

Intranasal corticosteroids for allergic rhinitis: How do different agents compare?

Jonathan Corren, MD *Los Angeles, Calif*

Intranasal steroids have proved to be an effective and safe form of therapy for allergic rhinitis. However, as the number of new glucocorticoid compounds has increased over the past decade, it has become important to consider whether significant differences exist between these agents. Pharmacologically, newer drugs such as mometasone furoate and fluticasone propionate appear to have substantially higher topical potencies and lipid solubilities and lower systemic bioavailabilities than do older compounds. In clinical use, however, all the available drugs appear to be equally effective in controlling symptoms of seasonal and perennial allergic rhinitis. With respect to adverse effects, emerging data suggest that mometasone furoate and fluticasone propionate may have less potential for systemic effects during prolonged use, particularly in children. Newer intranasal steroids appear to have practical advantages over older agents that may favor their use in some groups of patients with allergic rhinitis. (*J Allergy Clin Immunol* 1999;104:S144-9.)

Key words: Intranasal steroids, potency, lipophilicity, systemic bioavailability, onset of action

Since their introduction more than 2 decades ago, intranasal steroids have become established as first-line treatment for allergic rhinitis.¹ All the available agents, including beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide have been shown to be efficacious in the treatment of both seasonal and perennial allergic rhinitis and other chronic inflammatory nasal diseases. Despite the efficacy of these medications, however, some physicians have remained reluctant to prescribe them because of concerns about potential local and systemic adverse effects.² When an attempt is made to develop intranasal steroids that are safe and maximally efficacious for long-term use, several pharmacologic and clinical attributes must be considered, including topical potency, lipophilicity, systemic bioavailability, onset of action, and potential for local and systemic adverse effects. This article will compare the available intranasal glucocorticoid compounds in the context of these important issues.

Abbreviation used

HPA: Hypothalamic-pituitary-adrenal

PHARMACOLOGIC PROFILES OF TOPICAL INTRANASAL STEROIDS

Topical potency

Topical potencies of glucocorticoids are most often compared with use of the McKenzie assay, which assesses skin-blanching responses as a measure of cutaneous vasoconstriction.³ With use of this assay, newly developed compounds such as fluticasone propionate and mometasone furoate have been shown to be more potent than other corticosteroids used intranasally.⁴ Although the McKenzie assay is highly relevant to the vasoconstrictive effects of glucocorticoids, it is unknown to what extent these results correlate with the various anti-inflammatory properties of a drug.

Another recent method for comparing the biologic effects of topical corticosteroids has been to evaluate the inhibitory effects of various compounds on the production of T lymphocyte-derived cytokines. In one recent study purified peripheral blood CD4⁺ cells were stimulated with immobilized anti-CD3 or soluble anti-CD28 antibodies to induce the release of IL-4, IL-5, and IFN- γ (Fig 1).⁵ This study demonstrated that mometasone furoate and fluticasone propionate were equally and highly effective in preventing the release of IL-4 and IL-5 and were substantially more active than the other compounds tested. With use of an assay of T-cell proliferation, English et al⁶ demonstrated that fluticasone propionate was more potent than dexamethasone, beclomethasone dipropionate, and budesonide. Although these data are derived from an in vitro system, they do provide a potentially meaningful way of comparing selective anti-inflammatory effects of glucocorticoid compounds.

Glucocorticoid potencies have been postulated to be most highly related to glucocorticoid receptor binding affinity. A study by Smith and Kreutner⁷ compared the relative binding affinities of several intranasal steroids and determined that the ranked order of binding to the glucocorticoid receptor was, from highest to lowest, mometasone furoate, fluticasone propionate, budesonide, triamcinolone acetonide, and dexamethasone (Fig 2). In that same study mometasone furoate was also found to be the most potent stimulator of glucocorticoid

From the University of California, Los Angeles, and the Allergy Research Foundation, Inc, Los Angeles, Calif.

Supported by an unrestricted educational grant from Schering/Key Pharmaceuticals, Schering Corporation.

Reprint requests: Jonathan Corren, MD, University of California, Los Angeles, Allergy Research Foundation, 11620 Wilshire Blvd, Suite 200, Los Angeles, CA 90025.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/0/101680

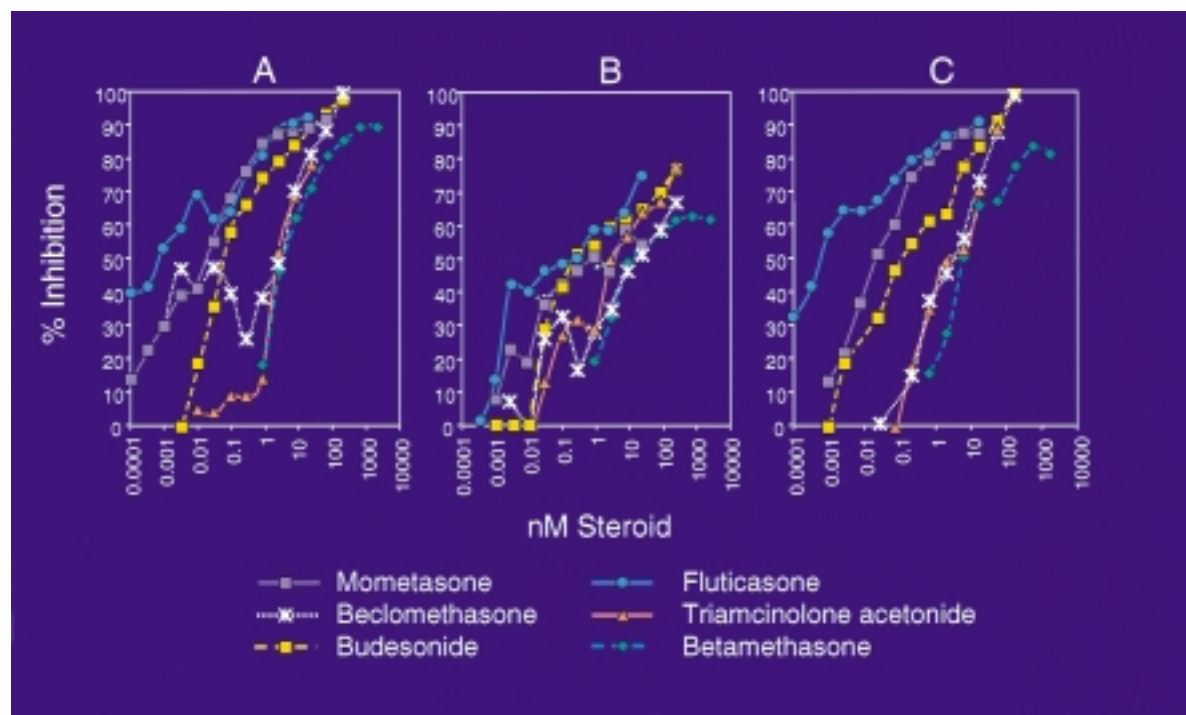


FIG 1. Potency of glucocorticoids as measured by inhibition of IL-5 (A), interferon- γ (B), and IL-4 (C). (Adapted with permission from Umland SP, Narhebe DK, Razac BS, Beavis A, Pinnline KJ, Egan RW, et al. The inhibitory effects of topically active glucocorticoids on IL-4, IL-5, and interferon- γ production by cultured primary CD4⁺ cells. *J Allergy Clin Immunol* 1997;100:511-9.)

receptor-mediated transactivation of gene expression. In another publication, Hogger and Rohdewald⁸ demonstrated that fluticasone propionate had a higher binding affinity than did dexamethasone, budesonide, and beclomethasone-17-monopropionate, the active metabolite of beclomethasone dipropionate. Importantly, the results of these 2 studies reflect the results of in vitro assessments of anti-inflammatory activities.^{5,6}

Lipid solubility

Lipophilicity is an index of the lipid-partitioning potential of glucocorticoid compounds. As such, highly lipophilic agents will demonstrate a higher and faster rate of uptake by the nasal mucous membrane, a higher level of retention within the nasal tissue, and an enhanced ability to reach the glucocorticoid receptor. The ranked order of lipid solubility of available topical intranasal steroids is, from highest to lowest, mometasone furoate, fluticasone propionate, beclomethasone dipropionate, budesonide, triamcinolone acetonide, and flunisolide.⁴

Systemic bioavailability

Systemic bioavailability is the sum of 2 components, including the portion of the drug that is swallowed plus the portion of the drug that is absorbed via the nasal mucosa. Because most of the dose of an intranasal steroid is swallowed, systemic bioavailability is primarily determined by the amount of the drug that is absorbed by the gastrointestinal tract. With the exception of dexamethasone, all the first-generation intranasal steroids

have significant first-pass hepatic metabolism, with oral bioavailabilities ranging between approximately 20% and 50% (Fig 3).^{9,10} In contrast, neither mometasone furoate nor fluticasone propionate are readily absorbed by the gastrointestinal tract, and, subsequently, both have been found to have extremely low oral bioavailabilities (ie, <0.1% and <2%, respectively).¹¹⁻¹³ Systemic bioavailability values of the intranasal steroids are similar to the oral values noted above, and studies of both mometasone furoate and fluticasone propionate have demonstrated extremely low plasma drug levels in the systemic circulation.

CLINICAL PROFILES OF INTRANASAL STEROIDS

Therapeutic efficacy

Intranasal steroids have been compared in a large number of clinical trials in patients with both seasonal and perennial allergic rhinitis. In general, these studies have consisted of 2- to 8-week parallel-group trials of patients with moderately severe rhinitis.

Comparisons of older agents. There have been relatively few trials comparing beclomethasone dipropionate, budesonide, flunisolide, and triamcinolone acetonide. Welsh et al¹⁴ compared beclomethasone dipropionate (168 μ g twice daily) versus flunisolide (100 μ g twice daily) in patients with seasonal allergic rhinitis and found the 2 drugs to be equally effective.

Older agents versus fluticasone propionate. Multip-

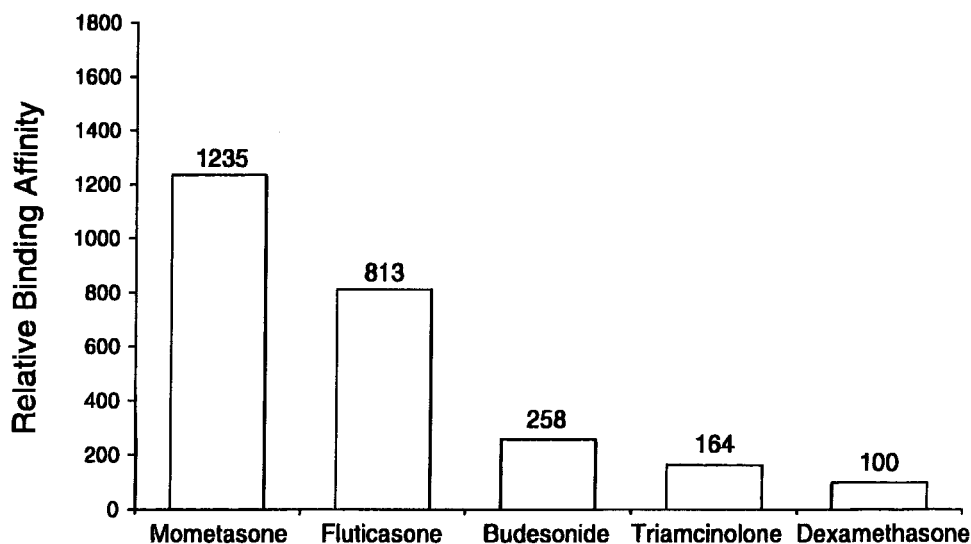


FIG 2. Binding affinities of glucocorticoids for the glucocorticoid receptor. Relative binding affinity is expressed as the reciprocal of the relative amount of test ligand needed to displace 50% of bound [^{3} H] dexamethasone. (Adapted with permission from Smith CL, Kreutner W. In vitro glucocorticoid receptor binding and transcriptional activation by topically active glucocorticoids. *Arzneim-Forsch/Drug Res* 1998;48:956-60.)

studies have compared beclomethasone dipropionate with fluticasone propionate. In a 2-week study of subjects with seasonal allergic rhinitis, beclomethasone dipropionate (168 μ g twice daily) and fluticasone propionate (200 μ g once daily) had comparable efficacy.¹⁵ In patients with perennial allergic rhinitis a 3-month¹⁶ and a 6-month¹⁷ study demonstrated clinical equivalence between beclomethasone dipropionate (168 μ g twice daily) and fluticasone propionate (200 μ g once daily), whereas a 12-month study showed fluticasone propionate (200 μ g once daily) to be substantially superior to beclomethasone dipropionate (200 μ g twice daily).¹⁸

Budesonide and fluticasone propionate have also been compared in a number of trials. In a 6-week study of patients with seasonal allergic rhinitis, budesonide (256 μ g once daily) was more effective in reducing sneezing than fluticasone propionate was (200 μ g once daily).¹⁹ In 2 separate 6-week studies of patients with perennial allergic rhinitis, budesonide (256 μ g once daily) was demonstrated to be more effective than fluticasone propionate (200 μ g once daily),²⁰ whereas another trial found budesonide (200 and 400 μ g once daily) to be as efficacious as fluticasone propionate (200 μ g once daily).²¹

Small et al compared triamcinolone acetonide (220 μ g once daily) with fluticasone propionate (200 μ g once daily) in seasonal rhinitis and noted no significant differences between the 2 treatments.²²

Older agents versus mometasone furoate. In a 4-week²³ and 8-week²⁴ study of patients with seasonal rhinitis, beclomethasone dipropionate (168 μ g twice daily) was found to be equivalent to mometasone furoate (200 μ g once daily). In patients with perennial allergic rhinitis the 2 drugs were again found to be equally effective given in the above dosages.²⁵

Mometasone furoate versus fluticasone propionate. Mandl et al²⁶ compared mometasone furoate (200 μ g once daily) with fluticasone propionate (200 μ g once daily) in patients with seasonal allergic rhinitis and found that the 2 drugs were clinically equivalent.

When all the above studies are considered, there do not appear to be clinically significant differences in efficacy among the available intranasal steroid preparations. This is somewhat surprising given the marked pharmacologic differences among the various agents. It may be that the inflammatory processes occurring in allergic rhinitis are easily inhibited by glucocorticoids of varying potencies and that the pharmacologic advantages of fluticasone propionate and mometasone furoate are not critical in most patients with nasal allergy. Alternatively, clinical trials primarily include patients with moderate symptoms, many of whom are able to remain in a trial for 2 to 4 weeks, taking only a placebo as treatment for their symptoms. To determine whether the newer agents are more effective than the older drugs, it would be necessary to study patients with rhinitis whose symptoms were poorly controlled on one of the older agents.

Onset of action

For many years it was a commonly held belief that intranasal steroids require several days of use to achieve symptom control. This belief existed, in part, because onset of action was considered unimportant in drugs that were to be used regularly for control of chronic symptoms. Subsequently, few clinical studies were designed to accurately determine the onset of action of these medications. Increasingly, however, it has become widely recognized that many patients use intranasal steroids on an as-needed basis only, stopping the drug when symptoms substantially abate. In support of this approach are recent

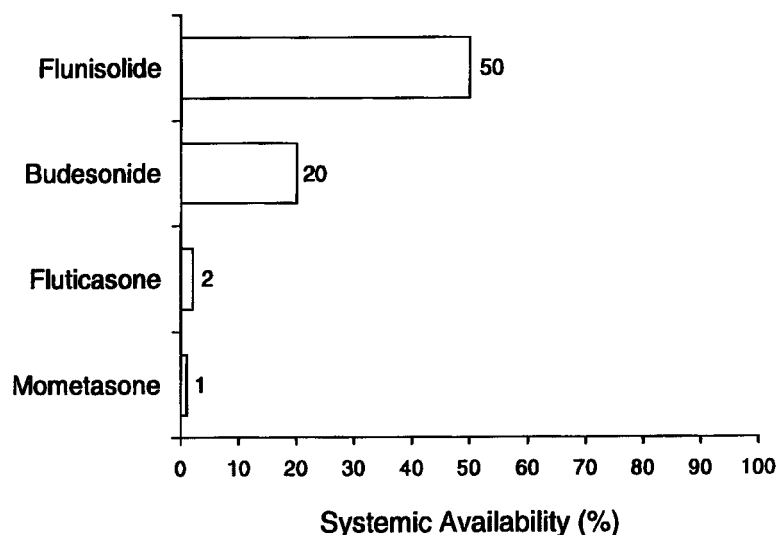


FIG 3. Bioavailability of intranasally administered first- and second-generation intranasal steroids. (Adapted from manufacturers' prescribing information. Bioavailability of intranasal triamcinolone acetonide and beclomethasone are not provided in labeling.)

studies demonstrating that intermittent use of intranasal steroids is moderately effective in many patients.²⁷ Because of this emerging style of use, it has become more important to determine the onset of action of these agents in allergic rhinitis. Historically, package inserts for older intranasal steroids have stated that several days to up to 2 weeks of use are usually required for clinical improvement. Recent clinical studies with budesonide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide have demonstrated clinical improvement within 1 to 2 days of the first dose.^{9-12,28,29} In a placebo-controlled study of mometasone furoate, 28% of patients treated with active therapy had symptom relief within the first 12 hours, in contrast to 13% of patients in the placebo group.³⁰ The median time to symptomatic relief was 36 hours with mometasone furoate and 72 hours with placebo. Future studies comparing the onset of action for all the topical glucocorticoids will be required to definitively show superiority of one agent over another.

Dosing frequency

Clinical trials have demonstrated the efficacy of once-daily dosing with many of the available intranasal steroids, including beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide.^{10-12,28,29} In this regard, there do not appear to be significant advantages of one agent over another.

Adverse effects

Local side effects. Use of intranasal steroids frequently results in symptoms of dryness, stinging, and burning in 5% to 10% of patients, irrespective of the compound or formulation used. Epistaxis is another common local

side effect, occurring in approximately 5% of patients; its incidence has not been shown to increase with use of the newer, more potent agents. Septal perforations have been reported to occur rarely and may best be averted by directing the spray toward the inferior turbinate rather than the septum. Atrophy of the nasal mucosa was once a concern with chronic use of topical steroids, particularly with the introduction of higher-potency compounds. However, long-term histologic studies with mometasone furoate and fluticasone propionate have demonstrated restoration of normal histologic features with no evidence of atrophy or metaplasia after 12 months of therapy in patients with perennial allergic rhinitis.^{31,32} There do not appear to be any increased risks of local side effects with more potent intranasal steroids.

Systemic side effects. As discussed above, all the available intranasal steroids except dexamethasone undergo substantial first-pass hepatic metabolism. As would be expected, systemic bioavailabilities of these drugs are universally low, reducing the risk of systemic exposure to glucocorticoid effects. Although intranasal steroids have a long track record of safety with no reports of serious side effects, the introduction of more potent glucocorticoid compounds to younger patient populations has renewed interest in the potential systemic effects of these medications. Laboratory evaluations of hypothalamic-pituitary-adrenal (HPA) axis function are frequently used to determine the systemic effects of intranasal steroids. As would be expected in patients absorbing extremely small doses of glucocorticoids, there have been no reports of acute adrenal crisis or chronic adrenal insufficiency with intranasal steroids. Therefore, rather than serving as an indicator of the risk of clinical adrenal dysfunction, measures of HPA axis function are of greater interest as biologic markers of systemic glucocorticoid

activity. Evaluations of the HPA axis can be divided into tests that assess basal (eg, morning plasma cortisol, integrated plasma cortisols, urinary cortisol) versus dynamic (ACTH stimulation, insulin tolerance tests) function. Studies that have sought to determine the effects of intranasal steroids on basal index values of HPA axis function have generally shown no significant effects with beclomethasone dipropionate at 200, 336, 400, and 800 μg per day^{33,35}; triamcinolone acetonide at 220 μg per day^{33,34}; fluticasone propionate at 200 μg per day³³; and mometasone furoate at 200 μg per day.³⁴ In one study, budesonide at 200, 400, and 800 μg per day caused significant suppression of urinary cortisol,³⁵ whereas in another study at 200 μg per day it did not.³⁴ Studies with ACTH stimulation have similarly shown no significant effects of intranasal corticosteroids, including beclomethasone dipropionate at 336 μg per day,³⁶ fluticasone propionate at doses of 200 and 400 μg twice daily,³⁷ and triamcinolone acetonide at 220 and 440 μg per day.³⁸ Few data exist regarding HPA axis effects of intranasal steroids in children; one study of children with allergic rhinitis failed to show any significant suppression of ACTH stimulation after the use of triamcinolone acetonide at 220 and 440 μg per day.³⁹ Overall, these data suggest that intranasal steroids have no or minimal effects on the HPA axis, even when given in relatively high doses.

Other investigators have evaluated intranasal steroids with use of techniques that are potentially more sensitive than measures of HPA axis function. Osteocalcin, commonly used as a peripheral blood marker of bone metabolism, was not significantly affected by short-term use of budesonide at 200 μg per day, mometasone furoate at 200 μg per day, or triamcinolone acetonide at 220 μg per day.³⁴ Using another approach, Fokkens et al⁴⁰ quantitated peripheral blood B cells, T cells, and lymphocyte subpopulations as a measure of systemic glucocorticoid activity and were unable to identify any effect with either budesonide or fluticasone propionate at dosages of 200 and 800 μg per day. Knutson et al⁴¹ examined the effects of budesonide and fluticasone propionate on specific gene expression in peripheral blood lymphocytes and noted that both drugs caused a decrease in glucocorticoid receptor messenger RNA and an increase in methallothionein messenger RNA, indicating a significant systemic effect. Although the results of this study suggest an effect of intranasal steroids on systemic immune cell function, the clinical relevance of this finding is uncertain.

Recent observations that inhaled steroids may alter growth velocity in young asthmatic children have prompted similar concerns regarding the chronic use of intranasal steroids.⁴² A 12-month, double-blind, placebo-controlled study of young children with perennial allergic rhinitis demonstrated that beclomethasone dipropionate 168 μg twice daily caused a small (0.9-cm difference) but statistically significant reduction in growth velocity.⁴³ In contrast, a recent 12-month trial of mometasone furoate in young children with perennial rhinitis failed to show any reduction in growth velocity at

dosages of either 100 or 200 μg once daily. Although there have been no studies of intranasal fluticasone propionate on growth rates in children, data extrapolated from trials of inhaled fluticasone propionate, 100 μg twice daily suggest that there are no significant effects.¹¹ Several important questions remain regarding the use of intranasal steroids in children, including (1) which specific agents can significantly affect growth velocity, (2) whether and how quickly growth velocity returns to normal after the medication is stopped, (3) whether ultimate attainment of height is equivalent in children who are treated with these drugs, and (4) whether there is an additive effect with inhaled steroids taken concomitantly for bronchial asthma. Comparative data regarding all the available agents are needed to resolve these issues, and only large, long-term clinical trials will be able to accomplish this.

CONCLUSION

Advances in our understanding of the structural-functional relationships of glucocorticoids have allowed for the development of new compounds with higher potencies and lower oral bioavailabilities. Although it has been difficult to demonstrate differences in symptom control between these agents and older drugs, future studies of patients with more severe rhinitis may reveal clinically relevant differences between intranasal steroids. With respect to safety, preliminary data from young children have demonstrated that beclomethasone dipropionate caused a reduction in growth velocity, whereas mometasone furoate and fluticasone propionate did not. Differences among available agents may be an even more important issue in children with asthma being treated concomitantly with an inhaled steroid. Until more information is available regarding the other available compounds, the new agents may be the most reasonable choices in young children requiring chronic treatment with intranasal steroids.

REFERENCES

1. Mygind N. Glucocorticosteroids and rhinitis. *Allergy* 1993;48:476-90.
2. International Rhinitis Management Working Group. International consensus report on the diagnosis and management of rhinitis. *Allergy* 1994;49(29 Suppl):1-34.
3. McKenzie AW. Percutaneous absorption of steroids. *Arch Dermatol* 1962;86:611-4.
4. Johnson M. Development of fluticasone propionate and comparison with other inhaled corticosteroids. *J Allergy Clin Immunol* 1998;101(Suppl):S434-9.
5. Umland SP, Narhebe DK, Razac BS, Beavis A, Pinnline KJ, Egan RW, et al. The inhibitory effects of topically active glucocorticoids on IL-4, IL-5, and interferon- γ production by cultured primary CD4⁺ cells. *J Allergy Clin Immunol* 1997;100:511-9.
6. English AF, Neate MS, Quint DJ, Sareen M. Biological activities of some corticosteroids used in asthma. *Am J Respir Crit Care Med* 1994;149:A212.
7. Smith CL, Kreutner W. In vitro glucocorticoid receptor binding and transcriptional activation by topically active glucocorticoids. *Arzneim-Forsch/Drug Res* 1998;48:956-60.
8. Hogger P, Rohdewald P. Binding kinetics of fluticasone propionate to the human glucocorticoid receptor. *Steroids* 1994;59:597-602.

9. Nasarel (flunisolide) In: Physicians' Desk Reference. 53rd ed. Montvale (NJ): Medical Economics; 1998. p 955-6.
10. Rhinocort (budesonide). In: Physicians' Desk Reference. 53rd ed. Montvale (NJ): Medical Economics; 1999. p 591-3.
11. Flonase (fluticasone propionate) In: Physicians' Desk Reference. 53rd ed. Montvale (NJ): Medical Economics; 1999. p 591-3.
12. Nasonex (mometasone furoate) In: Physicians' Desk Reference. 53rd ed. Montvale (NJ): Medical Economics; 1999. p 2861-2.
13. Brattsand R, Axelsson BI. New inhaled glucocorticoids. In: Barnes PJ, editor. New drugs for asthma. Vol 2. London: IBC Technical Service; 1992. p 193-208.
14. Welsh PW, Stricker WE, Chu CP, Naessens JM, Reese ME, Reed CE, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;62:125-34.
15. Ratner PH, Paull BR, Findlay SR, Hampel F Jr, Martin B, Kral KM, et al. Fluticasone propionate given once daily is as effective for seasonal allergic rhinitis as beclomethasone dipropionate given twice daily. *J Allergy Clin Immunol* 1992;90:285-91.
16. Scadding GK, Lund VJ, Jacques LA, Richards DH. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and non-allergic perennial rhinitis. *Clin Exp Allergy* 1995;25:737-43.
17. van As A, Bronsky EA, Dockhorn RJ, Grossman J, Lumry W, Meltzer EO, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate. *J Allergy Clin Immunol* 1993;91:1146-54.
18. Haye R, Gomez EG. A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. *Rhinology* 1993;31:169-74.
19. Stern MA, Dahl R, Nielsen LP, Pedersen B, Schrewelius C. A comparison of aqueous suspensions of budesonide nasal spray (128 micrograms and 256 micrograms once daily) and fluticasone propionate nasal spray (200 micrograms once daily) in the treatment of adult patients with seasonal allergic rhinitis. *Am J Rhinol* 1997;11:323-30.
20. Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once-daily treatment of perennial allergic rhinitis. *J Allergy Clin Immunol* 1998;102:902-8.
21. Andersson M, Berglund R, Greiff L, Hammarlund A, Hedbys L, Marcus I, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. *Rhinology* 1995;33:18-21.
22. Small P, Houle PA, Day JH, Briscoe M, Gold M, Brodarec I, et al. A comparison of triamcinolone acetonide nasal aerosol spray and fluticasone propionate aqueous solution spray in the treatment of spring allergic rhinitis. *J Allergy Clin Immunol* 1997;100:592-5.
23. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex™) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 1996;51:569-76.
24. Graft D, Aaronson D, Chervinsky P, Kaiser H, Melamed J, Pedinoff A, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. *J Allergy Clin Immunol* 1996;98:724-31.
25. Drouin M, Yang WH, Bertrand B, Van Cauwenberge, Clement P, Dalby K, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. *Ann Allergy Asthma Immunol* 1996;77:153-60.
26. Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis: 194-079 Study Group. *Ann Allergy Asthma Immunol* 1997;79:237-45.
27. Juniper EF, Guyatt GH, Archer B, Ferrie PJ. Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. *J Allergy Clin Immunol* 1993;92:66-72.
28. Nasacort (triamcinolone acetonide). In: Physicians' Desk Reference. 53rd ed. Montvale (NJ): Medical Economics; 1998. p 2956-9.
29. Vancenase AQ 84 µg (beclomethasone dipropionate, monohydrate). In: Physicians' Desk Reference. 53rd ed. Montvale (NJ): Medical Economics; 1999. p 2890-2.
30. Berkowitz RB, Nolop RB, Mesarina-Wicki BE, C93-184 Study Group. Onset of action of mometasone furoate (Nasonex) nasal spray in seasonal allergic rhinitis [abstract 1790]. *J Allergy Clin Immunol* 1997;99(Suppl):S441.
31. Minshall E, Ghaffar O, Cameron L, O'Brien F, Quinn H, Rowe-Jones J, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. *Otolaryngol Head Neck Surg* 1998;118:648-54.
32. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. *Clin Otolaryngol* 1998;23:69-73.
33. Wilson AM, McFarlane LC, Lipworth BJ. Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic-pituitary-adrenal axis activity. *J Allergy Clin Immunol* 1998;101:470-4.
34. 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.
35. Wihl JA, Andersson KE, Johansson SA. Systemic effects of two nasally administered glucocorticosteroids. *Allergy* 1997;52:620-6.
36. Brannan MD, Herron JM, Reidenberg P, Affrine MB. Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray administered to patients with allergic rhinitis. *Clin Ther* 1995;17:637-47.
37. Vargas R, Dockhorn RJ, Findlay SR, Korenblat PE, Field EA, Kral KM. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol* 1998;102:191-7.
38. Howland WC III, Dockhorn R, Gillman S, Gross GN, Hille D, Simpson B, et al. A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis. *J Allergy Clin Immunol* 1996;98:32-8.
39. Nayak AS, Ellis MH, Gross GN, Mendelson LM, Schenkel EJ, Lanier BQ, et al. The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis. *J Allergy Clin Immunol* 1998;101:157-62.
40. Fokkens WJ, van de Merwe JP, Braat JP, Overbeek SE, Hooijkaas H. The effect of intranasal and inhaled corticosteroids in healthy volunteers on the number of circulating lymphocytes and lymphocyte subsets. *Allergy* 1999;54:158-64.
41. Knutsson U, Stiernä P, Marcus C, Carlstedt-Duke J, Carlström K, Brönnegård M. Effects of intranasal glucocorticoids on endogenous glucocorticoid peripheral and central function. *J Endocrinol* 1995;144:301-10.
42. Simons FE. A comparison of beclomethasone, salmeterol, and placebo in children with asthma: Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med* 1997;337:1659-65.
43. Rachelefsky GS, Chervinsky P, Meltzer EO, Morris JM, Seltzer JM, Skoner DP, et al. An evaluation of the effects of beclomethasone dipropionate aqueous nasal spray (Vancenase AQ [VNS]) on long-term growth in children [abstract]. *J Allergy Clin Immunol* 1998;101(Suppl):S236.