Intranasal Corticosteroids in Management of allergic Rhinosinusitis

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ABSTRACT
BACKGROUND: Allergic rhinosinusitis is a significant health problem and impairs patient’s quality of life. It is hypersensitivity reaction to inhaled allergens. Accepted first line therapy for allergic rhinitis is intranasal corticosteroids. They are efficacious in treating seasonal and perennial allergic rhinitis both. They relieve nasal congestion, itching, rhinorrhea and sneezing that occurs in the early and late phases of allergic response with almost complete prevention of late-phase symptoms. Adverse effects include dryness, burning, stinging in nasal mucosa, sneezing, headache, and rarely epistaxis. Several intranasal corticosteroids are available; differences among them are limited to potency, patient preference, dosing regimens and delivery device.

Key words: Allergic Rhinitis, Fluticasone propionate, Fluticasone furoate, intranasal corticosteroids, Mometasone furoate.

INTRODUCTION
Allergic rhinosinusitis impairs patient’s quality of life and is a significant health problem leading to economic burdens. Allergic rhinitis is a risk factor for development of asthma and can cause serious complications to eustachian tubes, nose, and sinuses. The term ‘rhinosinusitis’ is preferred than ‘rhinitis’ alone because nasal and sinus mucosa are similar and are contiguous, so rhinitis without sinusitis is rare entity. Intranasal corticosteroids play significant role in improving health-related quality of life through their ability to control symptoms. Intranasal corticosteroids have proved to be safe and effective for treatment of allergic rhinosinusitis and are now accepted as first-line therapy. Commonly used intranasal corticosteroids are mometasone furoate, fluticasone propionate, fluticasone furoate beclomethasone dipropionate, budesonide and flunisolide.

Allergic rhinitis is a hypersensitivity reaction to inhaled allergens. It produces inflammation of the nasal mucosa resulting in rhinorrhea, sneezing, nasal congestion, and itching. Immediate symptoms of itching and sneezing occur within minutes of exposure to an allergen, followed by increase in rhinorrhea and nasal congestion at about 30 minutes, which seem to resolve within 1-2 hours. Some patients experience a late-phase response within 4-24 hours after exposure. It is characterized by nasal hyper responsiveness to subsequent exposures to the allergen or irritants such as tobacco smoke, fumes, or aerosols.

In allergic rhinitis primary mediator of inflammatory response is Immunoglobulin E (IgE). Early-phase response is caused by mediators and cytokines like leukotrienes, prostaglandins, bradykinins and platelet-activating factor. These mediators cause vasodilation, increased vascular permeability, stimulation of mucus secretion, and stimulation of afferent nerves. They result in nasal congestion, rhinorrhea, and itching and sneezing. After several hours of allergen challenge, late phase response occurs which is characterized by T lymphocyte activation, production of TH2-type cytokines, and tissue eosinophilia.

The primary nonpharmacologic treatment for allergic rhinitis is avoidance of the offending agent. Pharmacotherapy includes agents such as systemic and topical antihistamines and decongestants, mast cell stabilizers and intranasal corticosteroids.

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Monoclonal antibodies are being studied as therapy for patients who do not adequately respond to other treatment options. 

**DISCUSSION**

Intranasal corticosteroids are highly effective in preventing and relieving nasal symptoms associated with both early and late-phase allergic responses. Onset of action occurs within a few days, a full response to the drugs may take up to several weeks.

**Mechanism of action:** [Fig i]

Corticosteroids have specific effects on mediators and on the inflammatory cells involved in the allergic process. Affected mediators include prostaglandins, leukotrienes, and mast cells. The drugs also act by inhibiting T lymphocytes, particularly TH2 cells, and responses such as cytokine production and eosinophil recruitment.

After administration either topically or systemically, the unbound steroid molecule enters the cytoplasm of corticosteroid-responsive tissues by passively diffusing across the cell membrane. In the cytoplasm, it binds to a glucocorticoid receptor forming a complex that undergoes a conformational change. In addition, corticosteroids stabilize lysosomal membranes, block the effect of migratory inhibitory factor, decrease permeability, and inhibit pro-inflammatory cytokine production, including that of interleukin (IL)-1, IL-2, the IL-2 receptor, interferon (IFN)-α, tumor necrosis factor (TNF), and various colony-stimulating factors (CSFs) such as IL-3. Even in very low concentrations, corticosteroids can inhibit the synthesis of a variety of pro-inflammatory enzymes, including the macrophage products, collagenase, elastase, and plasminogen activator.

Use of topical corticosteroids in rhinitis results in adequate drug concentration at receptor sites in the nasal mucosa leading to symptom control and reduced risk of systemic adverse effects.

Differences in efficacy, side effects, and clinical attributes must be considered for choosing from the available intranasal corticosteroids. 

**Efficacy of intranasal corticosteroids:**

Topical potency of corticosteroids can be determined by degree of vasoconstriction activity. In regard to topical potency, fluticasone propionate and mometasone furoate, are more potent than other intranasal corticosteroids. Topical potency does not directly correlate with anti-inflammatory potency but does explain part of the clinical efficacy of the drugs in allergic rhinitis.
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binding affinity is another measure of potency of corticosteroids. In a study, fluticasone had higher affinity than the active metabolite of beclomethasone, dexamethasone, and budesonide. Lipid solubility of intranasal corticosteroids, from lowest to highest is flunisolide, triamcinolone acetonide, budesonide, beclomethasone dipropionate, fluticasone propionate, and mometasone furoate. Highly lipophilic agents have a greater degree and faster rate of absorption into the nasal mucosa than less lipophilic drugs and therefore enhanced ability to reach the glucocorticoid receptor due to longer retention time in nasal tissue. Lipophilicity characteristics and systemic bioavailability can be influenced by the performance of the inhaler device. Studies are in progress to determine whether there is any significant difference in clinical outcome or adverse reactions depending on delivery devices and formulations.

**Toxicity of intranasal corticosteroids:**

Systemic absorption of inhaled drugs can occur by direct absorption from lungs or by absorption from gastrointestinal tract after swallowing. Adverse effect usually occurs at higher dose. The common side effects are oropharyngeal candidiasis, dysphonia or hoarseness of voice due to direct effect on vocal cords, osteoporosis and cataract. Systemic side effects depend on systemic absorption which occurs by two routes: Fraction of drug absorbed through the nasal mucosa, and fraction of the dose that is swallowed and absorbed through the gastrointestinal tract. Mometasone furoate and fluticasone propionate have very low systemic bioavailability, 0.1% and less than 2%, respectively, and are believed to be poorly absorbed into systemic circulation due to high lipophilicity. Other inhaled corticosteroids have oral bioavailabilities ranging between 20% and 50%, with the exceptions of triamcinolone acetonide and beclomethasone whose bioavailability is not provided in product labeling. Systemic activity of topical nasal steroids can be determined by measuring hypothalamic-pituitary-adrenal (HPA) axis function. These analyses can be divided into tests to evaluate basal versus dynamic function, and have been used as biologic markers for systemic activity. Studies suggest that the drugs have little or no effect on the HPA axis when administered at recommended dosages. A small, but statistically significant reduction in growth velocity was reported in a 12-month study of young children (aged 6-9 yrs) treated for perennial allergic rhinitis with beclomethasone dipropionate 336 µg/day. The treated group had slower growth rates of 0.013 cm/day or 5 cm/year compared with a group receiving placebo, 0.017 cm/day or 5.9 cm/year. Local side effects includes nasal irritation, dryness, burning and stinging; sneezing, headache and epistaxis.

**Delivery device:** Intranasal steroids were initially delivered by Freon-propelled aerosols, which was not very effective. Metered-dose pump sprays were used to deliver fluticasone propionate solubilized in polyethylene glycol and propylene glycol, although this approach caused nasal stinging. Aqueous pump sprays and pure powder formulations are now the more commonly used methods of delivery.

**A review of important intranasal corticosteroids**

**Mometasone Furoate:** Mometasone furoate is a synthetic corticosteroid that has substantially higher topical potency and lipid solubility and lower systemic bioavailability. It is available in an aqueous suspension and administered by metered-dose manual pump spray delivering 50 µg for the treatment of seasonal and perennial allergic rhinitis. It is approved for adults and for children aged 3 years and older.

**Fluticasone Propionate:** It is highly potent intranasal steroid with long duration of action. It has negligible oral bioavailability and hence less systemic side effects. However there may be systemic side effects because of high absorption from lungs. In several trials the drug was highly effective in treating seasonal allergic rhinitis.
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by improving sneezing, nasal itching, nasal blockage, and rhinorrhea. It also increased the number of symptom-free days and reduced the need for rescue drugs, such as antihistamines, compared with placebo. Each 100 mg of spray contains 50 µg of the active agent and is approved for use in adults and children aged 4 years and older. The efficacy of fluticasone 100 µg twice/day, fluticasone 200 µg once/day, and placebo was assessed in patients with seasonal allergic rhinitis. Both dosages of fluticasone increased the number of symptom-free days and improved nasal symptom severity scores significantly more than placebo.

Fluticasone Furoate:
It is a new, topical, intranasal, enhanced-affinity trifluorinated glucocorticoid, with potent anti-inflammatory activity and low systemic exposure. Drug comes in a nasal spray, as an aqueous suspension of micronized fluticasone furoate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Each actuation delivers 27.5 µg of FF in a volume.

Budesonide:
Budesonide is indicated for treatment of seasonal and perennial allergic rhinitis in adults and children aged 6 years and older. It has high topical systemic ratio. It is available in an aerosol metered-dose canister that delivers 32 µg of micronized budesonide, and an aqueous formulation in a metered-dose nonaerosol pump spray that delivers 64 µg/spray.

Flunisolide:
Flunisolide is an intranasal corticosteroid, approved for treating seasonal and perennial allergic rhinitis in adults and children aged 6 years and older. It is available in an aqueous solution and administered by metered-dose manual pump spray that delivers 25 µg. The two formulations of flunisolide, Nasalide and Nasarel, are not bioequivalent. The frequency and nature of adverse events also differ. Nasalide was associated with more reports of nasal burning and stinging, and Nasarel with more problems related to taste.

Beclomethasone: Beclomethasone comes in two formulations, an aerosol and a spray, and is approved for use in adults and children aged 6 years and older. Each activation of the aerosol systems (Vancenase) and the manual pump aqueous spray (Beconase AQ) delivers 42 µg of drug. Vancenase AQ 84 µg (double-strength) delivers 84 µg of drug suspension by manual metered-spray pump.

CONCLUSION
Allergic rhinitis is a significant health problem and requires proper management to improve patient quality of life. Intranasal corticosteroids are first-line therapy for treatment of seasonal and prophylaxis of perennial allergic rhinitis. They are effective in treating both early- and late-phase responses. They reduce all nasal symptoms, suppress the inflammatory process of the late-phase allergic response, and improve patient’s quality of life. Adverse effects are usually local-nasal irritation, dryness, burning, stinging, sneezing, headache and epistaxis with rare systemic side effects like reduction in growth velocity of children’s. Intranasal corticosteroids differ by potency, patient preference, dosing regimens, delivery device and vehicle, though all are safe and effective. Mometasone furoate and fluticasone propionate are preferred intranasal corticosteroids because of their specific characteristics. Both are more topically potent than the other agents. Systemic adverse effects of these two drugs are minimal because of low systemic bioavailability.

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