

Intranasal Steroids and Oral Leukotriene Modifier Therapy in Residual Sleep-Disordered Breathing After Tonsillectomy and Adenoidectomy in Children

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ABSTRACT

OBJECTIVE. Tonsillectomy and adenoidectomy (T&A) is the primary therapeutic approach for sleep-disordered breathing (SDB) in children. However, residual mild SDB will be found in more than one third of these patients after T&A. We hypothesized that combined therapy with the leukotriene receptor antagonist montelukast and intranasal budesonide would result in normalization of residual SDB after T&A.

METHODS. During the period of October 2002 to February 2005, children who underwent T&A for SDB underwent a routine postoperative (second) overnight polysomnographic evaluation (PSG) 10 to 14 weeks after T&A surgery. In children with residual apnea hypopnea index (AHI) >1 and <5 /hour of total sleep time (TST), treatment with montelukast and intranasal budesonide aqueous solution was administered for a period of 12 weeks (M/B group), at which time a third PSG was performed. Children who had residual SDB and did not receive M/B therapy from their treating physicians were recruited as control subjects.

RESULTS. Twenty-two children received M/B, and 14 children served as control subjects. Mean age, gender distribution, ethnicity, and BMI were similar in the 2 treatment groups. The mean AHI at the second PSG was 3.9 ± 1.2 /hour of TST and 3.6 ± 1.4 /hour of TST in M/B-treated and control patients, respectively. Similar nadir arterial oxygen saturation ($87.3 \pm 1.2\%$) and respiratory arousal index (4.6 ± 0.7 /hour of TST) were recorded for both groups. However, the M/B group demonstrated significant improvements in AHI (0.3 ± 0.3 /hour of TST), in nadir arterial oxygen saturation ($92.5 \pm 3.0\%$), and in respiratory arousal index (0.8 ± 0.7 /hour of TST) on the third PSG, whereas no significant changes occurred over time in control subjects.

CONCLUSIONS. Combined anti-inflammatory therapy that consists of oral montelukast and intranasal budesonide effectively improves and/or normalizes respiratory and sleep disturbances in children with residual SDB after T&A.

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Key Words

leukotriene receptors, glucocorticoid receptors, sleep apnea, lymphoid hyperplasia, tonsils, adenoids, tonsillectomy and adenoidectomy, montelukast, sleep disordered breathing, budesonide

Abbreviations

SDB—sleep-disordered breathing
T&A—tonsillectomy and adenoidectomy
CPAP—continuous positive airway pressure
AHI—apnea hypopnea index
PSG—overnight polysomnographic evaluation
TST—total sleep time
M/B—oral montelukast and intranasal budesonide therapy
SpO₂—arterial oxygen saturation
ARtotl—total number of arousals per hour of sleep time
SPS—sleep pressure score

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OBSTRUCTIVE SLEEP APNEA and sleep-disordered breathing (SDB) is a common and highly prevalent disorder in the pediatric age range that affects 2% to 3% of all children.¹ When left untreated, SDB is associated with substantial morbidity, primarily affecting neurobehavioral and cardiovascular systems.²⁻⁹ Thus, because in otherwise normal children SDB is attributed primarily to adenotonsillar hypertrophy,^{10,11} tonsillectomy and adenoidectomy (T&A) is currently the most common treatment for children with SDB.¹² However, although a recent meta-analysis of the published literature suggested a relatively high success rate for T&A, averaging ~85%,¹³ the overall short-term cure rates for this surgical procedure in otherwise healthy children may not be as favorable as previously anticipated.^{14,15}

For children in whom T&A does not lead to complete resolution of SDB, the only currently tested interventional option consists of the administration of nasal continuous positive airway pressure (CPAP).¹⁶ This option is usually reserved for children in whom residual SDB after T&A is severe, such that the remainder of the children with milder forms of residual SDB are usually left untreated. Nevertheless, children with apnea hypopnea index (AHI) >1 but <5 events per hour of sleep are at significant risk for associated morbidity.¹⁷

Nonsurgical anti-inflammatory approaches have been advocated cautiously for SDB in children.^{18,19} Indeed, nasal and oropharyngeal mucosal inflammation are present in adult patients with SDB,²⁰⁻²³ and C-reactive protein, a systemic marker for inflammation, was reported recently to be increased in the serum of children with SDB and to correlate with the severity of their respiratory disturbance during sleep.²⁴ Thus, systemic anti-inflammatory agents with relatively safe therapeutic profiles for use in children could serve as an alternative intervention to nasal CPAP, especially when residual SDB is mild.

Montelukast is an orally bioavailable cysteinyl-leukotriene receptor antagonist that is effective, safe, well tolerated, and Food and Drug Administration approved for preventive therapy of the inflammatory component in asthma and allergic rhinitis in children 2 years and older,²⁵⁻²⁸ with no demonstrable development of tolerance in long-term studies.^{29,30} We recently found that the cloned human cysteinyl leukotriene receptors 1 and 2^{31,32} have increased expression in the tonsillar tissues of children with SDB³³ and that 12 to 16 weeks of treatment with montelukast leads to significant improvements in SDB.³⁴ Furthermore, expression of glucocorticoid receptors in upper airway lymphoid tissues suggests a favorable response to intranasal corticosteroid therapy in children,³⁵ with significant improvements in the severity of SDB resulting from such intervention.¹⁸ This study therefore was conducted to evaluate the response to the administration of a combination therapy that consists of orally administered leukotriene modifier and

an intranasal corticosteroid on mild residual SDB after T&A in children.

METHODS

Patients

The study was approved by the University of Louisville Human Research Committee, and informed consent was obtained from the legal caregiver of each participant. Assent was also obtained from children when they were >6 years of age.

Open-Label Treatment With Oral Montelukast/Intranasal Budesonide

During the period of October 2002 to February 2005, 22 consecutive patients who after an initial diagnostic overnight sleep study underwent T&A for SDB at the Kosair Children's Hospital Sleep Medicine and Apnea Center were recruited to the study after a second overnight polysomnographic evaluation (PSG) that was performed 10 to 14 weeks after T&A surgery revealed mild residual SDB (ie, AHI >1 but ≤5/hour of total sleep time [TST]). As control subjects, 14 children who fulfilled the same inclusion criteria and were not offered this therapeutic modality while receiving care from other attending physicians at the sleep center were identified and recruited to the study.

Criteria for inclusion were children who were older than 2 and younger than 10 years and were found to have AHI >1 but <5/hour of TST in a PSG that was conducted 10 to 14 weeks after T&A for SDB. Exclusion criteria were moderate to severe SDB after T&A (AHI >5/hour of TST), which required institution of CPAP via a nasal mask. In addition, the presence of history of asthma; craniofacial, neuromuscular, syndromic, or defined genetic abnormalities; current or previous use of montelukast; acute upper respiratory tract infection; use of any corticosteroids or antibiotics in the 4 weeks preceding the initial sleep study; and already having undergone surgical treatment for SDB before the T&A led to exclusion from the study. Although the presence of allergic rhinitis was not specifically assessed in the patients, clinical assessment included parental reports on nasal symptoms.

Oral montelukast therapy consisted of the daily administration of a chewable tablet (Singulair; Merck, Whitehouse Station, NJ) of 4 mg for children who were younger than 6 years and a 5-mg tablet for children who were ≥6 years. Parents were instructed to give the tablet at bedtime. Intranasal budesonide in aqueous solution (Rhinocort AQ; Astra Zeneca, Wilmington, DE) was administered once daily at bedtime in a standard dose of 1 squirt into each nostril. Parents were contacted weekly by the investigators to determine compliance and to follow-up on potential adverse effects. On completion of the 12-week course, patients underwent a third PSG.

PSG

All children who participated in the study were studied polysomnographically on 3 different occasions. The first PSG was conducted for diagnostic purposes after referral to the Kosair Children's Hospital Sleep Medicine and Apnea Center for habitual snoring and suspected SDB. This study confirmed the presence of SDB, and all children were referred for surgical removal of enlarged tonsils and adenoids (T&A). The second PSG was performed 10 to 16 weeks after T&A and revealed the presence of mild SDB, at which point those who were receiving therapy (see below) were enrolled into the study within 1 week. The third PSG was performed immediately at the end of the 16-week intervention period with either the combination of montelukast and intranasal budesonide (M/B) or no treatment (control subjects) for historical controls.

Sleep studies were performed in a dedicated, quiet, dark room. No sleep deprivation or sedation was used. Children were studied for at least 8 hours in a quiet, darkened room with an ambient temperature of 24°C in the company of 1 of their parents. The following parameters were measured: chest and abdominal wall movement by respiratory impedance or inductance plethysmography; heart rate by ECG; and air flow with a side-stream end-tidal capnograph, which also provides breath-by-breath assessment of end-tidal carbon dioxide levels (Pryon, Menomonee Falls, WI), as well as a nasal pressure transducer (Braebon, New York, NY) and a oronasal thermistor. Arterial oxygen saturation (Sao₂) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc, Hayward, CA), with simultaneous recording of the pulse waveform. The bilateral electro-oculogram, 8 channels of electroencephalogram, chin and bilateral anterior tibial and forearm electromyograms, and analog output from a body position sensor were also monitored. All measures were digitized using a commercially available polysomnographic system (REMBRANDT, Amsterdam, The Netherlands). Tracheal sounds were monitored with a microphone sensor, and a digital time-synchronized video recording was performed.

Analysis of the polysomnogram was performed using standard techniques. In brief, sleep staging was assessed using standard criteria.³⁶ The AHI was defined as the number of apneas and hypopneas per hour of TST, and obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for a duration of at least 2 breaths.^{37,38} Hypopneas were defined as a decrease in nasal flow of $\geq 50\%$ with a corresponding decrease in Spo₂ of $\geq 4\%$ and/or arousal.³⁷ The mean Spo₂ together with Spo₂ nadir was determined. Arousals were defined as recommended by the American Sleep Disorders Association Task Force report³⁹ and include respiratory-related (occurring immediately after an apnea, hypopnea, or snore), technician-induced, and spontaneous arousals. Arousals were expressed as

the total number of arousals per hour of sleep time (ARtotI). In addition, as a surrogate measure for sleepiness, the recently developed sleep pressure score (SPS)⁴⁰ was calculated for each patient's polysomnographic record as follows: $SPS = (RAI/ARtotI) \times (1 - SAI/ARtotI)$, where RAI is the respiratory-related arousal index and SAI is the spontaneous arousal index. An SPS ≥ 0.25 was used as the threshold for evidence of increased sleepiness.^{40,41}

Statistical Analysis

Results are presented as means \pm SD, unless stated otherwise. All numeric data were subjected to statistical analyses using either *t* tests or analysis of variance procedures followed by Neuman-Keuls post hoc tests, as appropriate. A 2-tailed *P* < .05 was considered statistically significant.

RESULTS

Twelve boys and 10 girls completed the 12-week M/B treatment, and 14 children served as control subject. Mean age (6.3 ± 1.3 years), gender distribution (60% male), ethnicity (35% black), and BMI (30% with relative BMI >95%) were similar in the 2 treatment groups (Table 1). In addition, the presence of nasal symptoms such as stuffiness, potentially suggestive of allergic rhinitis, was similar in the 2 groups. The mean AHI during the initial PSG that led to T&A was 20.3 ± 4.3 /hour of TST in the M/B group and 19.5 ± 4.7 /hour of TST in the control group (*P* not significant). Similarly, there were no significant differences in the nadir Spo₂, peak end-tidal carbon dioxide levels, total arousal index, and respiratory arousal index among the 2 groups during the first PSG.

The mean AHI at the second PSG was 3.9 ± 1.2 /hour of TST and 3.6 ± 1.4 /hour of TST in M/B and control groups, respectively (*P* not significant). Similar nadir Spo₂ ($87.3 \pm 1.2\%$) and respiratory arousal index (4.6 ± 0.7 /hour of TST) were recorded for both groups during the second PSG (Table 1).

Significant improvements in AHI (0.3 ± 0.3 /hour of TST; *P* < .001), in nadir Spo₂ ($92.5 \pm 3.0\%$; *P* < .01), and in respiratory arousal index (0.8 ± 0.7 /hour of TST; *P* < .001) were found in the third PSG for the M/B group (ie, on completion of the 12-week treatment period), whereas no significant changes occurred over time in the control group (*P* < .001 analysis of variance; Table 1). No significant changes occurred in TST, sleep efficiency, number of awakenings, or the mean saturation values recorded during sleep. Similarly, no significant changes emerged in the distribution of sleep stages except for a decrease in the percentage of time spent in stage 1 non-rapid eye movement sleep in the M/B group. However, increased sleep latency occurred in the treated group (*P* < .01; Table 1). There were no adverse drug reactions reported throughout the study, except for 1

TABLE 1 Demographic and Polysomnographic Characteristics in 36 Children Who Had Mild SDB and Were Treated With M/B for 12 Weeks or Received No Therapy at Diagnosis of Residual Sleep Apnea After Undergoing T&A and at Follow-up

	M/B Treatment (n = 22)			No Treatment (n = 14)		
	Pre-T&A	Post-T&A	P	Pre-T&A	Post-T&A	P
Age, y	6.3 ± 1.3			6.5 ± 1.8		
Gender, n						
Female	9			7		
Male	13			9		
Race, n						
White	14			11		
Black	8			5		
BMI, mean ± SD, kg/m ²	19.4 ± 1.2	19.7 ± 1.4	NS	19.1 ± 1.4	19.5 ± 1.3	NS
Arousal index (total), mean ± SD, per h of TST ^a	18.9 ± 2.5	15.4 ± 2.1	NS	17.7 ± 2.7	19.5 ± 3.3	NS
Arousal index (respiratory), mean ± SD, per h of TST ^a	4.6 ± 0.6	0.8 ± 0.3	<.001	4.7 ± 0.7	5.9 ± 1.3	NS
SPS ^a	0.27 ± 0.05	0.07 ± 0.02	.001	0.28 ± 0.06	0.35 ± 0.08	NS
Apnea index, mean ± SD, per h of TST ^a	1.9 ± 0.3	0.1 ± 0.3	<.01	1.7 ± 0.2	2.4 ± 0.5	.055
Obstructive AHI, mean ± SD, per h of TST ^a	3.9 ± 1.2	0.3 ± 0.3	<.001	3.6 ± 1.4	4.7 ± 1.5	<.04
TST, mean ± SD, h	8.55 ± 0.33	8.76 ± 0.44	NS	8.68 ± 0.37	8.50 ± 0.42	NS
Mean sleep latency, mean ± SD, min	11.7 ± 1.8	19.8 ± 1.5	<.01	12.8 ± 1.9	9.9 ± 2.3	NS
Sleep efficiency, mean ± SD, %	88.3 ± 6.5	89.0 ± 5.9	NS	88.0 ± 5.6	85.6 ± 6.3	NS
Nadir Spo ₂ , mean ± SD	87.3 ± 3.1	92.5 ± 3.0	<.01	87.4 ± 3.4	84.0 ± 4.9	NS
Mean Spo ₂ , mean ± SD	95.4 ± 1.0	96.1 ± 1.3	NS	95.2 ± 2.1	95.0 ± 2.7	NS
Awakenings, mean ± SD	8.0 ± 5.4	7.4 ± 4.2	NS	7.9 ± 4.4	8.9 ± 4.9	NS
Wake, mean ± SD, %TST	4.1 ± 1.0	3.5 ± 1.1	NS	4.2 ± 0.9	4.8 ± 1.1	NS
Stage 1, mean ± SD, %TST	14.1 ± 1.3	8.1 ± 1.0	<.05	13.5 ± 1.4	15.7 ± 1.5	NS
Stage 2, mean ± SD, %TST	40.1 ± 2.0	44.3 ± 1.8	NS	42.3 ± 2.1	41.3 ± 2.5	NS
Stage 3 + 4, mean ± SD, %TST	22.0 ± 1.7	28.8 ± 1.5	NS	21.9 ± 2.1	18.4 ± 2.9	NS
Stage REM, mean ± SD, %TST ^a	21.0 ± 1.5	20.5 ± 1.9	NS	22.0 ± 1.9	20.5 ± 2.0	NS

NS indicates not significant; REM, rapid eye movement.

^a M/B versus CO: *P* < .01.

child who reported mild epistaxis that resolved within 3 days on discontinuation of the M/B regimen and did not recur after resumption of M/B treatment 1 week later. Otherwise, excellent compliance based primarily on parental report and no attrition occurred.

DISCUSSION

This study shows that a 12-week course of an orally administered leukotriene receptor antagonist combined with intranasal administration of a corticosteroid is associated with significant improvements in upper airway patency and in the severity of SDB that occurred after T&A in children and that these improvements fail to occur when no treatment is administered. Before we discuss the potential implications of our findings, 2 issues deserve comment. First, in this study we did not specifically assess the prevalence of residual SDB in children after T&A. This particular problem is not infrequently recognized around the world and is likely to take a more important clinical dimension with the increased awareness and diagnosis of sleep apnea in the pediatric population and the resultant increase in the number of T&A procedures for this particular diagnosis.^{15,42,43} Second, the intervention that was used herein followed an open-label design, such that some degree of subjective bias may have been introduced despite all of

the precautions taken to prevent such problem. Therefore, although the overall outcome satisfaction was extremely high among parental reports among patients who were treated with M/B compared with those who were on no treatment (data not shown), we opted for exclusion of such subjective data from the study.

The conceptual premises under which therapy for SDB in children is based are not yet well defined. In recent years, it has become apparent that SDB is associated with substantial morbidities, particularly affecting cognitive, behavioral, and cardiovascular functions.^{3,5,6,9,17} However, neither the thresholds of disease severity that delineate the cost-benefit ratios for T&A nor the outcomes that are derived from such intervention have been well established. Notwithstanding such uncertainties, when AHI >5 are found in symptomatic children with SDB after T&A, there is a priori consensus for implementation of secondary lines of therapy, which at present consist mainly of administration of nasal CPAP.^{16,44-48} However, for children who remain symptomatic but display AHI >1 and <5 events per hour of sleep, there is no consistent agreement on whether to treat or not to treat and, if so, what the optimal modality of treatment may be. Such considerations led us to the search for nonsurgical therapeutic alternatives that would not incorporate use of CPAP. On the one hand,

topical intranasal application of high-potency corticosteroids led to significant improvements in AHI and oxygenation in a cohort of children with SDB (AHI >5)¹⁸; furthermore, we showed recently that the expression patterns of glucocorticoid receptors α and β in the upper airway suggest the potential for favorable therapeutic responses to steroid treatment in children with SDB.³⁵ On the other hand, both the expression of inflammatory mediators such as leukotrienes and the expression of leukotriene receptors were increased in children with SDB,^{33,34} suggesting a potential beneficial role for a leukotriene receptor antagonist in residual SDB after T&A. Thus, the current study opens a new therapeutic modality for symptomatic pediatric patients with mild SDB after T&A. Although the mechanisms underlying the resolution of SDB in conjunction with M/B treatment are unclear, we postulate that increased inflammatory processes indeed are operative in the upper airway of such children. This is not surprising overall, considering the cumulative evidence in adult patients supporting the presence of inflammation in patients with SDB.^{21,23,49} The mechanisms that mediate such inflammatory processes most likely are related, at least in part, to the vibratory mechanical damage associated with snoring. In addition and particularly pertinent to children, the residual lymphadenoid tissue left behind after T&A may continue to release inflammatory mediators, which can lead to upper airway dysfunction and promote sustained upper airway collapsibility.^{49,50} If indeed these putative biological inflammatory processes are pathophysiologically involved in the generation of increased upper airway collapsibility during sleep, then treatment with leukotriene receptor blockers and intranasal topical corticosteroids should abrogate such processes and thereby lead to progressive improvements in the residual respiratory disturbances during sleep.⁴⁹

One of the leading concepts resulting from this and other studies supports the existence of a chronic inflammatory process in children with SDB. Indeed, C-reactive protein serum levels, an important systemic marker for inflammation, is elevated in both children and adults with obstructive sleep apnea,²⁴ suggesting that systemic processes may either initiate or maintain the localized inflammatory process and associated upper airway collapsibility. In addition, inflammatory changes in the upper airway mucosa elicited by the recurrent vibratory mechanical stress of snoring could contribute to the upregulation of leukotriene receptor expression and to the accelerated regrowth of the adenotonsillar tissues, followed by recurrence of more severe forms of SDB.⁵¹ Some corroboration to the slow, albeit progressive, nature of these processes is exemplified by the small, albeit significant, increases in respiratory disturbance during sleep during the 12-week period in the control cohort (Table 1). In contrast, we observed significant improvements in airway patency, as documented by the substan-

tial reductions in respiratory-related sleep disturbances, after the 12-week course of M/B. Although it is evident that randomized, double-blind, placebo-controlled trials are needed to confirm current findings, the present study suggests the potential beneficial role of anti-inflammatory approaches for symptomatic children with mild SDB after T&A. Furthermore, the duration of such combination therapy and the potential occurrence of rebound SDB on discontinuation of anti-inflammatory agents will need to be investigated thoroughly to define the standards of practice in residual SDB after T&A.

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