

REVIEW ARTICLE

The safety of intranasal steroids

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The increasing use of intranasal steroids in the management of allergic rhinitis reflects their efficacy, tolerability, and safety. However, issues related to the safety of intranasal steroids continue to generate debate and confusion among clinicians. Consequently, there is often reluctance and uncertainty in prescribing these effective agents for the treatment of perennial and seasonal allergic rhinitis. Issues of particular concern are whether intranasal steroids adversely affect various homeostatic systems, influence growth and bone metabolism, and compromise ocular function. Furthermore, the expanding role of intranasal steroids in the pediatric, geriatric, and postmenopausal populations has raised concerns that these agents may result in a steroid burden that more readily causes adverse effects. An extensive review of the literature overwhelmingly supports the assertion that intranasal steroids are safe in prescribed doses and should allay the misconceptions regarding their appropriate use in the management of allergic rhinitis. (Otolaryngol Head Neck Surg 2003;129:739-50.)

Issues related to the safety of the use of intranasal steroids have generated both increasing awareness and debate over the past several years, largely a consequence of their evolving and expanding role in the management of allergic rhinitis. The introduction of newer agents and their increased use in the management of chronic disease, as well as in the treatment of pediatric and geriatric popula-

tions, has resulted in considerable interest in the efficacy and safety profile of these drugs. Some discussion of this topic has been covered in the pediatric and general allergy and immunology literature, but there remains a paucity of information in the otolaryngology literature. As otolaryngologists, we encounter patients with seasonal and perennial allergic rhinitis on a regular basis. This experience underscores the need for a thorough review of the current literature to elucidate the nature of intranasal steroid safety. Therefore, it is of paramount importance to understand whether treatment with intranasal steroids will result in local or systemic adverse effects.

BACKGROUND

Intranasal steroids have gained widespread acceptance as the first-line treatment of allergic rhinitis.¹ Earlier management paradigms involved the use of first-generation antihistamines in conjunction with topical and oral decongestants for optimal improvement in rhinitis symptoms. Growing recognition of the sedative and adverse cardiac effects of certain antihistamines, the rebound nasal congestion associated with prolonged topical decongestant use, and the limitations of the use of oral decongestants in various groups of patients have reduced the use of these drugs as the initial choice in the chronic management of allergic rhinitis.² Second generation, nonsedating antihistamines have largely filled some of the gap lost by the first-generation drugs, although they do not manage all of the most-common symptoms of allergic rhinitis, particularly congestion. The efficacy and convenience of intranasal steroids, however, has established these agents as indispensable in controlling the symptoms of perennial and seasonal allergic rhinitis.³

Intranasal steroids act locally on the nasal mucosa, and most available preparations are effective with once daily dosing, which reflect the safety, efficacy, and convenience of these drugs. The cur-

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rently available agents in the United States include the following: the first generation intranasal steroids (beclomethasone dipropionate, triamcinolone acetonide, flunisolide, budesonide) and the newer preparations (fluticasone propionate and mometasone furoate). All of these agents have demonstrated efficacy in the treatment of seasonal and perennial allergic rhinitis.

Allergic rhinitis affects over 40 million people annually in the United States and is associated with approximately \$4.5 billion dollars a year in direct costs and approximately 4 million missed school and work days a year.⁴ Thus, the socioeconomic ramifications of this condition are enormous, creating a burden not only for the patient but also for the health care delivery system. The introduction of intranasal steroids made a significant impact in the ability to manage the debilitating symptoms of allergic rhinitis, while controlling the costs of the disease.

Although studies on allergic rhinitis have demonstrated the therapeutic efficacy and safety of intranasal steroids compared with placebo and antihistamines,^{3,5} there remains apprehension in prescribing these agents because of concerns about their potential systemic effects. Underutilization of intranasal steroids reflects the misconception that consistent use of these agents will cause systemic effects. This is attributed to several factors. First, there have been reports of adverse effects on the hypothalamic-pituitary-adrenal (HPA) axis, as well as on childhood growth, bone metabolism, and ocular function. Though some reports demonstrate changes in surrogate markers of activity in these systems, these neither correlate with, nor predict clinically relevant systemic effects. Second, intranasal steroids are often used in conjunction with inhaled corticosteroids for the concomitant treatment of asthma, commonly seen in patients with an allergic diathesis. This cumulative steroid burden is perceived as a potential excess of steroid load. And lastly, as these agents are increasingly prescribed on a chronic basis and in broader patient populations, concerns have been raised about the long-term effects of these drugs. A review of the current literature would serve not only to allay these misconceptions but also to provide the clinician with evidence-based support of their safety. Thus, our assertion is that the benefits of intranasal

steroid use far outweigh any risks associated with these agents.

Mechanism of Action of Corticosteroids

Corticosteroids are highly effective in mitigating inflammation.⁶ The ability to modulate the expression of various arms of the immune response has led to widespread use in various inflammatory states. Corticosteroids act primarily by regulating protein synthesis. This function results from its specific mechanism of action. Whether administered 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. The steroid-receptor complex translocates to the nucleus, where it binds reversibly to specific sites on chromatin, known as glucocorticoid response elements, which are located in the 5'-upstream promoter region of the steroid-responsive genes.⁷ The binding of the complex to the DNA results in either induction or suppression of gene transcription. The resulting mRNA transcripts are transported to the cytoplasm where they undergo translation by ribosomes, resulting in the production of proteins.^{8,9} These proteins are responsible for a plethora of effects within the inflammatory cascade.

Corticosteroids inhibit pro-inflammatory cytokine production, including that of interleukin-1 (IL-1), IL-2, the IL-2 receptor, interferon- α (IFN- α), tumor necrosis factor (TNF), and various colony-stimulating factors (CSFs) such as IL-3.^{10,11} 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. Furthermore, lymphocyte proliferation and delayed type hypersensitivity are also inhibited by corticosteroids *in vitro*.¹²

The role of corticosteroids in the management of allergic rhinitis is influenced by their effect on the inflammatory cells and chemical mediators that are released in the early- and late-phase allergic responses.¹ The early-phase allergic response (EPR) is characterized by an initial period of sen-

sitization to a specific allergen. Subsequent exposure to the inciting allergen causes cross-linking of IgE antibodies located on the surface of mast cells residing in the nasal mucosa, which results in mast cell degranulation and the release of various chemical mediators, such as histamine. These mediators cause the infiltration of inflammatory cells in the peripheral blood to the site of exposure. The ensuing cascade of events is termed the late-phase allergic response (LPR) and is characterized by hyperreactivity of the nasal mucosa. The efficacy of corticosteroids in mitigating these responses has been well established.

Corticosteroids are produced endogenously and are regulated by feedback loops involving the hypothalamic-pituitary-adrenal (HPA) axis at several levels. If the steroid load exceeds the normal physiological output or disrupts the normal daily diurnal rhythm, this would inhibit further release of corticosteroid and precipitates an adrenal crisis. This situation can potentially cause significant problems. The concern to clinicians is whether a therapeutic dose of exogenous steroid results in an increased steroid load, and hence, a negative feedback inhibition of corticosteroid production. Several studies, discussed below, have demonstrated that intranasal steroids, when taken appropriately, are safe and present no significant risk for systemic adverse effects. Furthermore, these studies demonstrate that the dosage of these agents is well below the level that causes clinically relevant adverse effects. Most of the available preparations are effective at once-daily dosing, which enhances safety and improves compliance.

Pharmacologic Properties of Intranasal Steroids

There are several variables that require assessment when determining the safety profile of intranasal steroids. Among these are absorption characteristics, which are related to topical potency, lipid solubility, and systemic bioavailability.^{13,14} The amount of intranasal steroid that is available to target cells is influenced by several factors. The aqueous pump sprays that deliver the drug ensure that a significant portion will be deposited on the nasal mucosa. Nevertheless, as with inhaled corticosteroids, most of the intranasal steroid dose is

swallowed and this must be accounted for when determining actual systemic bioavailability.

The abundant vascularity of the nasal mucosa provides a large surface area for drug absorption. Although this represents a less significant route than the swallowed fraction, the amount entering the systemic circulation is not subject to first-pass metabolism. Hence, a significant portion of the drug deposited on the nasal mucosa is directly accessible to the systemic circulation. Two other factors determine the quantity of drug that diffuses across the nasal mucosa and penetration into the bloodstream. These are the topical potency and lipid solubility of the drug (Fig 1).

Topical Potency

The potency of various intranasal steroids is often assessed by the McKenzie assay, which measures topical vasoconstriction through skin-blanching responses.¹⁵ An article from Johnson et al demonstrated that the newer generation agents, fluticasone propionate and mometasone furoate, are more potent than other intranasal steroids.¹⁶ Though this assay reflects the relative vasoconstrictive properties of various agents, its usefulness in predicting anti-inflammatory activity is limited. Another measure of potency involves the inhibitory action of intranasal steroids on the generation of CD4+ cell-derived cytokines, such as IL-4, IL-5, and IFN- γ .¹¹ A study using this method demonstrated that fluticasone propionate and mometasone furoate were equally effective at inhibiting cytokine release, and they also had greater inhibition than the other intranasal steroids studied (beclomethasone, triamcinolone, budesonide, and betamethasone).¹¹ Thus, this method of potency incorporates a measure of anti-inflammatory action.

Corticosteroid receptor binding affinity is arguably the best available comparative measure of potency and reflects the stimulation of glucocorticoid receptor-mediated transactivation of gene expression. It has been determined that the rank order of receptor binding affinity is, from highest to lowest, mometasone furoate, fluticasone propionate, budesonide, triamcinolone acetonide, and dexamethasone.⁹ However, none of these theoretical differences in potency have been found to be associated with better or worse clinical outcome.

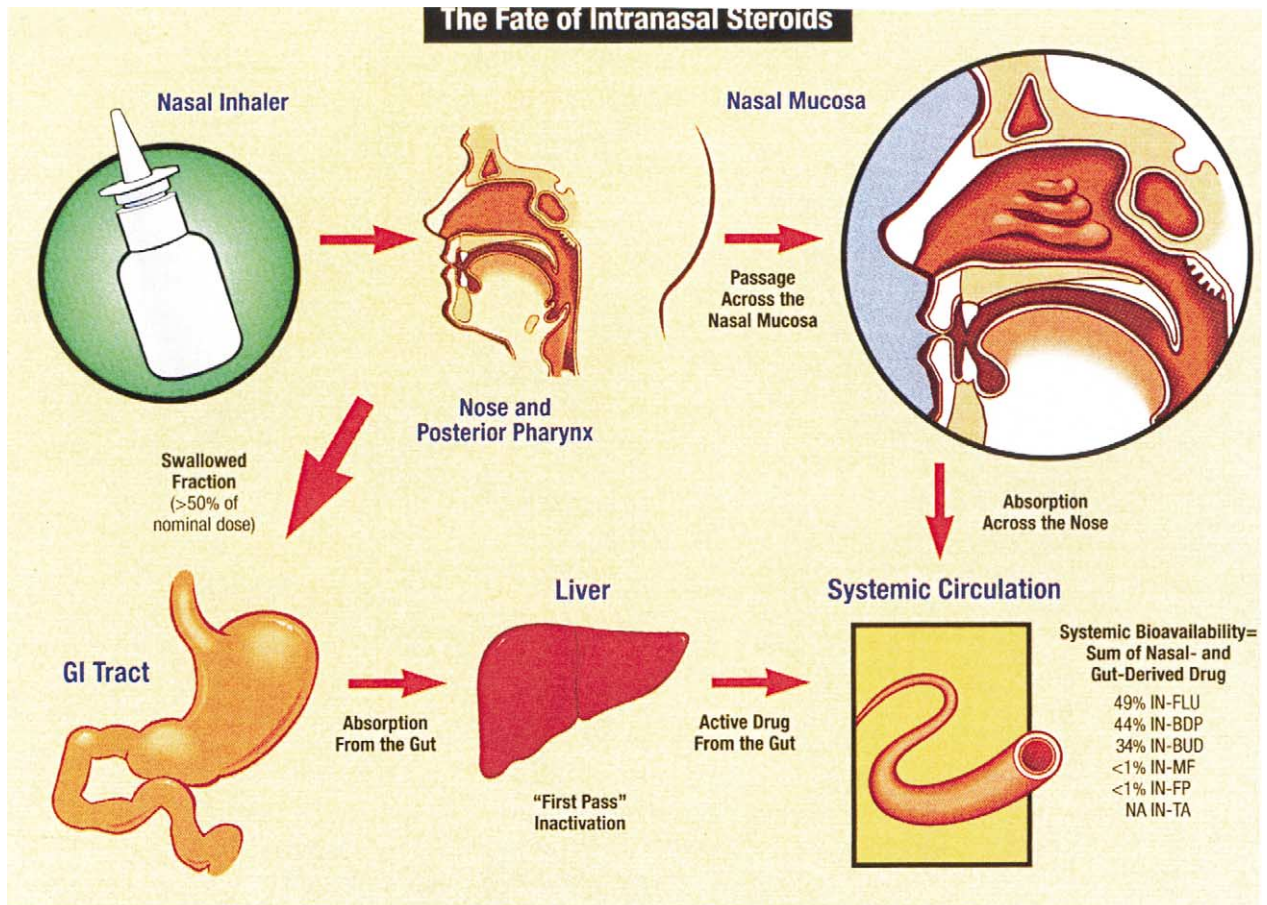


Fig 1. The fate of intranasal steroids. The amount of intranasal corticosteroid that reaches the systemic circulation is the sum of the nasal and oral bioavailable fractions. The majority of the drug is swallowed, and systemic bioavailability will be determined by the absorption from the gastrointestinal tract and the degree of first-pass hepatic inactivation. The absorption of the fraction that is deposited on the nasal mucosa varies from drug to drug and is influenced by solubility characteristics and other factors. (NA, not available.) (Reprinted with permission from *J Allergy Clin Immunol*.¹⁴ 2000;106: S179-90.)

Lipid Solubility

The lipophilic nature of a compound refers to its lipid-partitioning properties. Thus, a highly lipophilic substance shows a higher and faster uptake by the nasal mucosa, greater retention within the tissue, and an enhanced glucocorticoid receptor binding.^{13,14} The descending rank order of lipophilicity of the available topically active steroids is mometasone furoate, fluticasone propionate, budesonide, triamcinolone acetonide, and flunisolide.¹⁶

Systemic Bioavailability

Pharmacokinetic studies have demonstrated that newer intranasal steroids (fluticasone and mometasone) have significantly lower systemic bioavailabilities than the older compounds. After ad-

ministering a single oral dose, the systemic bioavailability of these newer topical steroids are <2% and 0.1%, respectively.^{13,14} As mentioned previously, systemic bioavailability reflects both the portion of the drug absorbed via the nasal mucosa and the amount swallowed and subsequently absorbed by the GI tract. The contribution of the nasally absorbed fraction is minimal relative to the amount of drug absorbed via the GI tract.¹⁷ Although different compounds exhibit variable absorption across the nasal mucosa, systemic bioavailability is primarily determined by the different degrees of first-pass hepatic metabolism. The oral bioavailability for the first-generation intranasal steroids are as follows: 10.6% for triamcinolone acetonide, 21% for flunisolide, and 41% for

Table 1. Relative bioavailabilities of various anticosteroid preparations when administered intranasally or orally

Corticosteroid	Bioavailability (%)	
	Intranasal administration	Oral administration
Fluticasone propionate	<1	<1
Mometasone furoate	<1	<1
Triamcinolone acetonide	NA*	10.6
Budesonide	34	11
Beclomethasone dipropionate	44	41
Flunisolide	49	21

NA, Not available.

Table adapted from Allen et al.⁴

beclomethasone dipropionate.^{13,14} These oral values correlate well with the systemic bioavailability values of the intranasal steroids (Table 1).

SYSTEMIC ADVERSE EFFECTS

As the indications for topical steroid use continue to expand, there is growing concern over the potential harmful effects of these drugs on various physiologic systems. The increased use of intranasal steroids in the pediatric, postmenopausal, and geriatric patient populations have led to renewed interest in the clinical safety profile of intranasal steroids. Furthermore, intranasal steroids are increasingly used in combination with either oral or inhaled steroids for concomitant conditions such as allergic dermatitis and asthma, which commonly occur in patients with allergic rhinitis. Although the probability of serious adverse effects in these populations is low, this potential increased steroid burden contributes to the reluctance in prescribing these medications.

The effects of intranasal steroids on the HPA axis, growth and bone metabolism, and ocular function have been extensively studied and overwhelmingly support the safety of these drugs. The following discussion provides the clinician with an analysis of the current literature and illustrates the various methods of assessing the systemic effects of intranasal steroids.

Effects on the HPA Axis

The secretion of cortisol in response to stress and to metabolic demands exerts a negative feedback on the hypothalamus and pituitary gland. An increasing plasma concentration of cortisol de-

creases the release of corticotropin-releasing factor (CRF) from the hypothalamus and the secretion of ACTH from the pituitary, which thereby decreases the secretion of cortisol by the adrenal glands. This feedback loop, thus, determines the appropriateness of cortisol secretion. An exogenous glucocorticoid also has the potential to affect this physiologic feedback of the HPA axis.

Measurements of the HPA axis can be divided into tests of basal (steady-state) and reserve adrenal function.^{14,18} However, there is considerable confusion in the interpretation and clinical relevance of these tests. A discussion of these tests will highlight their relative clinical importance.

There are 3 useful tests of basal HPA axis activity that measure cortisol concentrations: measurements of morning plasma cortisol concentration; 24-hour urinary-free cortisol excretion; and the 24-hour integrated concentration (IC) of plasma cortisol concentrations. These test results are surrogate markers for the systemic bioavailability of cortisol and, hence, are used in assessing and comparing the systemic effects of intranasal steroids.^{14,18}

Random plasma cortisol levels exhibit a diurnal secretion pattern and are regulated by ACTH production from the pituitary gland. Levels of cortisol peak in the early morning (10 to 20 $\mu\text{g}/\text{dL}$), usually an hour before awakening, decline by the late afternoon (3 to 10 $\mu\text{g}/\text{dL}$), and are at their lowest within an hour of usual bedtime (3 to 5 $\mu\text{g}/\text{dL}$). The measurement of morning plasma cortisol concentration is subject to individual variability and, thus, is not sufficiently sensitive to detect all de-

degrees of HPA axis suppression. Measuring urinary cortisol excretion over a 24-hour period detects excessive cortisol secretion rather than detecting a low secretion of cortisol. Therefore, its validity and clinical importance are less certain. The 24-hour integrated concentration of plasma cortisol concentrations is a sensitive assessment of the steady-state activity of the HPA axis, however, it requires blood sampling from a subject over a 24-hour period in a hospital setting. The limitation of these tests in demonstrating a clinically adverse effect reflects the notion that the effects of exogenous glucocorticoids on HPA axis activity do not reliably predict a clinically adverse effect with their use.

Stimulation tests or measures of reserve adrenal function provide a less sensitive indicator of the bioavailability of intranasal steroids. However, these tests have the potential of identifying clinically adverse effects with intranasal steroid use. There are 4 adrenal stimulation tests common in clinical use to determine whether intranasal steroids cause suppression of the HPA axis.

The cosyntropin stimulation test measures the response of the adrenal glands to ACTH stimulation. A normal test demonstrates a 200 nmol/L increase in plasma cortisol, 30 minutes after intravenous cosyntropin injection. A lower value is suggestive of impaired adrenal function. The corticotropin-releasing factor (CRF) test assesses the response of pituitary secretion of ACTH to CRF stimulation. A normal response to a 100 µg intravenous injection of CRF is a clear increase in the plasma concentration of ACTH. Insulin-induced hypoglycemia, an insulin tolerance test, is a sensitive yet rarely used measure of HPA axis activity. It assesses the responsiveness of the entire HPA axis, however, it is limited by its expense and potential danger. Another test of the pituitary secretion of ACTH, though limited by its potential side effects, is the metapyrone test. Metapyrone acutely inhibits an enzyme involved in cortisol synthesis, which decreases plasma cortisol concentrations and results in a stimulus to ACTH secretion.

Thus, tests of basal or steady-state cortisol concentrations in the blood and urine are useful in detecting the presence of noncortisol exogenous steroids (such as systemically absorbed intranasal

steroids), but do not accurately predict resulting clinically significant adverse effects. Conversely, reserve adrenal function tests are more predictive of an adverse clinical effect of exogenous glucocorticoids, but generally lack sensitivity. The positive predictive value of these tests makes them more reliable in assessing whether the use of intranasal steroids results in any degree of clinical adrenal suppression.^{14,18}

The vast majority of data in the literature indicate that therapeutic doses of intranasal steroids have very minimal effects on the HPA axis function. The time of administering the dose has demonstrated a variable effect on the HPA axis. A few studies have shown that doses administered in the late afternoon and evening affect the normal, nocturnal decrease in plasma cortisol concentrations. Also, in one study, once-daily intranasal budesonide (400 and 800 µg/day) administered in the evening resulted in suppression of the urinary free cortisol level.¹⁹ In the same study, intranasal beclomethasone (200, 400, 800 µg/day), administered in morning and evening doses, also demonstrated a decrease in cortisol excretion.

Of note, most currently available intranasal steroid preparations are given once-daily in the morning and thus, do not have significant adverse effects on the circadian rhythm of the HPA axis. Several studies, using both tests of basal and reserve adrenal function, have demonstrated normal to negligible effects on the HPA axis with once-daily morning dose of intranasal steroid.

Studies assessing the effect of intranasal steroids on basal adrenal function have generally demonstrated no significant effect on the HPA axis. Once-daily, morning administration of intranasal beclomethasone dipropionate (200, 336, 400, and 800 µg/day), triamcinolone acetonide (220 µg/day), fluticasone propionate (200 µg/day), budesonide (200 µg/day), and mometasone furoate (200 µg/day) have all shown no effect on basal HPA axis function.^{20,21}

Similarly, studies using ACTH stimulation tests have demonstrated no significant effects of intranasal steroids on HPA axis activity (ie, adrenal responsiveness). These studies included beclomethasone dipropionate given at 336 µg/day, fluticasone propionate at 200 and 400 µg twice daily, and triamcinolone acetonide at 220 and 440

$\mu\text{g/day}$.²²⁻²⁴ Wilson et al²⁰ demonstrated in a placebo-controlled study comparing budesonide (200 $\mu\text{g/day}$), mometasone furoate (200 $\mu\text{g/day}$), triamcinolone acetonide (220 $\mu\text{g/day}$), and placebo, that there were no significant differences in measures of adrenal suppression.

Additionally, studies have shown that intranasal steroids given at even higher than therapeutic doses have negligible effects on the HPA axis. In one study, based on 24-hour plasma and urinary cortisol measurements, mometasone furoate administered at 20 times higher than the therapeutic dose (1 to 4 mg), showed no adverse effect on the HPA axis.²⁵ Studies involving fluticasone at 200 $\mu\text{g/day}$ and mometasone furoate at 200 and 400 $\mu\text{g/day}$ administered over an extended period (up to 5 weeks), similarly demonstrated no effect on the HPA axis.²⁶

A major concern to clinicians is prescribing intranasal steroids to children. Several studies have demonstrated a similar safety profile of intranasal steroids with respect to the HPA axis, as that observed in adults. Children with allergic rhinitis that were treated with intranasal beclomethasone dipropionate (336 $\mu\text{g/day}$), triamcinolone acetonide (220 and 440 $\mu\text{g/day}$), and mometasone furoate (100 $\mu\text{g/day}$) had no demonstrable effect on the results of the cosyntropin stimulation test.²⁷⁻²⁹ Furthermore, children aged 6 to 12 years, had no HPA axis effects as measured by plasma cortisol and 24-hour urinary-free cortisol levels, when treated with mometasone furoate for 7 days at a dose of 200 $\mu\text{g/day}$. The same result was seen in younger children (3 to 5 years) treated over 14 days.³⁰ These studies corroborate results from those seen in adults and demonstrate that use in children is safe and effective.

Although variability exists among available intranasal steroids in terms of potency, lipophilicity, systemic bioavailability, receptor binding affinity, and tissue retention, the data from an overwhelming majority of studies suggest that once-daily administration of intranasal steroids have minimal effects on the HPA axis. Furthermore, there are only case reports of adrenal insufficiency in patients treated with these agents, mostly from older preparations such as dexamethasone nose drops. Thus, intranasal steroids in recommended doses are both safe and effective.

Effects on Growth and Bone Metabolism

The reluctance of many clinicians to use intranasal steroids has also been influenced by concerns over their effects on linear growth and bone metabolism. It is well known that steroids exert a suppressive effect on growth. An increased steroid burden has the potential to impair normal growth through several mechanisms. These include decreasing the release of growth hormone, the activity of insulin-like growth factor-1, the expression of growth hormone receptor, and the production of collagen (Fig 2). However, the use of topical steroids with minimal systemic bioavailability lessens this steroid burden. Overall, studies have shown that intranasal steroids administered at recommended doses are not associated with impairment in growth and subsequent final adult height. However, these studies are limited since there have been no prospective, long-term data analyzing the effect of regular intranasal steroid use on final adult height.

Studies that analyze the effects of intranasal steroids on growth have conventionally been divided into short-term (up to 6 months), intermediate-term (beyond 6 months), and long-term (over several years) growth effects. Short-term studies have used knemometry, which is a measure of lower-leg growth. The limitation of this measurement is that it does not exactly correlate with overall linear growth and, hence, is not a reliable clinical predictor of negative growth effect.¹⁴ Similarly, intermediate-term studies do not evaluate final adult height. Intermediate and long-term studies generally use stadiometry, which is a measure of statural growth. As mentioned previously, long-term studies are lacking and would provide the most convincing evidence of an effect on growth velocity. It is important to note that measurements of the effects of intranasal steroids on growth velocity do not take into account several confounding variables such as the patient's nutritional status, physical activity, comorbidities, and previous steroid exposure. Furthermore, growth occurs over several distinct phases. There are 3 phases that have been described in the literature: an initial rapid growth phase that occurs during infancy and is followed by a period of rapid deceleration related to the child's nutritional sta-

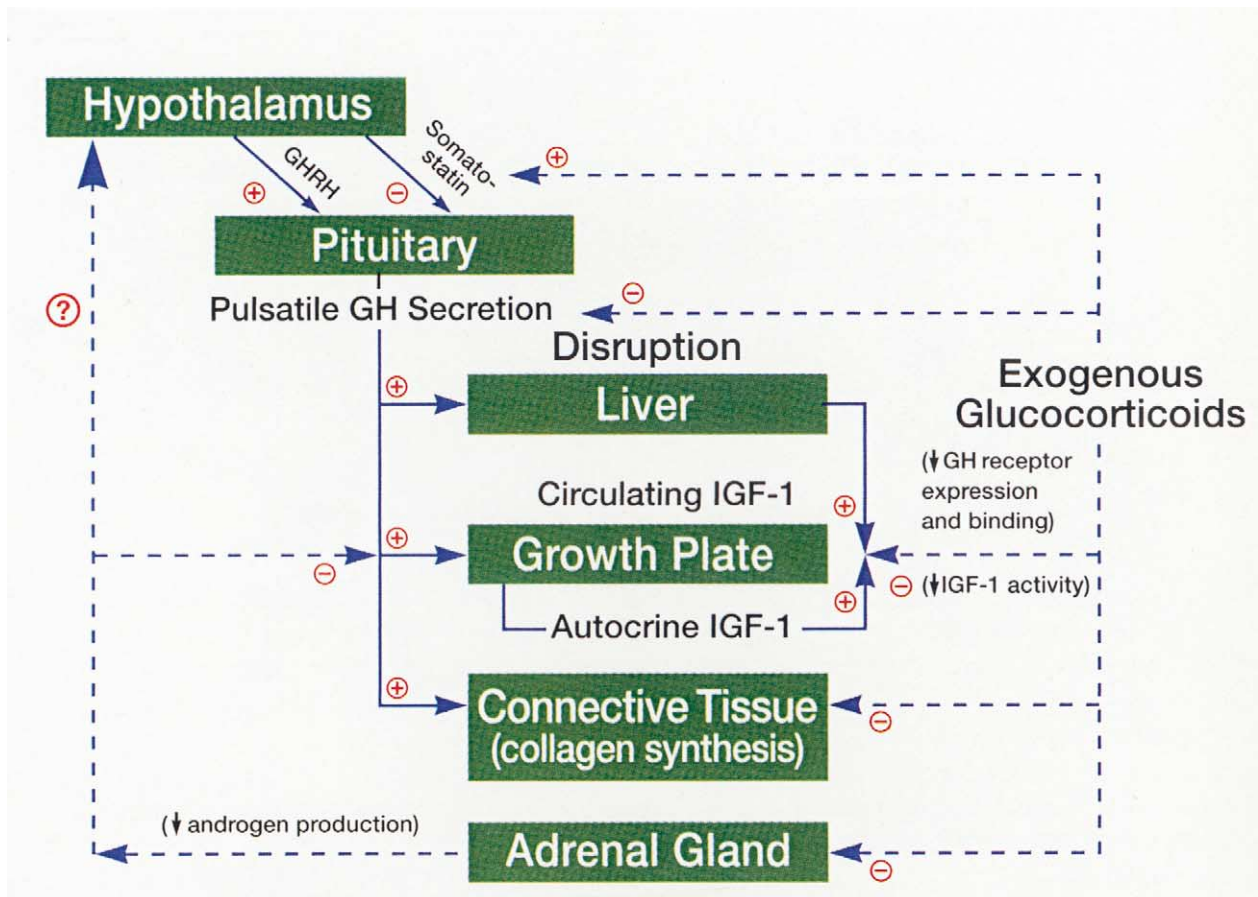


Fig 2. Mechanisms of growth suppression by corticosteroids (derived from both in vivo and in vitro studies). (*GHRH*, growth hormone releasing hormone; *GH*, growth hormone; *IGF-1*, insulin-like growth factor-1.) (Reprinted with permission from *J Allergy Clin Immunol*.¹⁴ 2000;106:S179-90.)

tus; childhood growth that is influenced by growth hormone release; and pubertal growth, which is regulated by both growth hormone and sex steroids. It is difficult to assess the effects of intranasal steroids on each of these phases as well as the intervening periods where susceptibility to steroid-induced growth impairment may occur. Studies incorporating these phases would provide a more realistic approximation of the effects of intranasal steroids on growth.

There are 3 studies that demonstrate contrasting results on the effects of intranasal steroids on growth. In a 12-month, placebo-controlled, double-blind study of children aged 6 to 10 years with perennial allergic rhinitis treated with 168 μg twice daily of beclomethasone dipropionate, there was a small (0.9 cm difference) but statistically significant reduction in total growth and growth velocity (0.004 cm/day difference).³¹ A similar

study evaluating mometasone furoate (100 to 200 $\mu\text{g}/\text{day}$) in children aged 3 to 9 years demonstrated no reduction in growth velocity.³² Furthermore, a 1-year, double-blind study conducted by Allen et al³³ demonstrated that fluticasone propionate aqueous nasal spray at the maximum recommended dose of 2 sprays per nostril (200 μg) once daily was equivalent to placebo with no effects on growth rate in prepubescent children. These contrasting results reflect the current limitation, which is that effective long-term studies have not yet addressed whether intranasal steroids can indeed significantly affect growth velocity. Further long-term studies that evaluate the final adult height attained, as well as the additive effect of inhaled or oral steroids on growth velocity are needed to accurately assess the effects of intranasal steroids on growth. This is currently being facilitated by gradually lowering ages of approval

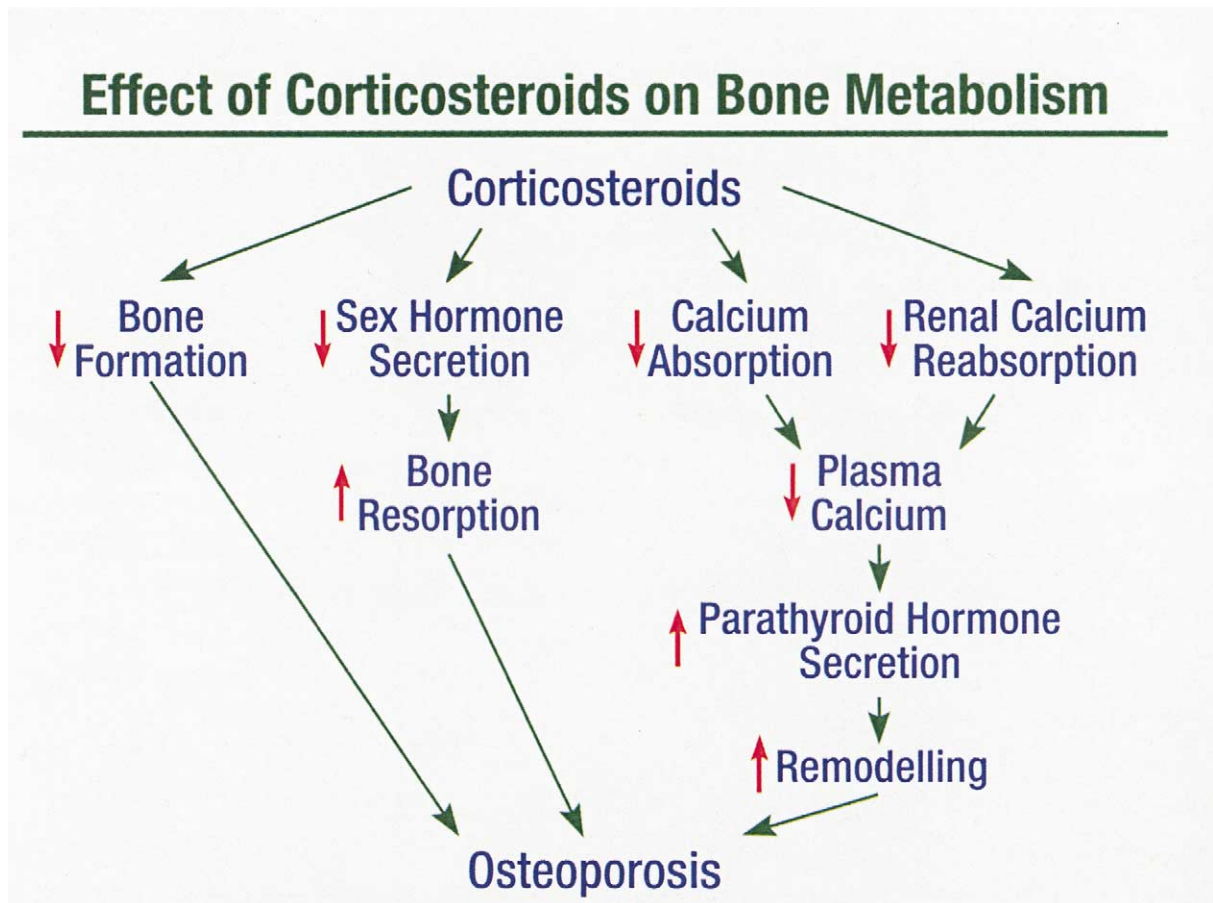


Fig 3. Interaction of corticosteroids with bone metabolism, which contributes to the increased risk for osteoporosis. (Reprinted with permission from *J Allergy Clin Immunol*.¹⁴ 2000;106:S179-90.)

for the use of intranasal steroids by the Federal Drug Administration.

The effects of intranasal steroids on bone metabolism are a specific concern in certain patient groups such as children, the elderly, postmenopausal women, and those receiving steroids for other concurrent conditions. These patients are more susceptible to the potential adverse effects of steroid use as their thresholds may more readily be reached or exceeded.

Steroids exert their negative effect on bone metabolism by altering both calcium homeostasis and adrenal sex hormone production. An excess steroid burden affects calcium regulation by altering osteoblastic and osteoclastic activity,³⁴ thereby resulting in increased bone resorption and increased urinary calcium levels. Acutely, steroids increase osteoclastic activity, but chronically, they decrease osteoblastic activity and promote osteoblas-

tic apoptosis. Additionally, vitamin D-dependent calcium absorption in the intestine is inhibited, further contributing to a decrease in total body calcium. A vicious cycle ensues as secondary hyperparathyroidism results in an attempt to restore calcium homeostasis. Steroids also alter sex steroid release, which may also contribute to decreased bone mass, a particular concern when prescribing intranasal steroids to postmenopausal women (Fig 3).

Biochemical markers of bone turnover, such as osteocalcin, have been used to detect the presence of excess steroid in the systemic circulation. In one study, the short-term use of 200 $\mu\text{g}/\text{day}$ of budesonide, 220 $\mu\text{g}/\text{day}$ of triamcinolone acetonide, and 200 $\mu\text{g}/\text{day}$ of mometasone furoate was not associated with a significant alteration in osteocalcin levels. Wilson et al²⁰ demonstrated no significant effect on osteocalcin levels in patients

treated with intranasal steroids compared to placebo. Another study,³⁵ which evaluated the effect of intranasal steroids on several biochemical markers of bone turnover, showed that children with grass pollen sensitivity treated with either intranasal beclomethasone dipropionate or cromolyn sodium over an 8-week period had no effect versus baseline on serum levels of osteocalcin, parathyroid hormone, or total alkaline phosphatase.

A more valid measure of bone mineral density (BMD) is obtained by dual x-ray absorptometry. In studies evaluating inhaled corticosteroids, there have been reports of decreased BMD with their use in asthmatic patients.³⁶ This has generated concern among clinicians, who may perceive that these results are reflective of intranasal steroid use. However, a short-term study by Boulet et al³⁷ demonstrated no changes in BMD with inhaled corticosteroid use in children and adults. As with studies of growth velocity, there are no long-term assessments of the effects of intranasal steroids on BMD.

Current studies that have evaluated the effects of intranasal steroids on bone metabolism have also been limited by the lack of long-term studies. As with growth effects, it is difficult to assess the effects of intranasal steroids on bone, due to confounding factors such as nutritional status and underlying disease. Short-term studies in both children and adults, however, demonstrate no significant effect on bone mineral metabolism.

Ocular Changes

Chronic oral corticosteroid use has been documented to increase the risk of ocular side effects, such as glaucoma and cataract.³⁸ Studies have suggested a link between inhaled corticosteroid use and the increased risk of cataract, which is often cited to be dose-dependent.^{39,40} However, studies evaluating the effect of intranasal steroids on intraocular pressure and cataract formation have demonstrated that the incidence of these side effects is similar to that among nonusers. Derby et al⁴¹ showed that the use of intranasal steroids was not associated with an increased risk of cataract formation. Another study demonstrated no risk of ocular hypertension or posterior subcapsular cataract

with prolonged intranasal steroid use.⁴² A case control study of 9,793 patients, age 66 or older, with a new diagnosis of borderline glaucoma, open angle glaucoma, or ocular hypertension, and 38,325 controls randomly selected was conducted by Garbe and Suissa.⁴³ They concluded that there was no increased risk for these diseases with intranasal steroid use but that current users of high dose (1600 mcg/day) of inhaled corticosteroids for 3 or more months were at increased risk with an odds ratio of 1.44. The risk of ocular side effects appears to be negligible due to the low systemic bioavailability of most available intranasal steroid preparations.

Local Side Effects

Intranasal steroids have been associated with several local side effects such as epistaxis, dryness, and burning. These local side effects occur in approximately 5% to 10% patients and occur with most available intranasal steroid preparations.^{13,14} Studies have focused on the effects of these drugs on the nasal mucosa. Initial concerns regarding atrophy of the nasal mucosa with chronic topical steroid use were addressed in a study evaluating the long-term effects of the newer generation, more potent intranasal steroids on nasal mucosa histology. The use of mometasone furoate and fluticasone propionate over a 12-month period demonstrated no evidence of atrophy or metaplasia.^{44,45} A study⁴⁶ evaluating the effect of intranasal triamcinolone acetonide on nasal mucosa thickness and mucociliary function demonstrated no mucosal atrophy or impairment in mucociliary function with sustained treatment. There have been a few case reports of septal perforations associated with intranasal steroid use,⁴⁷ but this complication occurs mostly with the very early preparations and can be avoided with appropriate use of these agents. The general recommendation is to spray the contents toward the lateral nasal wall as opposed to the septum to maximize the anti-inflammatory action on the nasal mucosa while avoiding the potential dryness, crusting, and bleeding from the septum. Thus, intranasal steroids, even the more potent agents, are not associated with any significant risk of local side effects.

CONCLUSIONS

The incidence of systemic and local adverse effects with the use of intranasal steroids is minimal. Isolated studies (with low sample sizes, biases, and less than ideal measures of physiologic and clinical effects) and a few case reports, in conjunction with studies evaluating the safety of inhaled and oral corticosteroids, have resulted in considerable apprehension among clinicians prescribing intranasal steroids. Because most studies demonstrate no significant adverse effect on the HPA axis, it is reasonable to assume that the safety of these drugs outweighs the risk associated with their use. Although long-term assessments of the safety of intranasal steroids on linear growth and bone metabolism are lacking, the evidence of their general safety and efficacy is overwhelming. There have also been a number of claims suggesting that there is greater or lesser safety of various intranasal steroids based on lipophilicity and bioavailability. However, no clinical differences in safety have been identified and no significant differences in HPA axis suppression, linear growth, or bone metabolism have been reported.

We have had extensive experience with the use of intranasal steroids, and have found them to be efficacious, convenient to use and safe. Once-daily administration at the recommended doses has been proven to yield the desired therapeutic effect without compromising the health of the patient. The concern regarding the safety of intranasal steroids use in combination with inhaled and/or oral corticosteroids needs further study. Furthermore, long-term studies assessing the effects of intranasal steroids on linear growth in children and bone and mineral metabolism in both adults and children are needed to determine if clinically significant adverse effects occur. Despite these limitations, studies involving the HPA axis have overwhelmingly shown that these drugs do not result in significant physiologic perturbations or clinical effects. Thus, intranasal steroids have proven to be both efficacious and safe in the treatment for allergic rhinitis.

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