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Intranasal steroids for children with allergic rhinitis

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Intranasal steroids have traditionally been reserved for patients with severe allergic symptoms not controlled by antihistamines alone. Recently, the use of these agents as a first-line therapy has become more common, especially after the release of newer formulations requiring only once or twice daily dosing. In a recent consensus paper, the American College of Allergy, Asthma, and Immunology listed intranasal steroids as the most effective therapy in controlling the symptoms of allergic rhinitis.[1] There are currently six corticosteroids available in an intranasal dosage form: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetate.[2-6]

Mechanisms of action

Intranasal steroids work through a variety of mechanisms. It is believed that the benefits of these agents are largely due to the inhibition of proinflammatory secretions, such as interleukins, tumor necrosis factor-alpha, histamine, tryptase, and leukotrienes, as well as a reduction in the numbers or apoptosis of inflammatory cells in the nasal epithelium. The final result of these actions is a reduction in T lymphocytes, eosinophils, basophils, monocytes, and mast cells within the upper airway, producing a decrease in nasal congestion, rhinorrhea, sneezing, and itching.[2-5]

Potency

The potency of some of the commonly used glucocorticoids has been assessed using dexamethasone as a standard (Table 1).[2] Potency represents the relative binding affinity of the drug for glucocorticoid receptors, as determined by the reciprocal of the relative amount of drug needed to replace 50% of bound dexamethasone (the positive control).

Table 1. Binding Affinity

Product	Relative Affinity
Mometasone	1235
Fluticasone	813
Budesonide	258
Triamcinolone	164
Dexamethasone	100

The relative anti-inflammatory activity of these agents has also been assessed by the degree of cytokine inhibition. *In vitro* studies of histamine release show fluticasone > mometasone > budesonide > beclomethasone = triamcinolone. Mometasone and fluticasone have also shown the greatest inhibition of interleukins (IL-4 and IL-5) in T cell samples taken from healthy donors. Budesonide, beclomethasone, and triamcinolone also inhibit IL-4 and IL-5, but require higher concentrations of drug to do so.[2-5]

Lipophilicity

Efficacy of the intranasal steroids is also dependent on the degree of lipophilicity. The more highly lipophilic the agent, the higher and faster the rate of uptake by the nasal mucosa. This results in an increased penetration of glucocorticoid receptors and a prolonged effect. The intranasal steroids can be ranked from highest degree of lipophilicity to lowest as follows: mometasone > fluticasone > beclomethasone > budesonide > triamcinolone > flunisolide.[5]

Onset of effect and time to maximum effect

Most intranasal steroid products work within the first several days of use, with some producing

symptomatic relief in as few as 12 hours after the first dose (Table 2).[2] There is typically a 3 to 7 day period before full benefit is seen.

Table 2. Onset of effect

Product	Onset
Beclomethasone	within 3 days
Budesonide	24 hrs
Flunisolide	4-7 days
Fluticasone	12 hrs-3 days
Mometasone	12 hrs-3 days
Triamcinolone	24 hrs

Systemic absorption

The use of the intranasal route for drug administration significantly lessens the risk for systemic adverse effects. There are differences among the group, however, that may influence selection of a specific product (Table 3).[2] Fluticasone and mometasone have negligible systemic bioavailability and may be preferable in children requiring chronic therapy.

Table 3. Systemic availability

Product	% bioavailability
Mometasone	< 0.1
Fluticasone	< 2
Budesonide	11
Beclomethasone	17
Triamcinolone	22
Flunisolide	20-50

Clinical efficacy

All of the currently available intranasal steroids have been found to be effective in controlling the symptoms of allergic rhinitis. In addition to demonstrating superiority to placebo, there are numerous studies comparing agents within the class and comparing intranasal steroids to antihistamines.[7-14] In two recent meta-analyses, intranasal steroids were found to be equal to or better than oral antihistamines in reducing symptoms of congestion, rhinorrhea, sneezing, and ocular itching.[15,16] Despite their differences in potency, pharmacokinetics, and pharmacodynamics, studies comparing intranasal steroids have failed to demonstrate any clinically significant differences among the intranasal steroids currently in use.[5,7-14]

Adverse effects

Intranasal steroids are generally well tolerated. The most frequently reported adverse effects include: irritation of the nose, nasal stuffiness, dry nose and mouth, minor nasal bleeding, sneezing, throat discomfort, nausea, headache, and dizziness. These reactions are more frequent with the older agents, but several of those products have been reformulated as aqueous (AQ) preparations to reduce adverse effects.[2-6] Although rare, children receiving long-term therapy should also be monitored for irritation of the nasal septum, which could lead to ulceration or perforation. Localized infections of the nose and pharynx with *Candida albicans* can occur, but are infrequent. Hypersensitivity reactions, with facial edema, rash, pruritis, and anaphylaxis or anaphylactoid reactions have occurred with these agents, but appear to be rare.[6]

Because of the limited systemic availability with the newer agents, the risk of adrenal suppression is minimal. Excessive doses of the older agents, such as beclomethasone, administered over a prolonged period could potentially lead to suppression of hypothalamic-pituitary-adrenal (HPA) axis function or signs of hypercorticism, including cushingoid features, arthralgia, and myalgia. It has been suggested that mometasone or fluticasone may be preferred in children requiring chronic therapy. Both have been shown to have minimal effect on the HPA axis in children during clinical trials, even at high doses or after prolonged periods of regular use.[9,17,18]

Effect on growth

One of the greatest concerns for most families is the effect of long-term steroid use on growth. In 1998, the Food and Drug Administration mandated that all inhaled and intranasal steroid products carry a warning regarding the risk of growth suppression. This warning was based, in part, on data from a year-long trial of intranasal beclomethasone.[19] In this study, 100 children between the ages of 6 and 9 years were given beclomethasone (168 mcg twice daily) or a placebo. Ninety children completed the study. The children receiving beclomethasone had grown an average of 5 cm, while the placebo group had grown an average of 5.9 cm ($p<0.01$).

The newer intranasal steroids are still being evaluated. A recent study comparing once daily mometasone or budesonide to placebo in 22 children (7-12 years old) for two weeks found no differences in lower leg growth rate.[20] A longer study of mometasone has produced similar results. In 2000, Schenkel and colleagues[17] evaluated 98 children between the ages of 3 and 9 years. The children were randomized to receive either mometasone, 100 mcg once daily, or placebo. Eighty-two subjects competed the study. After a year, there was no evidence of growth suppression, and mean standing heights were similar in the two groups.

While these recent studies are encouraging, it is important to remember the lack of long-term studies documenting safety. Until those data are available, it appears prudent to select those agents with minimal systemic availability to reduce the risk of growth impairment and assess growth at regular intervals during treatment.[21]

Dosing

Dosing should be initiated as listed below and titrated to patient response.[6] In many patients, dose escalation is necessary until symptoms are relieved, after which the dose or frequency can be reduced to minimize adverse effects.

Beclomethasone (Beconase® or Beconase AQ®)
Children 6-12 years: 1 spray (42 mcg) in each nostril twice daily
Adults: 1-2 sprays in each nostril twice daily
Budesonide (Rhinocort® or Rhinocort Aqua®)
Adults and children ≥ 6 years: 2 sprays of Rhinocort® in each nostril twice daily or 4 sprays in each nostril once daily; or 1 spray of Rhinocort Aqua® in each nostril once daily
Flunisolide (Nasalide® or Nasarel®)
Children 6-14 years: 1 spray (25 mcg) in each nostril three times daily
Adults: 1 spray in each nostril three times daily or 2 sprays in each nostril twice daily
Fluticasone (Flonase®)
Children 4-12 years: 1 spray (50 mcg) in each nostril once daily
Adults: 2 sprays in each nostril once daily
Mometasone (Nasonex®)
Children 3-12 years: 1 spray (50 mcg) in each nostril once daily
Adults: 2 sprays in each nostril once daily
Triamcinolone (Nasacort® or Nasacort AQ®)
Children 6-12 years: 1 spray (55 mcg) in each nostril once daily
Adults: 2 sprays in each nostril once daily

Cost

The intranasal steroid sprays are roughly equivalent in cost (Table 4).

Table 4. Costs for steroid nasal sprays[a]

Product	AWP ($)
Beclomethasone (Beconase)[b]	46.14
(Beconase AQ)[b]	47.32
Budesonide (Rhinocort)[b]	39.50
(Rhinocort Aqua)[c]	49.92
Flunisolide (Nasalide)[b]	45.59
(Nasarel)[b]	43.51
Fluticasone (Flonase)[d]	56.03
Mometasone (Nasonex)[d]	55.85
Triamcinolone (Nasacort)[e]	45.82
(Nasacort AQ)[d]	44.46

[a]average wholesale price(Drug Topics Red Book 2001)
[b] 200 doses [c] 60 doses [d] 120 doses [e] 100 doses

Summary

Intranasal steroids are useful alternatives or adjuncts to antihistamines in children with allergic rhinitis. These products can provide a significant reduction or elimination of allergic symptoms with few systemic adverse effects.

References

1. Dykewicz MS, Fineman S, eds. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81:478-518.
2. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. J Allergy Clin Immunol 1999;104:S150-8.
3. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Safety 2000;23:11-33.
4. Stempel DA. Intranasal corticosteroids for first-line treatment of allergic rhinitis: what's the evidence? Formulary 2001;36:276-93.
5. Corren J. Intranasal corticosteroids for allergic rhinitis: how do different agents compare? J Allergy Clin Immunol 1999;104:S144-9.
6. Olin BR. Drug Facts and Comparisons. St. Louis: Facts and Comparisons, Inc. 2001:673-5.
7. Meltzer EO. Clinical and antiinflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 1998;81:128-34.
8. Brannan MD, Herron JM, Affrime MB. Safety and tolerability of once-daily mometasone furoate aqueous nasal spray in children. Clin Therapeut 1997;19:1330-9.
9. Meltzer EO, Berger WE, Berkowitz RB, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. J Allergy Clin Immunol 1999;104:107-14.
10. Ngamphaiboon J, Thepchatri A, Chatchatee P, et al. Fluticasone propionate aqueous nasal spray treatment for perennial allergic rhinitis in children. Ann Allergy Asthma Immunol 1997;78:479-84.
11. Fluticasone Propionate Collaborative Pediatric Working Group. Treatment of seasonal allergic rhinitis with once-daily intranasal fluticasone propionate therapy in children. J Pediatr 1994;125:628-34.
12. Small P, Houle P, Day JH, et al. A comparison of triamcinolone acetonide nasal aqueous spray and fluticasone propionate aqueous solution spray in the treatment of spring allergic rhinitis. J Allergy Clin Immunol 1997;100:592-5.
13. Mandl M, Nolop K, Lutsky BN, et al. Comparison of once daily mometasone furoate and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. Ann Allergy Asthma Immunol 1997;79:237-45.
14. Foresi A. A comparison of the clinical efficacy and safety of intranasal fluticasone propionate and antihistamines in the treatment of rhinitis. Allergy 2000;62:12-4.
15. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H_1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998;317:1624-9.
16. Stempel DA, Thomas M. Treatment of allergic rhinitis: an evidence-based evaluation of nasal corticosteroids versus nonsedating antihistamines. Am J Manag Care 1998;4:89-96.
17. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis

after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics 2000;105:e22.
18. Affrime MB, Kosoglou T, Thonoor CM, et al. Mometasone furoate has minimal effects on the hypothalamic-pituitary-adrenal axis when delivered at high doses. Chest 2000;118:1538-46.
19. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics 2000;105:e23.
20. Agertoft L, Pedersen S. Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone and budesonide. J Allergy Clin Immunol 1999;104:948-52.
21. Allen DB. Systemic effects of intranasal steroids: an endocrinologist's perspective. J Allergy Clin Immunol 2000;106:S179-90.

Pharmacology Literature Review

Antiepileptic hypersensitivity syndrome

This retrospective review describes 14 children from a single institution with antiepileptic hypersensitivity reactions. Eight of the patients had received phenytoin, six were taking carbamazepine, and the remaining children were taking phenobarbital, alone or in combination with other agents. The average time from initiation of therapy to symptoms was 23.0±14.8 days. All patients had rash and fever, with 71.4% exhibiting an elevated white cell count and over half having an elevated sedimentation rate, elevated aminotransferases, and lymphadenopathy. Bessmertny O, Hatton RC, Gonzalez-Peralta RP. Antiepileptic hypersensitivity syndrome in children. **Ann Pharmacother 2001;35:533-8.**

Compatibility of spacers and MDIs

This brief technical report focuses on the utility of spacer devices for improving the function of metered-dose inhalers (MDIs). Spacer-MDI combinations that fail to provide a good fit or are difficult to use, as well as reviews of spacer size, special features, cost, and cleaning instructions are included in tables. Lakamp RE, Berry TM, Prosser TR, et al. Compatibility of spacers with metered-dose inhalers. **Am J Health-Syst Pharm 2001;58:585-91.**

Naratriptan pharmacokinetics

In this study, the authors evaluated the pharmacokinetic profile of naratriptan in 8 patients between 12 and 16 years of age. Serial blood samples were obtained after a single 2.5 mg oral naratriptan dose. Median time to peak serum concentration was 4 hours, with a range of 1.5-4 hours. Average maximum concentration was 8.0 ng/ml, elimination half-life was 4.9 hrs, and apparent clearance was 558.8 ml/min. Blood pressure, pulse, and electrocardiogram parameters did not change significantly from baseline. From these data, the authors concluded that naratriptan pharmacokinetics in adolescents were similar to values in adults and that no dosing change was necessary. Christensen ML, Eades SK, Fuseau E, et al. Pharmacokinetics of naratriptan in adolescent subjects with a history of migraine. **J Clin Pharmacol 2001;41:170-5.**

Phenytoin in children with traumatic brain injury

The authors of this study evaluated the metabolism of phenytoin in 10 children after head injury. The patients received a 15-20 mg/kg phenytoin loading dose followed by 7 mg/kg/day. The unbound fraction of phenytoin increased over the 9 day study period from 0.14±0.04 to 0.17±0.04 ($p<0.05$). A time variant model provided a superior fit of the data in most patients, revealing a low baseline Vmax of 2.82±2.35 mg/kg/day rising to an induced Vmax of 20.79±13.71 mg/kg/day, approximately twice that of most noninjured children, suggesting a more rapid removal of drug. Stowe CD, Lee KR, Storgion SA, et al. Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. **J Clin Pharmacol 2001;40:1452-61.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/27/01:

1. Esomeprazole (Nexium®), the s-isomer of omeprazole, was added to the Formulary for the treatment of gastrointestinal reflux, erosive esophagitis, and duodenal ulcers. Omeprazole (Prilosec®) was removed from the Formulary. Pediatric studies have not been conducted with esomeprazole, but dosing of esomeprazole in adults is the same as for omeprazole.
2. Indocyanine green (IC Green®) was added to the Formulary for ophthalmic angiography.
3. Caspofungin (Cancidas®), a echinocandin antifungal, was added for the treatment of invasive aspergillosis in patients refractory or intolerant of other therapies.
4. Liposomal amphotericin B (Ambisome®) was also added to the Formulary. Amphotericin B lipid complex (Abelcet®) was removed.
5. The restrictions for eptifibatide (Integrilin®) were amended to include use as an adjunct to angioplasty with or without stenting.

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