



Efficacy of a steroid nasal spray compared with an antihistamine nasal spray in the treatment of perennial allergic rhinitis

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Allergic rhinitis is a common disease with a lifetime prevalence of 20% among the United States population. The cost of medication alone to manage allergic rhinitis in the United States was estimated to be \$3.1 billion. The two most commonly prescribed classes of medications are antihistamines and topical nasal steroids. The data on comparing the efficacy of a commonly used antihistamine (azelastine hydrochloride) with that of topical steroids, however, are conflicting. Therefore, the reported study was undertaken to determine the efficacy of azelastine with that of a topical nasal steroid (flunisolide) in treating patients for the symptoms of perennial allergic rhinitis. Forty-four subjects were enrolled in a double-blind, placebo-controlled study using Balaam's design. In one group, patients were treated with topical nasal corticosteroids or placebo. In the other group, patients were treated with the antihistamine nasal spray or placebo. Subjective data were collected by the use of questionnaires and a daily diary, which focused on nasal symptoms, sleep, and daytime sleepiness.

The results demonstrated that the topical nasal corticosteroid performed superiorly to the antihistamine nasal spray in improving sleep, daytime sleepiness, sneezing, ocular and nasal pruritus, and nasal congestion. Thus, the topical nasal corticosteroid was found to be more effective than antihistamine nasal spray in reducing symptoms of allergic rhinitis. This study provides further support for the use of topical nasal corticosteroids as first-line treatment for perennial allergic rhinitis.

(Key words: azelastine hydrochloride, antihistamines, allergic rhinitis, flunisolide, corticosteroids, nasal congestion, sleep, fatigue, sleep disorders, sleep disturbances, allergic disease)

Allergic rhinitis is a common disease with a lifetime prevalence of 20% among the population of the United States.¹ The use of antihistamines and topical nasal steroids represents the cornerstones of pharmacologic treatment

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for allergic rhinitis. Topical intranasal corticosteroids inhibit the influx of inflammatory cells and result in a decrease in the number of mast cells, Th2 lymphocytes, and eosinophils.^{2,3} The mechanism of action of antihistamines involves preventing the H₁-receptor-histamine interaction. Azelastine hydrochloride represents a novel antihistamine in this class as a result of its probable anti-inflammatory effects and topical application.⁴

Previous studies have demonstrated the effects of the topical nasal steroid flunisolide and the antihistamine nasal spray azelastine hydrochloride compared with those of placebo in treating perennial allergic rhinitis and its associated

congestion, effect on sleep, and daytime fatigue.^{5,6} Our study was conducted to compare the efficacy of the topical nasal steroid (flunisolide) with the antihistamine (azelastine) nasal spray in the treatment of symptoms associated with perennial allergic rhinitis.

Materials and methods

The investigation was designed to compare two double-blind, placebo-controlled, crossover studies performed at our institution which analyzed the effect of a topical nasal corticosteroid (Nasarel, Dura, San Diego, Calif) versus placebo and an antihistamine nasal spray (Astelin, Wallace Laboratories, Cranbury, NJ) versus placebo. Both studies were randomized using Balaam's design with four groups: AA (active-active), PA (placebo-active), AP (active-placebo), and PP (placebo-placebo).

Twenty patients with perennial allergic rhinitis were selected for the topical nasal corticosteroid study whereas 24 patients with perennial allergic rhinitis were selected for the antihistamine nasal spray study. These patients were selected through a screening process on the basis of certain inclusion and exclusion criteria. The sample size was appropriate to demonstrate a 20% reduction in congestion at a power of 80% and a level of significance of .05.⁷ Advertisement, with institutional review board approval, was used to recruit subjects.

Inclusion criteria included:

- age 18 to 55 years,
- daytime fatigue,
- daytime somnolence,
- nasal congestion,
- perennial allergic rhinitis with a positive skin test response for perennial allergen (wheal diameter ≥ 3 mm), and
- a negative skin test response for seasonal allergens.

Exclusion criteria included:

- seasonal allergies,
- known sleep apnea,
- nasal polyps,
- obesity,
- recent upper respiratory tract infection,

Table 1
Demographics Reflecting Population Characteristics for Study
Comparing a Steroid Nasal Spray (Flunisolide) With an
Antihistamine Nasal Spray (Azelastine Hydrochloride)

Drug and Balaam's design sequence	Mean age, y	Male, No.	Female, No.	Study dropouts, No.
■ Flunisolide				
<input type="checkbox"/> Active-active	37.5	0	5	0
<input type="checkbox"/> Active-placebo	42.0	2	3	1*
<input type="checkbox"/> Placebo-active	33.6	3	2	0
<input type="checkbox"/> Placebo-placebo	42.0	2	3	0
■ Azelastine hydrochloride				
<input type="checkbox"/> Active-active	44.67	1	2	2†
<input type="checkbox"/> Active-placebo	34.2	4	1	2†
<input type="checkbox"/> Placebo-active	33.2	3	2	0
<input type="checkbox"/> Placebo-placebo	31.5	3	3	1‡

* Patient withdrew because of inability to continue receiving the placebo owing to the severity of the symptoms.
† Patients withdrew because of sedation.
‡ Patient withdrew because of relocating out of town.

- deviated septum, and
- asthma or other respiratory diseases.

Only the research treatment was allowed during the study.

Patients were screened by history, physical examination, symptom assessment, and skin testing. Skin testing was done by the prick method (Hollister Steir, Spokane, Wash) with mixed mite, dog, cat, roach, *Alternaria*, *Aspergillus*, *Penicillium*, and 10 seasonal allergens (Hollister Steir, Spokane, Wash). Only patients who met all criteria were enrolled. Each subject was seen every 2 weeks after the initial screening visit for a total of five visits.

During the initial visit, patients were randomly assigned to the treatment regimen that was dictated by the first period of the sequence to which they were designated. Reevaluation was done at weeks 2, 4, 6, and 8. At the third visit, which was during the middle of the 8 weeks, the patients were crossed over to the treatment that was required for the second period of the sequence to which they were assigned. Treatment consisted of two sprays twice daily of placebo (saline solution) or the topical nasal steroid or the antihistamine nasal spray in each nostril.

During the 8 weeks, patients completed a daily diary with questions pertaining to the severity of their nasal

symptoms, sleep, daytime somnolence, and response to the medication. The patients were seen every 2 weeks to ensure compliance with the medications and daily diary. The diary contained 9 questions about the severity of the symptoms (congestion, sneezing, rhinorrhea, itchy nose, irritated eyes, daytime sleepiness, daytime fatigue, quality of sleep, and number of awakenings); 4 questions about the patient's opinion of the improvement of the symptoms caused by the medication (sleep, daytime sleepiness, daytime fatigue, and congestion), and 1 question about the degree of the patient's sleepiness. The questions used were based on previously published diaries to determine the severity of the rhinitis.⁷⁻¹⁰

Questions on congestion, sleep, daytime sleepiness, and fatigue were asked in two different fashions. The first concerned the severity of symptoms, and the second concerned the improvement of symptoms with therapy. Severity of symptoms was rated on a scale that ranged from 0 (none) to 4 (severe). Improvement was rated on a scale that ranged from 0 (none) to 4 (greatly improved). Data were summarized from the 4th and 8th weeks for each subject, which would relate to the end of the first and second period of a sequence. We then took the average of each vari-

able over the 7 days in each week separately so that each patient would have a summary score for each variable of interest for the 4th and 8th weeks. Once the summary scores were calculated, we used the procedure PROC MIXED in SAS to analyze the data with the summary score being the response variable.^{11,12} The differences between the topical nasal and the antihistamine nasal spray in treating patients for allergic rhinitis were determined by comparing the difference between each treatment mean and its corresponding placebo mean (treatment mean-placebo mean) for each measure. In order to account for variation between the two studies, the data were adjusted for age and gender.

Results

Nineteen of the 20 patients who entered the topical steroid study completed the protocol while 19 of the 24 patients who entered the antihistamine nasal spray study completed the protocol. The data from the patients who did not complete the study were excluded from the final analysis. The demographics of the patient population are reflected in *Table 1*. The results, including means, standard errors, and *P* values from testing the difference between the placebo and the topical nasal steroid for each symptom, are outlined in *Tables 2* and *3*. The results of the com-

Table 2
Results in Improvement in Symptoms With Placebo Compared With a Steroid Nasal Spray (Flunisolide) as Evident by Daily Diary*

Symptom	Active treatment estimate (mean±SE)	Placebo estimate (mean±SE)	Difference estimate (mean±SE)	P value
<input type="checkbox"/> Congestion	2.744±0.276	1.611±0.324	1.134±0.334	.01
<input type="checkbox"/> Daytime sleepiness	2.284±0.322	1.494±0.389	0.790±0.400	.08
<input type="checkbox"/> Sleep	2.626±0.303	1.478±0.326	1.148±0.354	.01

*Improvement in sleep and congestion for patients treated with the steroid nasal spray was statistically significant ($P<.05$). Although the mean improvement was greater than with placebo, it did not reach statistical significance.

Table 3
Results of Rhinitis Severity Score Between Placebo and Steroid Nasal Spray (Flunisolide)*

Symptom	Active treatment estimate (mean±SE)	Placebo estimate (mean±SE)	Difference estimate (mean±SE)	P value
<input type="checkbox"/> Rhinorrhea	0.50±0.204	0.70±0.261	-0.200±0.284	.50
<input type="checkbox"/> Congestion	1.050±0.209	1.450±0.298	-0.400±0.234	.13
<input type="checkbox"/> Sneezing	0.575±0.148	0.825±0.160	-0.250±0.175	.19
<input type="checkbox"/> Ocular pruritus	0.675±0.175	0.925±0.186	-0.250±0.211	.27
<input type="checkbox"/> Nasal pruritus	0.738±0.235	0.713±0.219	0.025±0.269	.93

*Improvement in congestion and sneezing for patients treated with the steroid nasal spray was statistically significant ($P<.05$). Improvement in rhinorrhea and ocular and nasal pruritus did not reach statistical significance.

Table 4
Results in Improvement in Symptoms With Placebo Compared With an Antihistamine Nasal Spray (Azelastine Hydrochloride) as Evident by Daily Diary*

Symptom	Active treatment estimate (mean±SE)	Placebo estimate (mean±SE)	Difference estimate (mean±SE)	P value
<input type="checkbox"/> Congestion	2.223±0.317	1.417±0.372	0.806±0.413	.09
<input type="checkbox"/> Daytime sleepiness	2.086±0.311	1.263±0.342	0.823±0.377	.06
<input type="checkbox"/> Sleep	2.215±0.302	1.303±0.333	0.912±0.375	.04

*Improvement in sleep for patients treated with the antihistamine nasal spray was statistically significant ($P<.05$). Improvement in daytime sleepiness and congestion did not reach statistical significance.

Table 5
Results of Rhinitis Severity Score Comparing Placebo With an Antihistamine Nasal Spray (Azelastine Hydrochloride)

Symptom	Active treatment estimate (mean±SE)	Placebo estimate (mean±SE)	Difference estimate (mean±SE)	P value
<input type="checkbox"/> Rhinorrhea	0.408±0.185	0.992±0.158	-0.583±0.222	.03
<input type="checkbox"/> Congestion	1.271±0.329	1.746±0.198	-0.475±0.338	.20
<input type="checkbox"/> Sneezing	0.871±0.256	0.796±0.143	0.075±0.243	.77
<input type="checkbox"/> Ocular pruritus	0.963±0.299	1.004±0.260	-0.042±0.345	.91
<input type="checkbox"/> Nasal pruritus	0.933±0.301	0.933±0.290	0.000±0.356	1.00

*Improvement in rhinorrhea for patients treated with the antihistamine nasal spray was statistically significant ($P<.05$). Improvement in congestion, sneezing, and ocular and nasal pruritus did not reach statistical significance.

parison of the placebo and the antihistamine nasal spray are outlined in *Tables 4 and 5*. The results, including difference of means and 95% confidence interval, in comparing the antihistamine nasal spray with the topical nasal steroid, are outlined in *Tables 6 and 7*.

Although not much disparity exists between the topical nasal steroid and the antihistamine nasal spray for the summary score, the topical nasal steroid showed a greater decrease in severity from the placebo to the treatment than the antihistamine nasal spray for all symptoms except rhinorrhea. For the daily diary, use of the topical nasal steroid resulted in a greater decrease in severity from the treatment to the placebo for all symptoms but daytime sleepiness. Based on the improvement scale data from the daily diary, the topical nasal steroid was superior to antihistamine nasal spray in improving sleep as well as symptoms of daytime sleepiness and congestion.

Discussion

The cost of medications alone to manage allergic rhinitis in 1997 was estimated to be \$3.1 billion.¹ This figure does not include indirect costs such as decreased work productivity from the nearly 3.5 million lost workdays annually.¹³ Of the \$3.1 billion in medication costs, it has been estimated that 77% of this amount was used for prescription pharmaceuticals. The high cost in treating the disease coupled with the high prevalence mandates the importance of studying the different preparations to determine which have the greatest efficacy.

In order to compare the topical nasal steroid and the antihistamine nasal spray with placebo, we chose Balaam's design. Balaam's design results in the tendency for the estimated treatment difference to have less variability than that observed in a parallel design. Smaller variability leads to a smaller sample size as compared with a parallel study. In addition, the repeated-measurements feature of a crossover design eliminates the need for a lengthy run-in or baseline period. However, one disadvantage of the classic 2×2

Table 6 Results of Symptom Improvement as Reflected by Differences Between Means of a Steroid Nasal Spray (Flunisolide) and Placebo (Flunisolide) Versus Means Between an Antihistamine Nasal Spray (Azelastine Hydrochloride) and Placebo as Collected by Daily Diary*		
Symptom improvement	Difference between flunisolide mean and placebo mean	Difference between azelastine mean and placebo mean
<input type="checkbox"/> Sleep	1.359	1.101
<input type="checkbox"/> Daytime sleepiness	1.153	0.893
<input type="checkbox"/> Congestion	1.466	0.998

*Mean improvement in sleep, daytime sleepiness, and congestion was higher for the group treated with the steroid nasal spray than for the group treated with the antihistamine nasal spray.

Table 7 Rhinitis Severity Score Documenting the Difference in Treatment Mean and Placebo Mean for Each Symptom*		
Symptom improvement	Difference between flunisolide mean and placebo mean	Difference between azelastine mean and placebo mean
<input type="checkbox"/> Rhinorrhea	-0.326	-0.583
<input type="checkbox"/> Congestion	-0.477	-0.475
<input type="checkbox"/> Sneezing	-0.372	0.075
<input type="checkbox"/> Pruritic eyes	-0.410	-0.042
<input type="checkbox"/> Pruritic nose/throat	-0.131	0.0

*The more negative the mean difference, the greater the symptom improvement. Thus, patients treated with the antihistamine nasal spray showed greater improvement in rhinorrhea. Patients treated with the steroid nasal spray showed greater improvement in congestion, sneezing, and ocular and nasal pruritus.

crossover design in a placebo-controlled trial is the possibility of unequal carryover effects biasing the treatment difference. A carryover effect refers to the lingering effect of the previous treatment after a subject has crossed over to the other treatment. Balaam's design is a hybrid of a crossover design and a parallel design, whereby the estimated treatment difference is unbiased even in the presence of unequal carryover effects.^{11,12} It was for this reason that we chose to use Balaam's design in our study.

Symptoms reduced by the use of the topical nasal steroid included nasal congestion and rhinorrhea. The topical nasal steroid also improved subjective sleep quality and reduced daytime fatigue. In turn, the antihistamine nasal spray decreased only rhinorrhea and improved sleep quality. Other symptoms were not improved when the antihistamine nasal

spray was compared with placebo.

Azelastine is a nasally administered antihistamine that has been shown to be safe and effective for the treatment of seasonal and perennial allergic rhinitis.^{14,15} As a result of the many mechanisms of action for this antihistamine nasal spray, Storms¹⁶ noted that azelastine should be classified as an anti-inflammatory agent as well as an antihistamine.¹⁶ It blocks the synthesis, release, or target receptors of histamine, platelet activating factor, and acetylcholine.⁴ In addition to acting on many phases of the immediate inflammatory response, azelastine affects late-phase allergic responses by preventing the down regulation of β_2 receptors and through inhibition of leukotrienes.⁴ Other proposed mechanisms include inhibiting the production of interleukins 1 through 5 and tumor necrosis factor,^{17,18} decreasing



Checklist

■ Beclomethasone dipropionate

- Beconase AQ
- Vancenase
- Vancenase AQ
- Vancenase AQ double strength

■ Budesonide

- Rhinocort Aqua
- Rhinocort

■ Flunisolide

- Nasalide
- Nasarel

■ Fluticasone propionate

- Flonase AQ

■ Mometasone furoate monohydrate

- Nasonex

■ Triamcinolone acetonide

- Nasacort
- Nasacort AQ

Figure. Currently available corticosteroid nasal sprays.

eosinophilic accumulation and release of cytotoxic granules at the site of the allergic inflammation,¹⁹ and inhibiting the enzyme leukotriene C4 synthase²⁰ and calcium-mediated activation of 5-lipoxygenase to interfere with leukotriene synthesis.²¹

Adverse effects of azelastine include a distinct bitter taste and sedation.²² The frequency of sedation secondary to azelastine is difficult to ascertain because somnolence can occur secondary to allergic rhinitis.²³ In our study, four patients on azelastine therapy dropped out of the study secondary to sedation. In addition, other patients had an increased degree of sedation early in their treatment with azelastine that waned as its use continued.

Topical nasal steroids are effective in reducing the nasal congestion of patients with allergic rhinitis as a result of decreasing the number of eosinophils, mast cells,

and Th2 lymphocytes.^{2,3} Craig and colleagues⁵ attributed improved sleep with nasal steroids to the reduction of nasal resistance, and consequently, less collapse of the upper airway. The improvement in sleep results in less daytime fatigue as reported in the daily diary of those patients who were treated with nasal steroids. The results of the study are not surprising as Welch²⁴ found nasal steroids are effective in reducing symptoms of at least 75% of patients with allergic rhinitis.

The use of nasal corticosteroids can lead to nasal dryness, crusting, and epistaxis.²⁵ Nasal septal perforation and localized candidiasis are rare adverse effects of nasal corticosteroids. Although the potential for systemic absorption leading to suppression of the hypothalamic-pituitary axis exists, this side effect does not occur unless the normal dose is exceeded.²⁶ Suppression of growth has also been reported, which has led to the US Food and Drug Administration's mandate for pocket inserts warning of the potential of growth suppression.²⁷ During the study, patients randomly assigned to the topical nasal steroid reported no adverse events.

The results of this study demonstrate that a topical nasal steroid is significantly more effective in relieving the symptoms of allergic rhinitis when compared with an antihistamine nasal spray. The degree of improvement may be greater than reported owing to the therapeutic effect of aqueous nasal spray, which was used as the placebo in our study.^{28,29} The proposed mechanism of aqueous saline nasal spray involves its ability to wash away inflammatory mediators, cells, and secretions in the nasal mucosa.²⁹ Meltzer and Schatz²⁸ noted that response rates may exceed 30% with aqueous saline nasal spray. Therefore, aqueous nasal spray possesses a therapeutic effect and is not a true placebo.

Comment

The results of our study demonstrate that the topical nasal steroid administered twice daily to patients with perennial allergic rhinitis is superior to the

antihistamine nasal spray in alleviating allergic rhinitis symptoms. These data lend further support to the use of topical nasal steroids as first-line therapy for patients with allergic rhinitis. It also appears that as nasal symptoms decrease, there is a subjective improvement of sleep and a reduction in daytime somnolence. The topical nasal steroid again was superior to the antihistamine nasal spray in sleep improvement and reduction of daytime fatigue. The greatest effect of the antihistamine nasal spray was in the reduction of rhinorrhea. In summary, patients who have congestion with associated sleep problems and daytime fatigue are best treated with nasal steroids (*Figure*).

References

1. 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.
2. Meltzer EO. Nasal cytological changes following pharmacological intervention. *Allergy* 1995;50:15-20.
3. Baraniuk JN. Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 1997;99:S763-S772.
4. Weiler JM, Meltzer EO, Benson PM, Weiler K, Widlitz MD, Freitag J. A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model. *J Allergy Clin Immunol* 1994;94:972-980.
5. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol* 1998;101:633-637.
6. Golden, S, Lehman EB, Chinchilli VM, Craig TJ. The effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime fatigue in perennial allergic rhinitis. *J Allergy Clin Immunol* 1999;103;S252:Abstract No. 967.
7. Rather 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;90:285-291.
8. Storms W, Bronsky E, Findlay S, Pearlman D, Rosenberg S, Shapiro G, et al. Once daily triamcinolone acetonide nasal spray is effective for treatment of perennial allergic rhinitis. *Ann Allergy* 1991;66:329-334.
9. Tarlo SM, Cockcroft DW, Dolovich J, Hargreave FE. Beclomethasone dipropionate aerosol in perennial rhinitis. *J Allergy Clin Immunol* 1977;59:232-236.
10. Nathan AR, Bronsky EA, Fireman P, Grossman J, LaForce CF, Lemanski RF, et al. Once daily fluticasone propionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis. *Ann Allergy* 1991;67:332-338.
11. Vonesh EF, Chinchilli VM. *Linear and Nonlinear Models for the Analysis of Repeated Measurements*. New York: Marcel Dekker, Inc; 1997;160-165.

12. SAS/STAT Software: changes and enhancements through release 6.11. Cary, NC: SAS Institute Inc; 1996;531-656.
13. *Clinical Courier*. Contemporary issues in the management of allergic disorders: a focus on respiratory manifestations. 1998; vol 16.
14. Ratner PH, Findlay SR, Hampel F Jr, van Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1994;94:818-825.
15. Gastpar H, Dorow P, Aurich R, Petzold U. Investigation of long-term efficacy and tolerability of azelastine nasal spray in the treatment of perennial allergic rhinitis. *Arzneimittelforschung* 1993;43:771-776.
16. Storms W, Pearlman DS, Chervinsky P, Grossman J, Halverson PC, Freitag JJ, et al. Effectiveness of azelastine nasal spray solution in seasonal allergic rhinitis. *Ear Nose Throat J* 1994;73:382-386, 390-394.
17. Konno S, Asano K, Okamoto K, Adachi M. Inhibition of cytokine production from human peripheral blood leukocytes by anti-allergic agents in vitro. *Eur J Pharmacol* 1994;264:265-268.
18. Hamamoto Y, Nagai K, Muto M, Asagami C. Inhibitory effect of azelastine, a potent antiallergic agent, on release of tumor necrosis factor-alpha from activated human peripheral blood mononuclear cells and U937 cells. *Exp Dermatol* 1993;2:231-235.
19. Morita M, Oshima Y, Akutagawa H, Uenoyama Y. Inhibitory effects of azelastine hydrochloride on calcium influx, actin polymerization, and release of eosinophilic cationic protein. *Curr Med Res Opin* 1993;13:163-174.
20. Hamasaki Y, Shafiqeh M, Yamamoto S, Sato R, Zaitu M, Muro E, et al. Inhibition of leukotriene synthesis by azelastine. *Ann Allergy Asthma Immunol* 1996;76:469-475.
21. Nishihira J, Hayakawa T, Suzuki K, Kato K, Ishibashi T. Effect of azelastine on leukotriene synthesis in murine peritoneal cells and on thromboxane synthesis in human platelets. *Int Arch Allergy Appl Immunol* 1989;90:285-290.
22. *Astelín (azelastine hydrochloride) Product Monograph*. Cranbury, NJ: Wallace Laboratories. Division of Carter Wallace, Inc; 1997; AST757:11.
23. Spaeth J, Klimek L, Mosges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. *Allergy* 1996;51:893-906.
24. Welch MJ. Topical nasal steroids for allergic rhinitis. *West J Med* 1993;158:616-617.
25. Mabry RL. Topical pharmacotherapy for allergic rhinitis: new agents. *South Med J* 1992;85:149-154.
26. Mabry RL. Corticosteroids in otolaryngology: nasal aerosols. *Otolaryngol Head Neck Surg* 1989;100:636-637.
27. Littlewood JM, Johnson AW, Edwards PA, Littlewood AE. Growth retardation in asthmatic children treated with inhaled beclomethasone dipropionate. *Lancet* 1988;1:115-116.
28. Meltzer EO, Schatz M. Pharmacotherapy of rhinitis: 1987 and beyond. *Immunol Allergy Clin North Am* 1987;7:57-91.
29. Ratner PH, van Bavel JH, Martin BG, Hampel FC, Howland WC 3rd, Rogenes PR, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract* 1998;47:118-125.