

Corticosteroids in the treatment of pediatric allergic rhinitis

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The goal of treatment in pediatric allergic rhinitis is to provide effective prevention of or relief from allergic rhinitis symptoms as safely and effectively as possible. Removing or avoiding allergens is always advised; however, pharmacotherapy is often necessary. Pharmacologic options include systemic decongestants, which are associated with irritability and insomnia, particularly in children. Antihistamines are widely used; however, first-generation antihistamines are known to cause dry mouth and sedation. Oral corticosteroids are very effective but can have unwanted systemic effects. Over the past decade, intranasal corticosteroids have been shown to be the most effective form of pharmacologic treatment for allergic rhinitis. Data support the use of intranasal corticosteroids as first-line therapy over oral antihistamines; nonetheless, some clinicians have been reluctant to prescribe these agents, particularly for children, because of concerns for systemic effects. Overall, the newer corticosteroids, including mometasone furoate (MF), beclomethasone dipropionate, and budesonide have an improved risk-benefit ratio compared with older corticosteroids and are now considered the drug of choice for pediatric allergic rhinitis. A good deal of evidence exists that confirms the lack of systemic effects from intranasal corticosteroids. However, reports of decreased bone growth in children receiving intranasal budesonide short-term and beclomethasone dipropionate long-term have heightened concerns that some of these drugs may have systemic effects. A new intranasal corticosteroid, MF nasal spray, has been studied in children 3 to 12 years of age and has been shown to be effective. Intranasal MF is available with once-daily dosing, which has the potential to decrease systemic side effects. (*J Allergy Clin Immunol* 2001;108:S59-64.)

Key words: Allergic rhinitis, corticosteroids, intranasal corticosteroids, hypothalamic pituitary adrenal axis

Allergic rhinitis (AR) is a common childhood disease whose prevalence is increasing.¹ The symptoms of AR can have profound effects on the quality of life^{2,3}; furthermore, the presence of comorbid conditions such as asthma, sinusitis, and otitis media with effusion can complicate both the clinical presentation and the treatment of AR. Thus AR should be considered an important condition for which appropriate treatment is necessary to

Abbreviations used

AR: Allergic rhinitis
BUD: Budesonide
BDP: Beclomethasone dipropionate
FLU: Flunisolide
FP: Fluticasone propionate
HPA: Hypothalamic pituitary adrenal
INCS: Intranasal corticosteroid
MF: Mometasone furoate
TAA: Triamcinolone acetonide

improve quality of life in a cost-effective manner. Because AR is a chronic condition, often requiring long-term treatment, attention must be paid to issues such as safety, compliance, and cost.

One group of agents, the intranasal corticosteroids (INCS), offers significant advantages to the patient with AR. They are superior to both antihistamines and cromones and provide topical drug delivery that targets the actions of the drug molecules to the nasal mucosa to minimize the potential for systemic side effects. Whereas the older corticosteroid (CS) molecules, such as dexamethasone and betamethasone, exert systemic effects when administered intranasally, the risk of systemic effects is much lower with the newer molecules such as beclomethasone dipropionate (BDP), triamcinolone acetonide (TAA), flunisolide (FLU), budesonide (BUD), fluticasone propionate (FP), and mometasone furoate (MF). Still, some clinicians remain reluctant to prescribe INCS because of their concern for systemic effects, including suppression of growth, of bone metabolism, and of the hypothalamic-pituitary-adrenal (HPA) axis (Table I). These concerns are further heightened in the treatment of pediatric AR, where the benefits of appropriate therapy must be weighed against the risks of what is likely to be long-term INCS administration. These safety issues may be compounded by the presence of concomitant allergic or respiratory disorders, particularly asthma, in which corticosteroids are also the most effective therapeutic agents.

The goal of the clinician in selecting the most appropriate treatment regimen for pediatric allergic rhinitis is to balance the potential risks of treatment with the benefits to the patient. This article examines the issue of steroid exposure and discusses strategies for minimizing it in pediatric patients who require corticosteroid therapy.

AN APPROACH TO STEROID-SPARING

The goal of therapy in pediatric AR is to provide effective prevention or relief of symptoms in as safe and cost

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TABLE I. Major systemic effects of corticosteroids

• Suppression of the HPA axis	• Glaucoma, cataracts
• Growth retardation in children and adolescents	• Diminished immune response
• Osteoporosis	• Impaired wound healing
• Aseptic necrosis of bone	• Diabetes mellitus
• Hypertension	• Mental disturbance
• Centripetal obesity	• Proximal myopathy
• Peptic ulceration	

effective a manner as possible. A rational approach to this goal is to make appropriate use of the available treatment modalities, which are summarized in Table II and described below.

Allergen/irritant avoidance

An effective initial measure for treatment of AR is to identify the causes of the patients' allergies and to remove or avoid as many as possible.⁴ This makes sense because allergy itself is an inflammatory disorder in which repeated exposure to allergens and airway irritants results in increased sensitivity to these agents through recruitment of inflammatory cells to the reaction site. Thus avoidance of exposure after the initial sensitization is the best way to prevent the symptoms of atopic disease. Allergen avoidance is effective against all clinical manifestations of atopic disease (ie, asthma,⁵ eczema,⁶ and rhinitis^{7,8}), providing that the offending agents can be controlled or avoided.

House dust and mite control methods continue to improve. Allergen-proof bedding covers have been shown to decrease AR symptoms by about 40%, though frequent housecleaning, use of water that is adequately hot in the laundry, and vacuum cleaners with special filters (eg, HEPA) are necessary to keep dust mites in check. Likewise, thorough and frequent housecleaning helps remove cockroach antigens and animal dander. Avoidance of pets, cigarette smoke, fresh paint, perfumes, fog, smog and—during hay fever season—pollen, can also prevent the development of AR. Additional possible measures include control of humidity in the home through mechanical ventilation and heat exchanges and the use of high-temperature steam to destroy allergens. Although all of these measures can effectively control allergies and reduce the need for drug treatment, they require lifestyle changes and behaviors that patients and/or their families may find too difficult and too costly to follow. As such, they can be considered a valuable adjunct, but not a practical replacement, for a carefully chosen drug therapy.

Pharmacotherapy

The major therapeutic effects of drugs available for the treatment of pediatric allergic rhinitis are shown in Table III.^{9,10}

Decongestants are frequently prescribed for AR, although they only affect nasal blockage. Systemic decongestants are associated with side effects such as irritability and insomnia. Topical decongestants are most

TABLE II. Treatment options for pediatric allergic rhinitis

Allergen avoidance
Pharmacotherapy
Antihistamines
Decongestants
Cromones
Corticosteroids
Allergen immunotherapy

appropriate for occasional, short-term use because they have been associated with tachyphylaxis, rebound nasal congestion, and rhinitis medicamentosa. However, used for a few days, they can reduce the pain of acute otitis media or sinusitis and they may also be effective in aiding eustachian tube function during the pressure changes associated with flying.

Antihistamines are widely used for AR treatment and are effective in relieving sneezing, rhinorrhea, and itching. They have little effect on nasal congestion and are most effective when ocular symptoms are prominent. First-generation antihistamines cause side effects such as sedation and dry mouth. Their use is also associated with decreased academic performance³; therefore they are not recommended for routine, long-term use in children.

Second-generation antihistamines, on the other hand, are largely nonsedating and are available for use in children from 2 years of age and upward. Topical antihistamines have been developed and are available for use in children from 6 to 12 years of age and older. These agents have the advantage of rapid onset of action (15 to 30 minutes) as opposed to the hour it takes for some oral antihistamines to begin to take effect. The topical antihistamines are less effective, however, than oral antihistamines against nonnasal symptoms such as conjunctivitis and palatal itch.¹⁰ Some antihistamines have been demonstrated *in vitro* to have anti-inflammatory properties.¹¹ These are beginning to be demonstrated *in vivo* but are much weaker than those of topical corticosteroids.

The cromones are less effective anti-inflammatory drugs than INCS but may be useful in children, the elderly, and in people such as singers, who cannot afford to develop dysphonia. Sodium cromoglycate is available in topical form for use in the nose, eyes, and bronchi. It is highly ionized and therefore poorly absorbed and rapidly removed from the site of action. Regular use on a frequent basis is essential and this makes compliance difficult. It tends to be most effective in young people with a short history of allergic disease. A recent study has compared its activity with that of levocabastine, a topical antihistamine, with unfavorable results.¹²

Over the past decade, topical or INCS have been shown to be the most effective form of pharmacologic treatment for AR. They are effective against the entire spectrum of AR symptoms and are second only to oral corticosteroids with regard to their therapeutic effects. The major difference between topical and oral corticosteroids is the far lower risk of systemic adverse effects associated with topical administration.

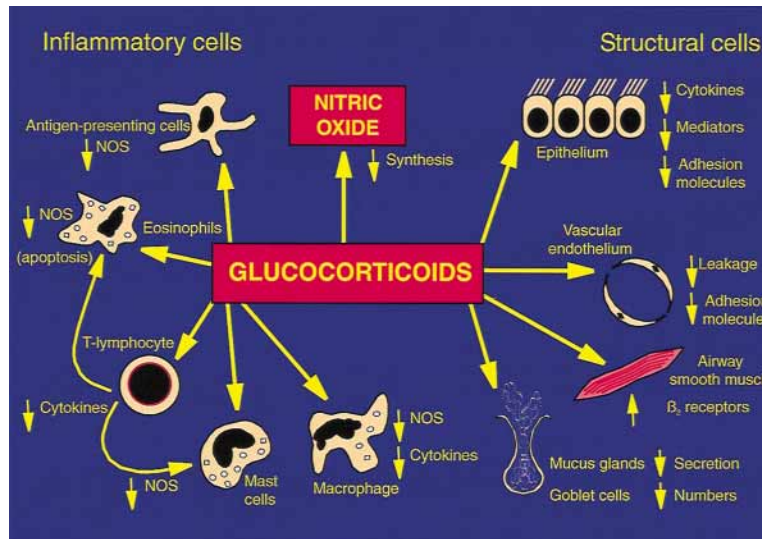


FIG 1. Effects of topical corticosteroids on nasal mucosa. Topical corticosteroids act at multiple sites; their major actions are on antigen presenting cells, T-cells, and eosinophils, but they also reduce mast cell numbers in epithelium. In addition, vascular permeability and mucus production are decreased.

TABLE III. Drugs available for pediatric allergic rhinitis

Drug	Effect on symptoms			
	Itch and sneeze	Nasal discharge	Nasal blockage	Smell
Topical decongestants	—	—	+++	+
Oral/topical antihistamines	++	++	+	—
Cromones	+	+	±	—
Topical corticosteroids	+++	+++	++	±
Oral corticosteroids	+++	+++	+++	++

A recent systematic review—together with data on safety and cost effectiveness—supports the use of INCS over oral antihistamines as first-line treatment for AR.¹³ In small children, there was a significantly greater benefit from a topical corticosteroid than from the antihistamine ketotifen, which has a cromoglycate-like action.¹⁴ This is probably because the INCS have a multiplicity of actions against inflammatory cells, which are involved in the allergic response, and also against some of the structural cells of the nasal mucosa (Fig 1).¹⁵

Some prescribers are still reluctant to use topical corticosteroids because of the concerns about side effects. This is based partly on the highly systemic activity shown by early molecules, such as betamethasone and dexamethasone. (The major systemic effects of corticosteroids are shown in Table I.) Patients themselves may be reluctant to comply with INCS treatment, possibly because of confusion among the general public between anabolic steroids and corticosteroids and about the differences between oral and topical corticosteroids.

Used concomitantly at single sites, such as the nose or lung, the newer-generation INCS rarely cause systemic effects.¹⁶ Nonetheless, children with AR may also have asthma and/or eczema and may receive topical corticosteroids at several sites. This raises the possibility of an additive effect that could result in steroid loading (Fig 2).

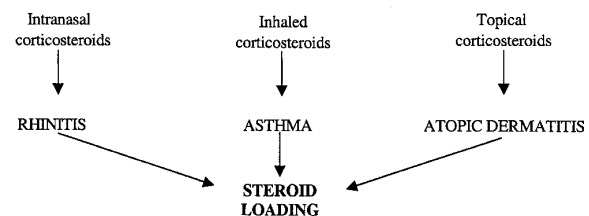


FIG 2. Steroid loading. Many children with rhinitis also have other atopic conditions, all of which may be treated with various topical formulations of corticosteroids. Total steroid burden should always be considered, and clinicians must take into consideration total risk of systemic side effects when corticosteroids are indicated in treatment of multiplicity of atopic conditions. This can be difficult if the child is attending several different clinics.

The potential for additive adrenal suppression has been investigated in a double-blind, placebo-controlled, cross-over study in which flunisolide (FLU) (300 µg/d) was added to baseline treatment with inhaled beclomethasone dipropionate (BDP) and oral prednisone in 19 subjects with steroid-dependent asthma and severe rhinitis or nasal polyposis. Morning serum cortisol levels and 24-hour urinary-free cortisol excretion after FLU or placebo treatment were not significantly different. Thus there appeared to be no important risk to endogenous adrenal function from adding intranasal flunisolide spray to other steroids. If higher dosages are used, however, the

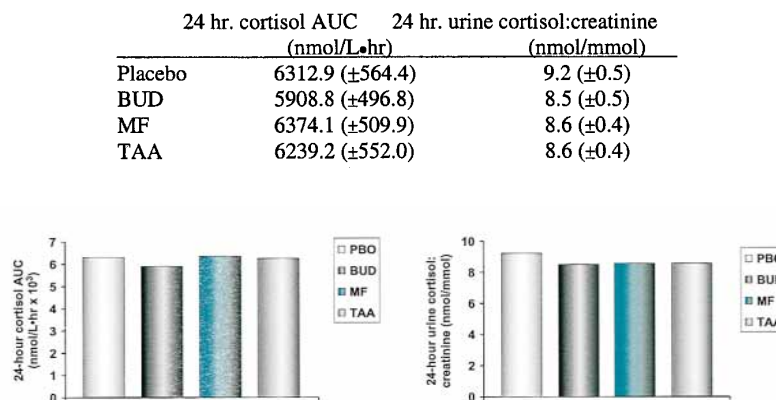


FIG 3. Effects of intranasal corticosteroids vs placebo on adrenal markers of systemic activity. (Adapted from Wilson AM, Sims EJ, McFarlane LC, Lipworth BJ. Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. *J Allergy Clin Immunol* 1998;102:598-604.)

TABLE IV. Methods of decreasing steroid load

- Allergen avoidance
- Titration of steroid use at different sites (adjust inhaled dose and intranasal dose)
- Method of use (head forward and down)
- Type of corticosteroid (efficacy at low doses; low bioavailability)
- Additional therapy (nonsedating antihistamines in AR; β_2 agonists, antileukotrienes, and others in asthma)
- Substitution of alternative drug (cromones)
- Immunotherapy

possibility of some additive adrenal suppressive effect cannot be excluded.¹⁷

The relative systemic activities of aqueous formulations of intranasal BUD, MF, and TAA have been investigated with regard to their effects on adrenal, bone, and white blood cell markers in 20 adult patients with allergic rhinitis.¹⁸ The study compared placebo with 200 μ g BUD daily, 200 μ g MF daily, and 220 μ g TAA daily. Serial blood and urine samples were taken for 24 hours after 5 days of treatment. Measurements of plasma cortisol and urine cortisol/creatinine excretion were taken. Compared with placebo, none of the active treatments produced significant systemic suppression of adrenal (Fig 3), bone, or white blood cell markers at the doses studied. This reflects the good safety profile of these aqueous intranasal formulations when taken at clinically recommended doses.

A recent study with mometasone furoate nasal spray showed that in children 3 to 12 years of age, there are no significant effects on the HPA-axis at doses of up to 200 μ g/d.¹⁹ In addition, intranasal TAA has been shown to have no effect on plasma cortisol levels in children when administered over a 6-week period.²⁰

Concerns regarding the safety of INGCs have arisen, however, after publication of reports of decreased bone growth in children receiving short-term 400 μ g intranasal BUD daily²¹ or 168 μ g intranasal BDP twice daily for 1 year.²² No significant effect was shown when BUD was

used at 200 μ g daily. There are, however, contradictory data that do not support these findings.

Mometasone furoate (100 μ g), taken daily for 1 year by children ages 3 to 9, did not suppress growth.²³ In this study and in a study by our group, using 100 or 200 μ g beclamethasone daily,²⁴ some increase in growth was seen, probably because of disease control and improved sleep. Growth studies may be a more sensitive marker of systemic effect than measures of pituitary function; in the study by Skoner et al,²² in which growth decrease was detected, no changes were found in these measurements.

Patterns of corticosteroid use

Decreasing steroid-load can be an issue; a number of methods can be used to affect steroid load. These are outlined in Table IV.

Dosing of corticosteroids in the morning has been shown to minimize potential impact on the HPA axis; in addition, a once-daily versus twice-daily dosing regimen can reduce the possibility of systemic steroid exposure. Whether used in nose, lung, skin, or gut, it is more effective to reduce acute inflammation rapidly with relatively high doses of topical corticosteroid, or even briefly with oral corticosteroid, and then to decrease the dosage to a maintenance level than to use moderate or low doses, which do not achieve adequate control of symptoms and signs of disease. The new asthma guidelines reflect this treatment regimen.^{25,26} Patients can be advised on how to titrate their treatment with management plans or charts. When a further exacerbation is threatened (eg, by viral infection or allergen exposure), a brief doubling of the corticosteroid dose for a few days can provide effective anti-inflammatory control without clinically significant systemic activity. Prophylactic use of a topical corticosteroid before seasonal allergen exposure has been shown to delay the onset of symptoms²⁷ and may decrease the need for higher-dosage therapy when pollen season begins. The use of depot steroids is not sensible where steroid loading is likely to be a problem since the dosage released is uncontrolled and the product cannot be removed if side effects occur.²⁸

Additional therapy

Simple measures, such as nasal lavage with saline solution²⁹ or the addition of oral or topical antihistamines to a low dosage of corticosteroids, may well help in the control of AR and also in chronic rhinosinusitis.

Recent research has demonstrated that treatment of rhinitis benefits concomitant asthma and that 400 µg of intranasal beclomethasone dipropionate has more effect on bronchial hyperreactivity than the same dose given by inhalation.³⁰ This requires confirmation, and it is both important and necessary to examine the noses of asthmatics and to ask about nasal symptoms. It may be that lowering the dosage of the inhaled corticosteroid and administering intranasal corticosteroid concomitantly could result in better asthma control.

Alternative anti-inflammatory agents

Nedocromil sodium is a possible alternative therapy. A pediatric study³¹ compared 1% of nedocromil sodium spray used 4 times daily with placebo in 149 children who exhibited symptoms of seasonal AR rhinitis and sneezing and showed reduction of symptoms ($P = .03$) after 1 week and at 4 weeks; both patients and clinicians favored the active treatment ($P < .01$), which was well tolerated.³² A comparative study suggests superior potency compared with sodium cromoglycate, with an equivalent safety profile. Both of these drugs can be used in conjunction with antihistamines or with topical corticosteroids.

Immunotherapy

The practice of immunotherapy largely disappeared from the United Kingdom after the Committee on Safety of Medicines report in the late 1980s. Classic immunotherapy is still recommended for severe hay fever that is unresponsive to conventional treatment provided the patient does not have concomitant asthma.³³ Recent trials of immunotherapy in the pediatric population have shown that benefit persists for several years with a reduction in comorbid disease manifestation. The concept of prevention of asthma by the immunotherapy of rhinitis exists, but it is as yet unproven. Safer methods of immunotherapy are under investigation, including sublingual application and the use of peptide fragments of allergen, which should not be able to cause anaphylaxis.³⁴ It is likely that in the long term, use of specific immunotherapy will increase.

CONCLUSIONS

Topical corticosteroids are extremely effective and have an excellent safety profile. Nonetheless, care must be taken when multiple sites such as the lungs, ear, and nose are being treated. Measurement of growth in children receiving topical corticosteroids should be routine practice in every asthma and rhinitis clinic, together with peak flow. Allergen avoidance should be the initial treatment in allergic diseases, with pharmacotherapy added as necessary. Because of their good anti-inflammatory

activity, poor absorption, and first-pass hepatic metabolism, second-generation topical corticosteroids are the treatment of choice for patients with allergic rhinitis. Patients should titrate dosage against need and to prevent complications from viral infections or increased allergen exposure by preemptive increase. Additional treatment with a different pharmacologic agent may help to reduce steroid dosage, or an alternative drug may suffice, especially when initial inflammation has been overcome.

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