

Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids

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Background: Allergic rhinitis (AR) is a frequent disease affecting up to 20% of the population. AR causes a hypersensitivity reaction, which results in inflamed nasal mucosa and nasal congestion. Negative pressure generated during inspiration in the nasal airway secondary to nasal congestion may lead to nasal collapse, airway obstruction, and an increased number of sleep microarousals. Sleep disturbances and microarousals can detrimentally affect daytime energy levels, mood, and daytime function. It is unknown whether treatment directed to reduce congestion may reduce these microarousals, sleep problems, and, consequently, associated daytime fatigue.

Objective: We sought to determine whether reducing nasal congestion with nasal steroids will reduce sleep complaints and daytime sleepiness.

Method: We enrolled 20 subjects in a double-blind, placebo-controlled study using Balaam's Design. Patients were treated with topical nasal corticosteroids or placebo. Subjective data were collected by use of a daily diary, which focused on nasal symptoms, sleep, and daytime sleepiness.

Results: The results demonstrated that nasal congestion and subjective sleep improved significantly in the topical corticosteroid-treated subjects but not in the placebo group. Sleepiness improved, but not significantly ($p = 0.08$).

Conclusion: Often, people with perennial allergies may attribute their daytime fatigue to causes such as the side effects of medications, when in fact, the fatigue may be a result of nasal congestion and associated sleep fragmentation. Decreasing nasal congestion with nasal steroids may improve sleep, daytime fatigue, and the quality of life of patients with AR. (J Allergy Clin Immunol 1998;101:633-7.)

Key words: Sleep, fatigue, rhinitis, corticosteroids, sleep disorders, sleep disturbances, nasal congestion, allergic disease

Patients with perennial allergic rhinitis (AR) are often first seen with nasal congestion and unexplained, yet significant, daytime fatigue. Objective data collected by

Abbreviation used

AR: Allergic rhinitis

rhinomanometry, acoustic rhinometry, and nasal peak inspiratory flow have defined this subjective sensation of congestion as significant nasal passage obstruction. Nasal obstruction in healthy young adults can lead to marked interruption of the sleep cycle, with an increase in microarousals and daytime somnolence.^{1,2}

Nasal steroids are one of the few therapeutic interventions available for AR that have a significant effect on nasal obstruction.³⁻¹³ Subjective nasal obstruction is decreased in both seasonal and perennial AR with topical corticosteroids. Objective data collected by acoustic rhinometry, rhinomanometry, and nasal inspiratory peak flow have demonstrated a reduction of congestion and increased nasal patency.^{3, 5, 10, 12, 14} Both placebo-controlled studies and comparative studies with antihistamines confirm the effectiveness of nasal steroids at reducing nasal congestion and increasing nasal patency.

The frequent complaint of daytime sleepiness in patients with AR has until now been attributed to tumor necrosis factor, interferons, and other cytokines.¹⁵ It is our opinion that daytime sleepiness is secondary to poor sleep, which in turn is secondary to nasal congestion. It is the intent of this investigation to determine the effect of topical nasal corticosteroids on AR and the associated congestion, sleep complaints, and daytime somnolence. Our hypotheses are that (1) the congestion that occurs in perennial AR results in sleep disordered breathing causing daytime somnolence and (2) nasal steroid therapy restores nasal patency and improves sleep quality and daytime sleepiness.

METHODS

The investigation was designed as a double-blind, placebo-controlled, crossover study and incorporated Balaam's design, which uses the sequences AP (active-placebo), PA (placebo-active), AA (active-active), and PP (placebo-placebo). In a crossover design each subject serves as his or her own control. Therefore the estimated treatment differences tend to have less variability than that observed in a parallel design. Smaller variability leads to a smaller sample size. Also, the repeated

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TABLE I. Results of symptom changes between placebo and active treatment collected by daily diary

Symptom	Mean active estimate	Standard error	Mean placebo estimate	Standard error	Difference estimate	Standard error	<i>p</i> Value
Stuffy nose	0.795	0.196	1.74	0.185	-0.946	0.192	0.0012
Daytime sleepiness	1.205	0.233	1.366	0.205	-0.162	0.244	0.5267
Daytime fatigue	1.208	0.213	1.481	0.183	-0.273	0.199	0.2069
Sleep problems	0.689	0.225	1.308	0.218	-0.618	0.239	0.0323

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 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.^{16, 17}

Twenty patients with perennial AR were selected through a screening process on the basis of certain inclusion and exclusion criteria. Twenty patients were estimated to be necessary to demonstrate a 20% reduction in congestion at a power of 80% and a level of significance of 0.05.¹¹ Advertisement, with institutional review board approval, was used to recruit subjects. Inclusion criteria included age 18 to 48 years, daytime fatigue, daytime somnolence, nasal congestion, perennial AR with a positive skin test response for perennial allergen (wheal diameter equal to 3 mm or greater), and a negative skin test response for seasonal allergens. Exclusion criteria included seasonal allergies, known sleep apnea, obesity, nasal polyps, recent upper respiratory tract infection, deviated septum, 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 with mite, dog, cat, roach, *Alternaria*, and 10 seasonal allergens. Only patients who met all criteria were enrolled. Five patients were randomly assigned to each sequence. A total of five visits were required. At the initial visit, patients were randomized to the treatment regimen, which was dictated by the first period of the sequence to which they were designated. Reevaluation was done on 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 of twice daily placebo (saline) or topical nasal flunisolide (Nasarel; Dura, San Diego, Calif.) in each nostril.

Over the 8-week period, patients completed a daily diary with questions pertaining to the severity of their nasal symptoms, sleep, daytime somnolence, and response to the medication. Patients were seen every 2 weeks to ensure compliance with the daily diary and medications. The diary contained nine questions about the severity of the symptoms (stuffy nose, sneezing, runny nose, itchy nose, irritated eyes, daytime sleepiness, daytime fatigue, quality of sleep, and number of awakenings), four questions about the patient's opinion of the improvement of the symptoms caused by the medication (sleep, daytime sleepiness, daytime fatigue, and stuffy nose), and one question about the degree of sleepiness of the patient. The questions used were

based on previously published diaries to determine the severity of rhinitis,^{7, 8, 11, 13} with additional questions added to assess the degree of daytime sleepiness and sleep quality. 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 symptom improvement 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). We analyzed four of the questions regarding symptoms (Table I) and three of the questions about improvement of the symptoms caused by the treatment (Table II). We focused on the fourth and eighth weeks of data 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 variable over the 7 days in each week separately so that each patient would have a summary score for each variable of interest for the fourth and eighth 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.^{16, 17}

RESULTS

Nineteen of the 20 patients who entered the study completed the protocol. Two patients who were randomized to active therapy first and later crossed over to placebo were unable to continue receiving the placebo because of the severity of their symptoms. One patient left the study, and the other was continued but switched to open-label therapy. The latter patient's data were analyzed in the group to which he was randomized (placebo) because the blind was not removed until completion of the study. The results, including means, standard errors, and *p* values from testing the difference between the placebo and active treatment groups for each symptom, are outlined in Tables I and II.

Although the symptoms, daytime fatigue and daytime sleepiness, were not significantly different between groups, there was a significant reduction in nasal stuffiness (*p* = 0.0012) and sleep problems (*p* = 0.032) as noted in Table I. Improvement with treatment ratings were statistically significant at *p* levels of 0.05 for sleep (*p* = 0.0119) and stuffy nose (*p* = 0.0095), but again not for daytime sleepiness (*p* = 0.08). Because the differences between the actively treated group and placebo group are less than 0.05, we can conclude that the patients showed a statistically significant reduction in the severity of symptoms of nasal congestion and sleep problems and improvement of the same symptoms (con-

TABLE II. Results in improvement in symptoms with placebo compared with active treatment as evident by daily diary

Symptom	Mean active estimate	Standard error	Mean placebo estimate	Standard error	Difference estimate	Standard error	p Value
Sleep	2.626	0.303	1.478	0.326	1.148	0.354	0.0119
Daytime sleepiness	2.284	0.322	1.494	0.389	0.790	0.400	0.0838
Stuffy nose	2.744	0.276	1.611	0.324	1.134	0.334	0.0095

gestion and sleep) caused by the use of the active treatment.

In the case of the improvement in ratings for daytime sleepiness, the mean for the active treatment was higher than the mean for the placebo with a *p* value of 0.0838. Although this approached significance, we were unable to demonstrate a reduction of daytime sleepiness with the number of subjects recruited. Similarly, the symptoms of daytime fatigue and daytime sleepiness were reduced in the treated subjects, but not significantly.

DISCUSSION

Allergic rhinitis is the most common allergic disease in the United States, with an incidence of approximately 15% to 20% in North America.¹⁸ Allergic rhinitis is characterized by an IgE-mediated nasal response to allergens resulting in activation of mast cells, release of chemical mediators, and the influx of inflammatory cells, especially eosinophils. It is this inflammation that gives rise to the congestion that frequently complicates perennial AR. Somewhere between 40% and 65% of patients with AR will experience congestion.¹⁹ Another frequent symptom in many patients with AR is daytime sleepiness or somnolence. The somnolence associated with AR is thought to be due to lymphokines such as γ -interferon and cytokines such as tumor necrosis factor and IL-1, which are released from mast cells.²⁰ Our results and the following discussion, however, suggests the possibility that daytime sleepiness originates from a nocturnal disturbance.

The 14 patients with AR studied by Lavie et al.¹ all had multiple microarousals from sleep. One-third of the studied patients complained of daytime sleepiness. Additionally, McNicholas et al.²¹ have demonstrated that the increase of nasal resistance associated with nasal obstruction from ragweed-induced rhinitis can lead to significantly increased numbers of obstructive sleep apneas, increased duration of apneas, and an increase in arousals in patients not preselected on the basis of sleepiness. His selection criteria included patients with nasal obstruction and AR but not daytime sleepiness. Despite this, four of the 10 patients studied complained of daytime sleepiness. Similar data from our laboratory showed an increased number of apneas and sleep arousals and a reduction in deep sleep with mechanical obstruction of the nose, a condition not unlike AR.²² The outcome of fragmented sleep is fatigue, daytime

somnolence, and impaired mood,²³ all of which can impinge upon the quality of life of a patient with rhinitis.

Others have demonstrated that sleep problems, which may be occult, and daytime fatigue are common among those with AR.²⁴ A small change in the patency of the nasal airway has a significant effect on breathing, which may produce episodes of apnea, hypopnea, arousals, and/or snoring.^{21, 25, 26} Even what appears to be a minor degree of sleep disruption can induce daytime somnolence. This is often expressed as fatigue. This fatigue can be very disruptive to life and, as demonstrated in a recent manuscript by Vuurman et al.,²⁰ can lead to poor school performance, which is amplified by sedating antihistamines such as diphenhydramine.

The mechanism of sleep apnea appears to be collapse of the airway. During the inspiratory phase of the respiratory cycle, increased effort is needed to inhale through the nose as airflow decreases. This creates negative pressure, which causes collapse of the nasal passage. It is the collapse of the airway that leads to obstruction and microarousals. As microarousals increase, sleep becomes fragmented and eventually leads to unsatisfactory sleep. Even with one night of fragmented sleep, daytime wakefulness, mood, and alertness are compromised.^{23, 27, 28} Nonvisible sleep fragmentation, produced by repetitive tones during slow-wave sleep, did not cause a visible change in electroencephalography, but did increase systolic blood pressure by 4 mmHg or heart rate by at least 4 beats/min. This change correlated with daytime fatigue in 12 nonobese adult subjects. After only one night of fragmented sleep, the subjects had increased daytime sleepiness as reported on the Multiple Sleep Latency Test and Maintenance of Wakefulness Test.²³ Thus it appears that sleep disruption, even without sleep loss, can cause daytime somnolence.²⁸⁻³⁰ The most serious consequences of daytime somnolence is the increased risk of accidents and poor performance.

If the nasal congestion can be reduced, then the microarousals and associated symptoms of daytime fatigue may improve. The most appropriate therapy in a patient with AR and significant congestion with poor sleep and daytime symptoms would be an intervention that increases nasal air flow, reduces nasal resistance, is nonsedating, and does not disturb sleep. Topical nasal steroids meet all four of these criteria.

Treatment with nasal steroids improves nasal airflow

and reduces congestion with few side effects.³⁻¹³ Congestion is reduced by the antiinflammatory effect of topical corticosteroids, which decrease the number of mast cells, T_{H2} lymphocytes and eosinophils.^{9, 15} The ability of nasal steroids to reduce resistance in the nose should lead to less collapse of the upper airway, less obstruction, and consequently less sleep disturbance. Improved sleep is expected to reduce associated daytime fatigue and somnolence. Our study supports these hypotheses. Our subjects, who were recruited with preexisting congestion, sleep problems, and daytime sleepiness, had a reduction in congestion and improvement of subjective sleep when treated with nasal steroids. We would have expected a statistical improvement in daytime sleepiness if we increased the number of subjects we enrolled. The two patients that were initially in the actively treated group but dropped out after crossover into the placebo group may have influenced our ability to demonstrate a statistical improvement in daytime sleepiness with nasal steroids. This is especially relevant because data from one of the two patients were analyzed as if he continued in the placebo arm.

Recent data on the prevalence of sleep disturbance and daytime sleepiness in subjects with asthma support our hypotheses that nasal congestion and not cytokines secondary to inflammation are responsible for daytime sleepiness.³¹ Although asthma, an inflammatory disease, is associated with decreased sleep quality and daytime sleepiness, it is the concurrent rhinitis that appears to be the key factor in the sleep impairment and daytime sleepiness that accompany asthma. If inflammation and associated cytokines, and not nasal congestion, accounted for poor sleep and daytime sleepiness, it would be expected that asthma without rhinitis would impair both.³¹

In at least 75% of patients, nasal steroids are an effective method of reducing symptoms.¹⁴ Nasal steroids are recommended as the first-line medical therapy in adults with AR with nasal congestion.^{32, 33} Our work suggests it is also the drug of choice for those with perennial AR and sleep problems and possibly daytime sleepiness. Similarly, in seasonal AR the regular use of nasal steroids during the pollen season improves sleep, nasal symptoms, and quality of life.³⁴ A larger study with collection of objective evidence on sleep quality and daytime sleepiness would help in confirming our findings.

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