

How do topical nasal corticosteroids improve sleep and daytime somnolence in allergic rhinitis?

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Therapy for rhinitis improves sleep quality and symptoms of daytime sleepiness. This improvement with therapy may be secondary to anti-inflammatory effects, leading to a reduction of inflammatory mediators, or to a mechanical reduction of congestion directly leading to improvement in sleep disturbance. We combined our data from 3 placebo-controlled studies of intranasal corticosteroids in patients with perennial rhinitis to determine whether a correlation between the reduction of congestion and improved sleep and daytime somnolence existed. The pooled data of budesonide, flunisolide, and fluticasone demonstrated significantly decreased nasal congestion, sleep problems, and sleepiness in treated patients. The data demonstrated a correlation between a reduction in nasal congestion and an improvement of sleep ($P < .01$) and daytime somnolence ($P = .01$). Thus, topical intranasal corticosteroids should be used to decrease nasal congestion and to improve sleep and daytime somnolence in patients manifesting these symptoms. (*J Allergy Clin Immunol* 2005;116:1264-6.)

Key words: Rhinitis, sleep, congestion, somnolence, quality of life

Previous articles have focused on sleep and sleepiness in allergic rhinitis (AR).¹⁻¹² A direct correlation between a reduction in congestion and an improvement in daytime somnolence is not easily demonstrated. Similarly, to demonstrate significant objective findings on polysomnography

Abbreviations used

AR: Allergic rhinitis

INCS: Topical intranasal corticosteroid

with treatment has been difficult.^{1,3,8,10,12} Our individual studies on nasal corticosteroids suggested a correlation between reduced nasal congestion and improved sleep and daytime sleepiness; however, small numbers inhibited demonstration of this association. It is our belief that congestion disturbs sleep in a manner similar to true obstructive sleep apnea, and the increase in airflow resistance results in disrupted sleep cycle, including arousals.¹³ Others have proposed that inflammatory mediators may be the main reason for the disturbed sleep and daytime somnolence.⁶ Credence for this position is that cytokines typically seen in atopic diseases have been associated with obstructive sleep apnea syndrome in patients without allergic disease. Additional evidence to support the effects of inflammatory cytokines and other mast cell and T-cell products released during allergic cascade on sleep includes fluctuations of the sleep cycle in association with alterations of IL-4, histamine, bradykinin, and cysteinyl leukotrienes. By compiling our data, it was the intent of this study to determine the extent of correlation between sleep and daytime somnolence and the reduction of congestion with topical intranasal corticosteroid (INCS) therapy. Such a correlation would support the theory that decreasing congestion is key in improving sleep and its associated consequences.

We previously conducted 3 separate but identical studies on intranasal budesonide (128 μ g daily), flunisolide (200 μ g daily), and fluticasone (200 μ g daily). Institutional review board approval and informed consent were obtained for each study. Participants were recruited by advertisement.

Inclusion criteria consisted of age 18 to 65 years with subjective nasal congestion, daytime somnolence and/or fatigue, and positive skin test to perennial allergens (wheal diameter > 3 mm) such as dust mite, dog, cat, roach, feathers, or *Alternaria* (Greer, Lenoir, NC).

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TABLE I. Correlation of the daily diary outcomes on a scale of 0 (not at all) to 4 (greatly) with nasal congestion on a scale of 0 (none) to 4 (severe) for subjects finishing treatment at week 4

Outcome	Visit	Active			Placebo		
		N	Correlation	P value	N	Correlation	P value
Improved sleep	3	42	−0.47	<.01	32	−0.17	.35
Improved daytime sleepiness	3	42	−0.42	.01	32	−0.12	.5

Subjects were excluded if they had a positive skin prick test result to seasonal allergens, or a history of known sleep apnea, asthma, atopic dermatitis, nonallergic rhinitis, nasal polyps, deviated septum, respiratory tract infection within 30 days, use of a nasal steroid or an oral antihistamine within 30 days, excessive use of alcohol, or use of β -blockers, antidepressants, decongestants, oral steroids, or H-2 blockers. Other medications for allergic rhinitis were not permitted during the studies.

Each investigation for budesonide, flunisolide, or fluticasone, respectively, was designed as an 8-week, double-blind, placebo-controlled (saline), hybrid crossover study that incorporated the Balaam design. This design uses 4 treatment arms, 2 parallel and 2 crossover. Thus, there are active-placebo, placebo-active, active-active, and placebo-placebo arms.⁷⁻⁹

Over the 8 weeks, subjects completed 5 visits at weeks 0, 1, 4, 5, and 8. In the first week, all participants received a run-in of nasal saline. At the end of week 1, treatment consisted of 2 sprays, each nostril once daily of placebo (saline), budesonide (AstraZeneca, Wilmington, Del) flunisolide (Dura, San Diego, Calif), or fluticasone (GlaxoSmithKline, Research Triangle, NC). The first treatment period ended at week 4. Subjects then completed a 1-week washout period with nasal saline. The second treatment period involved weeks 6 to 8.

Subjects completed daily symptom diaries based on previously published instruments to determine the severity of rhinitis.⁷ The diary assesses the severity of 8 symptoms (nasal congestion, sneezing, rhinorrhea, nasal pruritus, irritated eyes, daytime sleepiness, daytime fatigue, and sleep problems) on a scale of 0 (none) to 4 (severe). This instrument contains 1 question to determine the degree of sleepiness of the subject (Stanford Sleepiness Scale) on a scale of 1 (feeling active and vital; alert; wide awake) to 6 (almost in reverie; sleep onset soon; losing struggle to remain awake). On a scale of 0 (poor) to 4 (good), the diaries also ask subjects to rate the quality of sleep. The last 4 questions ask how the medication has improved the subject's sleep, daytime sleepiness, daytime fatigue, and nasal congestion on a scale of 0 (not at all) to 4 (greatly).

Subjects also completed a daily sleep measures diary. The first question asks subjects to compare their last night's sleep with their average sleep over the period of the past month on a scale of 1 (worse than average) to 5 (much better than average). A second question asks subjects to compare last night's sleep on a more absolute scale of 1 (extremely poor) to 5 (excellent sleep). Finally, this instrument asks how refreshing and restorative the

subject's sleep was last night on a scale of 1 (not at all restorative) to 5 (very satisfactory). For the variables in the daily diaries and the sleep measures diaries, the average of the last 7 days of each treatment period (ending at weeks 4 and 8) was used to get a single observation for each period.

The number of subjects in each nasal steroid study was estimated to determine a significant improvement in sleep at a power of 80% with a significance level of .05. Each study's data were combined, and the data were analyzed by using a mixed model specific to the Balaam design in SAS, a statistical analysis system, version 8.2 (SAS Institute, Cary, NC). The PROC MIXED fits a variety of mixed-effects linear models to data and allows the use of fitted models to make statistical inferences about data.^{14,15} The models include parameters for the mean active and mean placebo effects, parameters for the active-final treatment and placebo-final treatment carryover effects, nuisance parameters, and study as a blocking factor to remove any unwanted variation that differences between studies might introduce.

Last, the Spearman correlation was used to identify a relationship between decreasing nasal congestion and improved sleep or improved daytime somnolence as recorded in the daily diaries. The correlation was calculated at the end of week 4 within each treatment group.

Each of the 3 INCSs—budesonide, flunisolide, and fluticasone—was individually effective in improving sleep and daytime fatigue and somnolence, suggesting that all INCSs are effective in patients with these symptoms. Polysomnography was performed in the fluticasone study and failed to demonstrate significant changes with therapy. A total of 26 subjects completed the budesonide study, 20 subjects completed the flunisolide study, and 29 subjects completed the fluticasone study. Of the 75 total subjects, 26 were men and 49 women, and the mean age was 41.6. The following numbers of subjects were in each treatment sequence: 19 in active-active, 23 in active-placebo, 16 in placebo-active, and 17 in placebo-placebo.

The subjects on INCS had significantly decreased severity of congestion (1.66 vs 2.05; $P = .01$), significantly decreased sleep problems (1.25 vs 1.69; $P = .01$), and significantly decreased sleepiness on the sleepiness diary (2.89 vs 3.32; $P = .02$) compared with placebo. The symptom daily diary indicated that subjects on active treatment reported significantly improved nasal congestion (1.42 vs 0.86; $P = .01$), significantly improved sleep (1.49 vs 0.88; $P = .01$), and significantly improved daytime somnolence (1.40 vs 0.89; $P = .03$). For the sleep measures data, subjects indicated significantly better sleep compared with absolute (3.40 vs 3.10; $P = .04$). Total

sleep, sleep compared with average, and refreshing and restorative sleep variables improved with active drug but were not statistically significant.

Table I provides the correlation data that examine the relationship between a decrease in nasal congestion with an improvement of sleep and daytime somnolence. For the 42 subjects ending week 4 on active drug, there was a statistically significant negative correlation between a reduction in nasal congestion and an improvement in sleep ($P < .01$) and daytime somnolence ($P = .01$).

Currently, several theories attempt to describe the relationship between AR and daytime somnolence. In one theory, IFN- γ , TNF- α , IL-1 β , IL-4, and IL-10 may contribute to the disturbed sleep in patients with AR.⁶ Others have proposed that nasal obstruction secondary to AR directly leads to obstructive sleep apnea and an increase in microarousals during sleep.^{7-10,12} As a result, patients with AR have daytime somnolence, impaired mood, and poor performance.⁵ On the basis of the latter theory, a reduction in nasal congestion should lead to a decrease in sleep fragmentation caused by microarousals and sleep apnea. Some have demonstrated changes on polysomnography,^{2,3,10,12} but others have been unable to identify significant changes.^{1,8} Even without changes on polysomnography, symptoms of daytime fatigue and poor school performance improve. Nonetheless, topical nasal steroids are effective in reducing the nasal congestion of perennial AR by decreasing the number of mast cells, eosinophils, and T_H2 lymphocytes. It is thus difficult to believe that either the theory of mechanical obstruction or the theory of inflammatory cytokine occurs in isolation and is not interdependent.

Young et al¹¹ studied the relationship of sleep and rhinitis with subjective questionnaires issued to 4927 subjects. Their analysis found that participants with chronic symptoms of rhinitis were significantly more than twice as likely to indicate daytime sleepiness and nonrestorative sleep. Furthermore, their findings suggest that nasal obstruction is a risk factor for sleep-disordered breathing, but their data did not support a linear association between obstruction and severity of sleep-disordered breathing. They raise the possibility that rhinitis, independent of the effect on breathing, may cause cortical arousal and fragmented sleep.¹¹

However, from our data, all topical nasal steroids studied decrease the congestion in perennial AR and are able to improve sleep and sleepiness, a finding supported by others.^{1,3,4} Subjects treated with nasal corticosteroids also note significantly decreased sleep problems, improved sleep, decreased daytime sleepiness and improved daytime somnolence. There was a strong correlation between the reduction of congestion and improvement in these symptoms. Although this does not specifically

exclude an indirect effect of inflammatory mediators on sleep parameters, it strongly suggests that relief of mechanical obstruction plays a predominant role in sleep quality. Further studies to determine the exact mechanisms are needed. Whichever theory is most important is irrelevant to some extent, in that these data nonetheless suggest that nasal steroids are an effective therapy for patients with perennial AR who present with daytime somnolence or poor sleep quality.

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