

Original article

Efficacy of the topical nasal steroid budesonide on improving sleep and daytime somnolence in patients with perennial allergic rhinitis

Background: Improving quality of life is considered to be a major endpoint and motivation for clinical intervention in patients with perennial allergic rhinitis (PAR). In addition to classical symptoms of congestion, pruritus, and rhinorrhea, patients will often complain of not being able to sleep well at night and of feeling fatigued during the day. Like sleep apnea, PAR has also been shown to cause sleep disturbance and consequently worsen daytime fatigue and somnolence.

Hypothesis: It is proposed that by decreasing nasal obstruction due to allergic rhinitis by treating with the topical steroid budesonide, symptoms of daytime fatigue and somnolence can be improved.

Methods: Twenty-two subjects were enrolled in a double-blind, placebo-controlled, crossover study using Baalam's design. Patients were treated with either budesonide 128 µg/day or placebo. Subjective data include the Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, Rhino-conjunctivitis Quality of Life Questionnaire, and a daily diary recording nasal symptoms, sleep problems, and daytime fatigue.

Results: The results illustrated that the topical nasal corticosteroid significantly improved daytime fatigue ($P = 0.03$), somnolence ($P = 0.02$), and quality of sleep ($P = 0.05$) compared to placebo in patients suffering from PAR.

Summary: Budesonide is able to improve congestion, sleep, and daytime somnolence.

**K. Hughes¹, C. Glass¹, M. Ripchinski¹,
F. Gurevich¹, T. E. Weaver²,
E. Lehman³, L. H. Fisher⁴, T. J. Craig⁵**

¹College of Medicine, Hershey Medical Center, Hershey; ²University of Pennsylvania School of Nursing, Philadelphia; ³Department of Health Evaluation Sciences; ⁴Department of Internal Medicine, Hershey Medical Center; ⁵Department of Medicine, Penn State University, Hershey, PA, USA

Key words: allergic disease; allergic rhinitis; budesonide; fatigue; nasal congestion; sleep disordered breathing; sleep disturbance; somnolence; topical corticosteroids.

Timothy J. Craig
Division of Pulmonary, Allergy, and Critical Care
Department of Medicine, Penn State University
500 University Drive, PO Box 850
Hershey, PA 17033,
USA

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The importance of perennial allergic rhinitis (PAR) is underscored by its prevalence of 10–20% among the United States population and the morbidity it inflicts upon those with the diagnosis (1, 2). Allergic rhinitis strongly impacts the quality of life of those who live with it (3–8). In addition to classical symptoms of congestion, pruritus, and rhinorrhea, patients will often complain of not being able to sleep well at night and of feeling sleepy and fatigued during the day (1, 9). A classical hypothesis holds that feelings of excessive fatigue and malaise associated with allergic rhinitis are promoted by increased concentrations of inflammatory mediators such as tumor necrosis factor (TNF)- α interferon (IFN)- γ , and other cytokines acting on the hypothalamus (1, 10).

Abbreviations: BUD, budesonide; ESS, Epworth Sleepiness Scale; FOSQ, functional outcome of sleep questionnaire; IFN, interferon; MID, minimal important difference; OSA, obstructive sleep apnea; PAR, perennial allergic rhinitis; RQOLQ, rhino-conjunctivitis quality of life questionnaire; SSS, Stanford Sleepiness Scale.

Alternatively, data exist supporting that nasal congestion in PAR causes sleep disordered breathing leading to daytime hypersomnolence and fatigue (2, 7, 11).

Nasal obstruction is emerging as an accepted etiologic factor for sleep-disordered breathing (12, 13). Studies have shown that chronic nighttime rhinitis is a risk factor for sleep-disordered breathing resulting in an increase in chronic excessive daytime sleepiness (11). One of the major complaints of patients with PAR is nasal congestion secondary to inflammation of the nasal mucosa (9). Objective data has been collected by nasal peak inspiratory flow, acoustic rhinometry, and rhinomanometry and has shown the sensation of congestion to be a consequence of significant nasal passage obstruction (14). Furthermore, the symptoms of AR seem to follow a temporal pattern. Most patients report that peak symptom severity occurs in the morning or at night while in bed (1, 9).

Sleepiness, fatigue, irritability, and personality change have all been ascribed to sleep fragmentation associated

with upper airway closure in obstructive sleep apnea (OSA) (15–18). In addition to the well-known pharyngeal collapse of OSA, an increasing body of evidence supports the role of nasal obstruction as a determinant in sleep disturbance and daytime fatigue (19, 20). Shepard and Burger (21) showed that limiting nasal ventilation may significantly increase the frequency of sleep-disordered breathing in OSA. Nasal obstruction in patients with OSA has been shown to increase apneic episodes by a factor of up to 12 (12, 21). Moreover, artificial obstruction of the nasal passage in otherwise healthy individuals increases the frequency of sleep-disordered breathing events including apneas and hypopneas (12, 13).

Many different modalities have been employed to treat AR including nasal steroids, systemic steroids, antihistamines, cromolyn solutions, and others. Topical corticosteroid aerosols, a common treatment, have been shown to give greater symptom relief compared to other treatments, especially with respect to nasal congestion (9, 22–29). Intranasal corticosteroids inhibit the influx of inflammatory cells and result in a decrease in the number of mast cells, Th2 lymphocytes, and eosinophils (29) thereby down-regulating the inflammatory cascade of AR.

Budesonide (BUD), a potent and effective nasal steroid, controls the symptoms of AR without significant side effects at the dose used in this study (28). BUD effectively alters the molecular milieu following exposure to an allergen load (28, 29). However, no study has shown BUD to have a significant impact on subjective feelings of fatigue or somnolence. Since data support nasal obstruction as the cause of hypersomnolence and daytime fatigue, our hypothesis posits that subjective reports of sleepiness and fatigue would improve after relieving nasal congestion with BUD.

Methods

Subjects

The study was conducted with the approval from the institutional review board and informed consent was obtained from all participants. Advertisement was used to recruit subjects. Twenty-two subjects with PAR were selected through a screening process based on inclusion and exclusion criteria. Inclusion criteria included age 18–65 years, significant nasal congestion, daytime somnolence, fatigue, and PAR 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, atopic disease other than AR such as asthma or atopic dermatitis, nonallergic rhinitis, nasal polyps, deviated septum, recent respiratory tract infection, recent use of oral or nasal steroids, and the use of medications known to affect sleep, rhinitis, or level of alertness. Only the research treatment was allowed during the study. Subjects were screened by history, physical examination including ENT exam, symptom assessment, and skin testing. Skin prick testing was performed with dust mite, dog, cat, roach, feathers, *Alternaria*, and five seasonal allergens. Only patients who fulfilled the required criteria were enrolled.

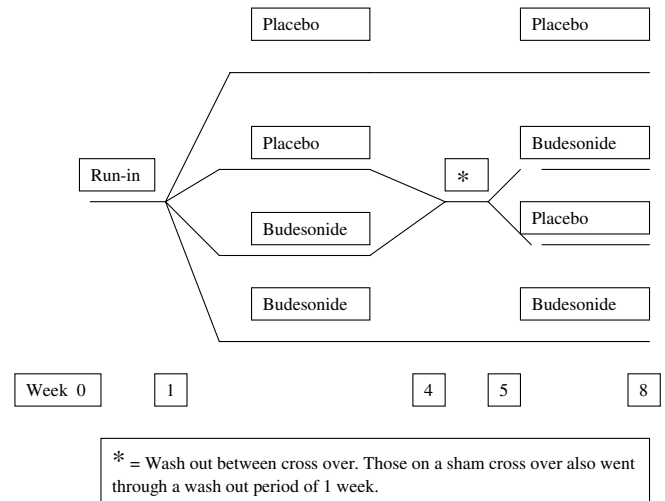


Figure 1. Diagram of the research study using Balaam's design.

Study design

The investigation was designed as a double-blind, placebo-controlled, crossover study that incorporated Balaam's design (Fig. 1) which uses four sequences: active–placebo (AP), placebo–active (PA), active–active (AA), or placebo–placebo (PP). A crossover design allows each subject to serve as his or her own control. This decreases the variability in the estimated treatment differences thereby increasing the power of the study compared to a parallel design. Furthermore, a smaller sample size can show a statistical significance. 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. 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.

The duration of the study was 8 weeks with five required visits. The study was completed during the months of May–September with all patients completing the study during this time period. The first week was devoted to a run-in period where all subjects received a standard nasal saline solution. Randomization to one of the four treatment arms occurred at the beginning of week 2. Treatment consisted of two sprays, each nostril, once daily of either placebo (saline) or topical aqueous nasal BUD (128 µg/day) (Rhinocort; AstraZeneca, Wilmington, DE). Baseline questionnaires and other data were collected at this time. Subjects were seen on weeks 0, 1, 4, 5, and 8 where diaries were collected and compliance was ensured. A 1-week washout period was interposed between the two treatment phases. Throughout the 8-week study period, subjects completed a daily diary commenting on their nasal symptoms, sleep, daytime somnolence, and response to the medication. During visits at weeks 1, 4, 5, and 8 they also completed subjective instruments selected for possible sensitivity to changes in quality of life, somnolence, and fatigue including Juniper's Rhino-conjunctivitis Quality of Life Questionnaire (RQOLQ) and the Functional Outcome of Sleep Questionnaire (FOSQ). This provided a baseline subjective report before each treatment phase, and reports at the end of each active treatment phase. The daily diary contains nine questions pertaining to 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), one question about the quality of the previous night's sleep, and about the degree of sleepiness of the patient (Stanford Sleepiness Scale or SSS). The questions used were based on previously published diaries to determine the severity of rhinitis (2), with additional questions added to assess the degree of somnolence (Epworth Sleepiness Scale or ESS), sleep duration, number of naps taken, and sleep quality. Symptom severity was rated on a scale ranging from 0 (none) to 4 (severe). Improvement was rated on a scale that ranged from 0 (none) to 4 (greatly improved).

The RQOLQ consists of seven sections devoted to: 1 – the impact of allergy symptoms on the subject's three most important activities; 2 – difficulty sleeping secondary to symptoms; 3 – other symptoms related to allergies (fatigue, thirst, tiredness, etc.); 4 – practical problems such as the inconvenience of handkerchiefs or repeated nose blowing; 5 – nasal symptoms; 6 – eye symptoms; and 7 – emotional impact including frustration, impatience, and irritability. The RQOLQ is scored on a 6-point scale with a lower score indicating better quality of life.

FOSQ is a tool that was designed to assess the impact of sleep disorders on multiple activities of daily living including activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome. This questionnaire reliably detects differences between normal individuals and those being treated for a sleep disorder (30). Answers to the 30 questions range from 4 (no problem) to 1 (extreme problem).

Statistical methods

All data were summarized, scored, and analyzed using a mixed model specific to Balaam's design in SAS, a statistical analysis system (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 (31, 32). The data for the diary, SSS, ESS, and the sleep measures were recorded daily. For these variables, the average of the last 7 days of each treatment period and the last 3 days of the run-in period were used to get a single observation for each period. A difference was then calculated between treatment period 1 and the run-in period, and treatment period 2 and the run-in period, and then analyzed to compare baseline to treatment differences between the placebo and BUD groups. Statistical significance was determined at $P = 0.05$.

Results

Twenty-two subjects completed the study (Table 1). From the daily diary data as shown in Fig. 2, the active treatment group experienced a significant decrease in daytime sleepiness when compared to placebo (-0.66 vs. 0.01 , $P = 0.02$). Treatment with BUD significantly reduced symptoms of daytime fatigue (-0.49 vs. 0.25 ,

$P = 0.03$). Active treatment also led to a significant decline in sleep problems (-0.56 vs. 0.03 , $P = 0.05$). A marginally significant decrease in severity of nasal congestion symptoms occurred with active treatment (-0.66 vs. 0.02 , $P = 0.08$). None of the remaining diary variables demonstrated statistical significance. However, all showed a greater decrease in severity or improvement in subjects on active treatment vs placebo.

As demonstrated in Table 2, the ESS data showed a significant difference in total score between active and placebo treatment groups. Subjects treated with BUD were far less likely to fall asleep during normal daily activities than those treated with placebo (-2.69 vs. 1.16 , $P = 0.02$). Treatment with nasal steroid or placebo showed no statistically significant difference in hours slept or sleep arousals. Although showing a difference towards improvement in the actively treated subjects, the SSS data did not achieve significance as shown in Table 2.

Despite the lack of statistically significant data using the FOSQ found in Fig. 3, all indices showed a more positive impact for subjects on active treatment. The sleep measures data in Fig. 4 revealed that sleep was significantly more refreshing and restorative for the active treatment group (0.21 vs. -0.48 , $P = 0.01$). Subjects on active treatment showed a marginally significant improvement in their quality of sleep when compared with their usual, overall sleep patterns (0.25 vs. -0.31 , $P = 0.06$).

The RQOLQ data failed to demonstrate statistically significant differences between active treatment and placebo. However, with the exception of 'difficulty falling

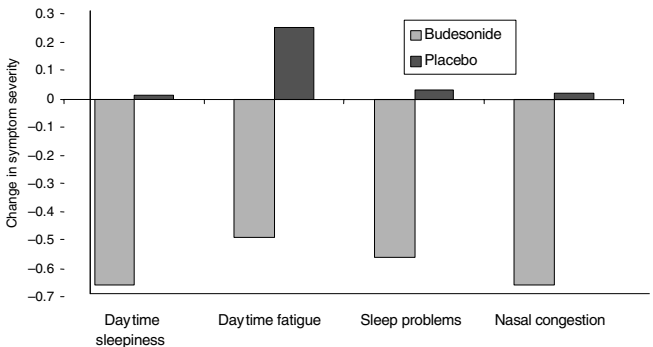


Figure 2. Severity of symptoms decreases in the BUD group when compared to placebo with respect to daytime sleepiness ($P = 0.02$), daytime fatigue ($P = 0.03$), sleep problems ($P = 0.05$), and nasal congestion ($P = 0.08$). Scale: 0(none) to 4(severe).

Table 1. Mean age and gender distribution for the four treatment arms

Balaam's design sequence	Mean age (years)	Number of males	Number of females
Active-active	41.5	2	4
Active-placebo	47.9	2	6
Placebo-active	53.8	2	2
Placebo-placebo	44.3	3	1
Total	46.5	9	13

Table 2. Epworth Sleepiness Scale and Stanford Sleepiness Scale

	Budesonide	Placebo	Difference of the means	Standard of error	P-value
ESS*	-2.69	1.16	-3.85	1.45	0.02
SSS†	0.05	-0.35	0.4	0.31	0.22

* Scale: 0 (not likely to fall asleep) to 24 (very likely to fall asleep).

† Scale: 0 (wide awake) to 7 (sleep onset soon).

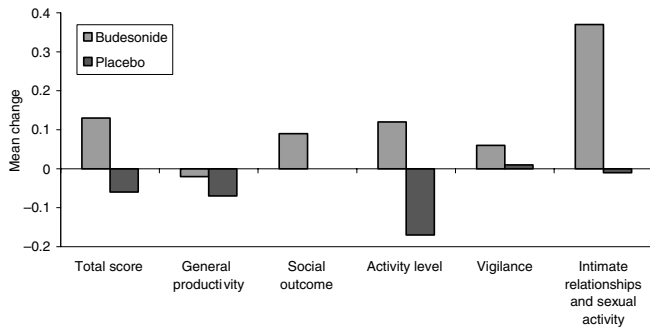


Figure 3. Mean change in score from baseline questionnaire. Improvement was noted in the BUD group compared to placebo: total, $P = 0.27$; productivity, $P = 0.72$; social, $P = 0.74$; activity, $P = 0.17$; vigilance, $P = 0.84$; intimacy, $P = 0.11$. Scale: 1 (extremely difficult) to 4 (no difficulty).

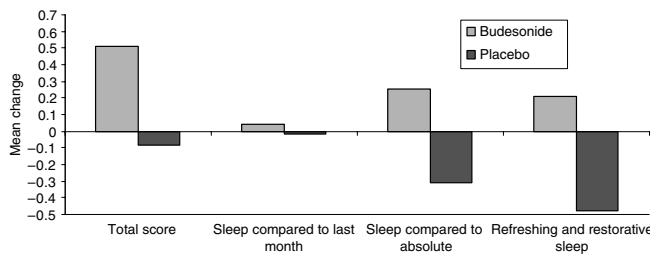


Figure 4. Mean change in score from baseline questionnaire. Improvement was seen in the BUD group while symptoms worsened in the placebo group: total, $P = 0.07$; last month, $P = 0.82$; absolute, $P = 0.06$; refreshing and restorative, $P = 0.01$. ¹ Scale: 1 (much worse than average) to 5 (much better than average). ² Scale: 1 (extremely poor) to 5 (excellent sleep). ³ Scale: 1 (not at all restorative) to 5 (very satisfactory).

asleep', 'wake up at night', and 'eye symptoms average', patients on active treatment were relatively less troubled by the listed variables in Table 3 compared with those on placebo.

Table 3. Rhino-conjunctivitis Quality of Life Questionnaire

	Budesonide	Placebo	Difference of the means	Standard of error	P-value
QOL average*	-0.58	-0.39	-0.19	0.43	0.67
Activities average*	-0.75	-0.42	-0.33	0.48	0.51
Sleep average*	-0.10	0.00	-0.10	0.42	0.81
Difficulty falling asleep*	-0.01	-0.20	0.19	0.45	0.68
Wake up at night*	0.11	-0.01	0.13	0.51	0.81
Poor sleep*	-0.41	0.20	-0.61	0.5	0.24
Non-eye/nose symptoms average*	-0.43	-0.03	-0.40	0.39	0.32
Fatigue*	-0.47	0.39	-0.86	0.54	0.13
Practical problems average*	-0.62	-0.58	-0.04	0.53	0.95
Nasal symptoms average*	-0.75	-0.53	-0.22	0.52	0.67
Eye symptoms average*	-0.46	-0.72	0.26	0.57	0.65
Emotional symptoms average†	-0.95	-0.47	-0.48	0.58	0.41

* Scale: 0 (not troubled) to 6 (extremely troubled).

† Scale: 0 (none of the time) to 6 (all of the time).

Discussion

The nasal pathway, preferred during sleep, accounts for half of the total respiratory system resistance (11, 20, 21). Therefore, nasal congestion increases the work of breathing. This leads to decreased intraluminal pressures and collapse of the soft tissues of the nasal cavity (11, 33). Upon nasal pathway occlusion, mouth breathing ensues. In the supine position, mouth breathing significantly increases the work of breathing and may trigger nasal-pulmonary reflexes leading to increased peripheral pulmonary resistance and alveolar hypoventilation (20). It is thought that during periods of nasal obstruction, mechanoreceptors present in the naso-, oro- and hypopharynx as well as the respiratory muscles, chest wall, and airway sense an increase in negative pressure and trigger arousal resulting in sleep fragmentation (34).

Nasal obstruction has a clinically significant impact on breathing during sleep and affects daytime performance. Millman et al. (13) showed that nasal occlusion of healthy adults leads to an increase of sleep fragmentation. In a similar study, Suratt et al. (12) demonstrated that obstruction of nasal passages produced obstructive apnea. Sleep-disordered breathing leading to sleep fragmentation causes significant disruption in daily function and wakefulness. With disrupted sleep architecture, slow wave and REM sleep is disturbed (35). Despite normal amounts of sleep, sleep fragmentation results in non-restorative sleep leaving one fatigued and hypersomnolent during the day (35–38).

Nasal congestion in association with AR has also been associated with episodes of periodic breathing, hypopneic and hyperpneic episodes, and microarousals measured by electroencephalographic monitoring (7, 35). In a study employing over 900 participants, Young et al. (11) demonstrated that subjective excessive daytime sleepiness and nonrestorative sleep correlated statistically with increasingly severe nocturnal symptoms of rhinitis. Other studies identified a relationship among AR, cognitive impairments, and learning difficulties in children (6, 8).

BUD, a potent and effective nasal steroid, controlled the symptoms of AR without significant side effects at the dose used in this study (25, 28). This study demonstrated that treatment of perennial AR with topical BUD was statistically effective in decreasing subjective daytime sleepiness and fatigue, decreasing sleep problems, and improving the quality of sleep.

Data from the daily dairies showed that patients on active treatment noted statistically decreased daytime sleepiness and fatigue with a difference in the means of 0.67 and 0.74, respectively ($P = 0.02$ and 0.03 , respectively). While the BUD group reported an improvement in symptoms, the placebo group actually reported an increase in fatigue and somnolence. A similar trend was seen with reports of subjective sleep problems as recorded in the diary. Sleep problems decreased in the treatment group and increased in the placebo group (-0.56 vs. 0.03 , $P = 0.05$). This increase in symptoms in the placebo group may have resulted from discontinuation of any pre-study medication the subjects were on before enrolment.

The data illustrated significant improvement detected by the ESS, one of the most common measurements of subjective daytime sleepiness (difference in means of 3.85 out of 24 with $P = 0.02$). This scale correlates with sleep latency measured during the multiple sleep latency test and during overnight polysomnography (39). These data suggested a subjective improvement in daytime somnolence after treatment with BUD.

Despite a greater amount of sleep reported by the placebo group ($+0.21$ vs. $+0.03$ h for active, $P = 0.43$), subjects treated with BUD described their sleep as more restorative and refreshing (difference in means of 0.69, $P = 0.01$). As discussed earlier, micro-arousals in AR disturb daytime alertness without affecting the total amount of sleep. The data suggested that treatment of AR improved the quality not quantity of sleep. As a result, daytime fatigue and alertness are improved.

The RQOLQ, a rhino-conjunctivitis specific quality of life assessment, evaluates the impact of the most common problems confronting patients with AR. This assessment significantly detects quality of life differences between treatment groups of subjects with rhino-conjunctivitis (4). Furthermore, the RQOLQ correlates with total daily nasal symptoms and response to treatment

with antihistamines (5). Juniper noted that a change of 0.5 or more represents a minimal important difference (MID). The MID is defined as 'the smallest difference in score in the domain of interest that patients perceive as beneficial and that would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management' (4). Instead of the traditional statistical approach, this measures significance as to whether the effect is important to the patient. A clinically significant improvement in quality of sleep and fatigue was detected in the active treatment group using the RQOLQ (difference of 0.61 and 0.86, respectively). The BUD group reported less emotional symptoms such as irritability, frustration, and impatience, which severely affect quality of life (difference in means of 0.48). This represents a marginal MID. Although traditional statistical significance was not achieved using the RQOLQ, these improvements may still warrant change in clinical management.

Congestion had a marginally significant improvement as recorded by the daily diary (a difference in means of 0.68 on a 4-point scale, $P = 0.08$). The failure to detect statistical significance may be attributed to study size. Despite this crossover study using Balaam's design, a larger group may have contributed the power to detect significance. This decrease in congestion does trend with the decline in sleepiness, fatigue, and sleep disturbance. Based on the discussion and past studies, it is not unreasonable to suggest that improved nasal congestion decreases sleep problems and improves the quality of sleep.

In conclusion, treatment with nasal corticosteroid improved daytime fatigue and somnolence as well as quality of sleep in patients suffering from PAR. In patients presenting with symptoms of PAR dominated by congestion and complaints of daytime fatigue and somnolence, the physician should consider the possibility of sleep-disordered breathing. We have shown that the topical corticosteroid, BUD, is statistically and clinically effective and improved the symptoms of fatigue and sleep problems which have a substantial impact on patients' quality of life. In patients suffering from PAR with complaints of fatigue and somnolence, the clinician should consider the use of BUD to relieve these symptoms.

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