with nasal pH's closer to 8.0 seemed to respond more favorably to the vitamin C therapy.[29]

Vitamin C is nontoxic and virtually free of side effects, diarrhea and abdominal distention being the most common. For allergic rhinitis, a dosage of at least 2 grams per day should be administered.[30]

Summary

Evaluation of current therapeutic strategies for the management of allergic rhinitis revealed that only 26 percent of the reported population suffering from allergic rhinitis believed their symptoms were "well-controlled" or "completely controlled;" while 52 percent believed effective treatments were available.[31] Health-care practitioners can utilize a combination of botanical medicines and nutrients based on the diagnostic impression developed via physical examination, patient history, and other diagnostic measures. *Urtica dioica*, bromelain, quercetin, and vitamin C have relatively well-documented individual outcomes on their efficacy in treating allergic conditions; NAC has some well-documented benefit for various respiratory disorders. The combination of all of them as part of a therapeutic treatment plan has yet to be validated. Other supplements that may be useful for the treatment of allergic rhinitis, but not reviewed in this paper, include chamomile, elder flower, eyebright, garlic, goldenrod, feverfew, yarrow, vitamins A, B, and E, selenium, royal jelly, ephedra, hydrangea root, *Ligusticum porteri*, and olive leaf.

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