

Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea

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Objective: We tested the hypothesis that a 6-week course of a nasal glucocorticoid spray would decrease the severity of obstructive sleep apnea in children with adenotonsillar hypertrophy.

Study design: We conducted a randomized, triple-blind, placebo-controlled, parallel-group trial of nasal fluticasone propionate versus placebo in 25 children aged 1 to 10 years with obstructive sleep apnea proven on polysomnography. The primary outcome was the change from baseline in the frequency of mixed and obstructive apneas and hypopneas.

Results: Thirteen children received fluticasone, and 12 received placebo. The mixed/obstructive apnea/hypopnea index decreased from 10.7 ± 2.6 (SE) to 5.8 ± 2.2 in the fluticasone group but increased from 10.9 ± 2.3 to 13.1 ± 3.6 in the placebo group, $P = .04$. The mixed/obstructive apnea/hypopnea index decreased in 12 of 13 subjects treated with fluticasone versus 6 of 12 treated with placebo, $P = .03$. The frequencies of hemoglobin desaturation and respiratory movement/arousals also decreased more in the fluticasone group. Changes from baseline in tonsillar size, adenoidal size, and symptom score were not significantly different between groups.

Conclusion: Nasal fluticasone decreased the frequency of mixed and obstructive apneas and hypopneas, suggesting that topical corticosteroids may be helpful in ameliorating pediatric obstructive sleep apnea. (*J Pediatr* 2001;138:838-44)

In children, obstructive sleep apnea is most often associated with adenotonsillar hypertrophy. The prevalence of pediatric OSA has been estimated at 1% and occurs most frequently in children between 2 and 6 years old, when the adenoids and tonsils are largest

relative to the pharyngeal space.¹⁻⁵ Chronic sleep-related airway obstruction results in repetitive hypoxemia and sleep disturbance that can cause neurocognitive disturbance, growth failure, and cor pulmonale.⁴⁻⁷ Pediatric OSA is usually managed with adeno-

tonsillectomy, but such surgical therapy is expensive, painful, and sometimes associated with complications, including bleeding and perioperative respiratory compromise.⁸⁻¹²

See editorial, p 795.

It is generally accepted that corticosteroids are not useful in the management of pediatric OSA.¹³ We previously determined that a 5-day course of systemic prednisone therapy was ineffective in reducing the severity of pediatric OSA.¹⁴ By contrast, Demain and Goetz¹⁵ showed that topical nasal corticosteroids over a 24-week treatment reduced adenoidal size and improved symptoms of nasal airway obstruction.¹⁵ However, these investigators did not study children <5 years old, nor did they evaluate the efficacy for OSA. In a preliminary open-label pilot study of nasal fluticasone in 7 children with OSA, with the use of the same protocol described for this study, we found a decrease in the mixed/obstructive apnea/hypopnea index from 11.3 ± 3.6 to 4.9 ± 3.2 ($P = .06$). Six of 7 children had a decrease in the mixed/obstructive apnea/hypopnea index after 6 weeks of fluticasone treatment.

OSA Obstructive sleep apnea

We therefore designed a randomized, triple-blind, placebo-controlled, parallel-group trial to test the hypothesis that topical nasal corticosteroids would decrease the severity of pediatric OSA. The primary outcome was the change from baseline in the frequency of mixed

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and obstructive apneas and hypopneas after a 6-week treatment.

METHODS

Study Subjects

The study was approved by the Institutional Review Board of the Montreal Children's Hospital. The study subjects were children between 1 and 10 years old who were referred from otolaryngologists and met the following 3 inclusion criteria: (1) adenoidal hypertrophy, assessed on radiography as an adenoidal/nasopharyngeal ratio >0.5 ^{16,17} or 2+ or 3+ tonsillar hypertrophy assessed on clinical evaluation, (2) signs and symptoms of OSA including loud snoring, difficulty breathing, OSA witnessed by parents, parental concern about breathing during sleep, or restless sleep,¹⁸ and (3) a mixed/obstructive apnea/hypopnea index >1 proven by laboratory or home polysomnography.^{13,19,20} Children were enrolled between November 1997 and October 1999. Informed consent was obtained from the parents of each child, and assent was obtained from children >6 years old.

Children were excluded if they had any of the following: craniofacial abnormalities, genetic abnormalities including Down syndrome, neurologic disease, acute upper respiratory infection, severe OSA requiring urgent surgery, 4+ tonsillar hypertrophy, exposure to varicella, or use of any corticosteroids or antibiotics within the past 3 weeks.

Study Protocol

Randomization was performed from a table of random numbers. Subjects were allocated to treatment groups with simple randomization in blocks of 4. The study drug was dispensed by a pharmacist to an investigator, who then demonstrated the use of the medication to the subjects and parents. Parents were contacted weekly by an investigator to determine whether the study drug was being given and

whether any complications had occurred. Only the study pharmacist was aware of the group assignment. Sleep laboratory personnel, subjects, parents, and physicians were all blinded to group assignment until the entire study was completed and analyzed.

Fluticasone propionate (Flonase, GlaxoWellcome) and placebo were provided in identical containers by the drug manufacturer. The appearance and smell of the fluticasone and placebo were indistinguishable. Each fluticasone spray delivered 50 μg of active drug. The study drug was given as one spray per nostril twice daily for the first week and once daily for the subsequent 5 weeks. These doses were chosen because they have been found to be safe and effective for children with allergic rhinitis.²¹ A 6-week course of treatment was chosen because in our hospital, the usual waiting time for adenotonsillectomy was 8 to 12 weeks. Thus participation in the study would not delay institution of standard therapy. After the post-study evaluations were completed, the parents and otolaryngologist, who remained blinded to the treatment group, were free to choose nasal fluticasone, adenotonsillectomy, or conservative follow-up.

Outcome Measures

Each subject had a polysomnographic, clinical, and radiographic assessment at baseline and after 6 weeks on treatment. The primary outcome measure was the change in the frequency of mixed and obstructive apneas and hypopneas during sleep from baseline until after the treatment protocol. Secondary outcomes included changes in the following measures: the frequency of hemoglobin desaturations, the frequency of movement/arousals terminating apneas and hypopneas, adenoidal size and minimal nasopharyngeal airway size measured with radiography, tonsillar size measured at clinical evaluation, and symptom score as assessed by the parents.¹⁶⁻²⁰

Specific Measurement Techniques

POLYSOMNOGRAPHY. Each child underwent polysomnography to document the severity of OSA and to evaluate the response to study drug treatment. Whenever possible, studies were performed in the child's home. The portable recording system comprised cardiorespiratory and video recordings and was designed to quantify the essential diagnostic elements of OSA: the frequencies (number per hour of sleep) of mixed and obstructive apneas and hypopneas, hemoglobin desaturation ($\geq 4\%$), and movement/arousals terminating apneas and hypopneas; sleep versus wakefulness; sleep position; and snoring.^{20,22-25} Obstructive apnea was defined as an 80% or greater decrease in amplitude on the respiratory inductive plethysmography summation channel of at least 3 seconds' duration; hypopnea was defined as a 50% to 80% decrease in amplitude of the summation channel accompanied by a decrease in saturation of 4% or more.^{19,20}

In the home, equipment was set up by a technician at the child's usual bedtime and was retrieved the next morning. The cardiorespiratory recording consisted of an electrocardiogram, pulse rate, SaO_2 , pulse waveform, and thoracic and abdominal excursions and their sum obtained from a respiratory inductive plethysmograph. The signals were recorded on a portable computer and later transferred to a computerized polysomnograph in the sleep laboratory. Audiovisual recordings were made under infrared lighting and provided complementary information about snoring and the subjects' movement and position. Videotape recordings were time-matched to the cardiorespiratory recordings and analyzed on a computerized movement detection system (SleepVision, Martinex, Montreal, Quebec).²²

In-laboratory polysomnographic studies were performed when the child lived far from the hospital or in a home

Table I. Baseline characteristics of the children in the fluticasone and placebo groups*

Characteristic	Fluticasone (n = 13)	Placebo (n = 12)
Age (y)	4.2 ± 0.7	3.4 ± 0.3
Sex (M/F)	5/8	9/3
No. with allergic rhinitis	3	1
No. of days on which study drug was given	44 ± 1	45 ± 1
Mixed/obstructive apnea/hypopnea index (No./h)	10.7 ± 2.6	11.0 ± 2.3
Desaturation index (No./h)	7.0 ± 2.0	5.6 ± 2.0
Sleep time with paradoxical movement of chest and abdomen (%)	17.4 ± 2.7	14.5 ± 3.7
Respiratory movement/arousal index (No./h)	6.1 ± 1.9	4.1 ± 0.8
Respiratory rate (breaths/min)	18 ± 1	18 ± 1
Heart rate (beats/min)	89 ± 2	98 ± 4
SaO ₂ mean (%)	97.6 ± 0.3	98.1 ± 0.3
SaO ₂ minimum (%)	85.9 ± 1.7	86.6 ± 1.2
Sleep efficiency (%)	92.1 ± 1.1	90.3 ± 1.7
Adenoidal/nasopharyngeal ratio	0.76 ± 0.03	0.79 ± 0.03
Minimal airway size (mm)	2.9 ± 1.3	1.1 ± 0.5
Tonsillar size (1+/2+/3+)	3/6/4	2/5/5
Symptom score	2.6 (−1.0, 4.0)	2.6 (−0.3, 2.6)

*Values are reported as mean ± SE or, if data were not normally distributed, as median (interquartile range). There were no significant differences between the 2 groups.

with an ungrounded electrical system. These studies included the same recording channels obtained for home polysomnography plus transcutaneous and end-tidal CO₂, an oronasal thermistor, electroencephalograms, electrooculogram, and chin electromyogram.²⁰ For each child the polysomnography setting remained the same before and after fluticasone or placebo treatment.

OTHER MEASUREMENTS. Lateral neck radiographs were taken as described previously for adenotonsillar hypertrophy measurement in children with OSA syndrome.^{3,16} The study radiologist (K.O.), blinded to treatment assignment, interpreted the radiographs and made measurements of the adenoidal/nasopharyngeal ratio and the diameter (in millimeters) of the nasopharyngeal airway at its narrowest point.¹⁶

An otolaryngologist blinded to treatment assignment performed a physical examination. Tonsillar size was graded from 0 to 4+.¹⁷ The grading was based

on the proportion of the distance between the anterior tonsillar pillars that was taken up by the tonsillar tissue: 0, tonsils not extending beyond the pillars; 1+, 0% to 25%; 2+, 25% to 50%; 3+, 50% to 75%; and 4+, 75% to 100%.

An interviewer administered a questionnaire based on an earlier study¹⁸; the questionnaire asks a battery of questions relating to signs and symptoms of OSA and other general health questions. A symptom score ("OSA score"; range, −3.83 to 3.97) derived from parental responses to questions about snoring, difficulty breathing, and obstructive apnea was calculated and used to assess the clinical response to study drug treatment.

Statistics

Results were expressed as the mean ± SEM or as the median, interquartile range, as indicated. To assess treatment effectiveness, the unpaired *t* test and Fisher's exact test were used for normally distributed and ordinal vari-

ables, respectively. The Mann-Whitney rank sum test was used to compare non-normally distributed variables across treatments.

A sample size of 26 subjects per group was initially estimated based on an alpha error of 0.05, a baseline mixed/obstructive apnea/hypopnea index of 12.4/h, with an SD of 7.7, and a potentially, clinically important decrease in mixed/obstructive apnea/hypopnea index of 50%.

Because of slow recruitment of subjects, because funding had expired, and because local clinicians were more frequently using nasal steroids for potential subjects, a statistician performed an analysis after 25 subjects had been recruited. The statistician knew that there were 2 groups but was blinded to which group was placebo and which treatment was used (triple-blind method). This analysis showed a statistically significant and clinically important difference between groups in the primary outcome measure and in 3 important secondary outcomes. Therefore the study was terminated, and the results are reported here.

RESULTS

A total of 278 patients underwent polysomnography during the study period. A total of 234 were excluded for the following reasons: mixed/obstructive apnea hypopnea index <1 (74), age <1 year old (8), age >10 years old (10), myelomeningocele (29), severe OSA requiring prompt surgery (10), use of steroids (13), bronchopulmonary dysplasia and other respiratory disorders (11), craniofacial abnormalities (11), neuromuscular and neurologic disorders (31), other genetic and medical disorders (15), use of antibiotics (5), tonsillar size 4+ (2), central hypoventilation syndrome (5), postadenotonsillectomy (4), child lived out of the province (4), and gastroesophageal reflux (2). A total of 44 subjects were eligible for recruitment, 25 of whom con-

sented to participate in the study. Thirteen subjects were randomized to fluticasone and 12 to placebo. There were no significant differences between study participants and those who refused participation for age, sex, or most baseline polysomnographic measures. There was a trend toward a lower mixed/obstructive apnea/hypopnea index in the refusal group than in the participant group, 6.3 ± 1.2 versus 10.8 ± 1.7 events per hour, respectively, $P = .06$.

The baseline characteristics of children allocated to the fluticasone and placebo groups were similar (Table I). Home polysomnography was used for 12 of 13 subjects in the fluticasone group and 10 of 12 subjects in the placebo group. Mixed/obstructive apnea/hypopnea indexes ranged from 1.9 to 37.0 events per hour of sleep, and mean values for the 2 groups were comparable.

Compliance with prescribed dosing was excellent in both groups, with parents reporting that $96\% \pm 1\%$ and $92\% \pm 3\%$ of doses were given in the fluticasone and placebo groups, respectively. Differences in container weights indicated that 116 ± 9 versus 111 ± 10 sprays were dispensed for the fluticasone and placebo groups, respectively; the protocol called for 98 sprays per subject. The only complication possibly related to topical nasal treatment was a nosebleed in 1 subject in the placebo group.

Polysomnographic Outcomes

Changes in polysomnographic, adenotonsillar hypertrophy, and clinical outcomes are summarized in Table II. The mixed/obstructive apnea/hypopnea index decreased by 5.0 ± 1.0 events per hour in the fluticasone group but increased by 2.2 ± 3.3 events per hour in the placebo group, $P = .04$ (Fig 1). The mixed/obstructive apnea/hypopnea index decreased in 12 of 13 subjects in the fluticasone group but in only 6 of 12 subjects in the placebo group, $P = .03$. The frequency of hemoglobin desaturation decreased more in

Table II. Changes in polysomnographic indexes, adenotonsillar hypertrophy, minimal nasal airway size, and symptom score in children receiving either fluticasone or placebo*

Characteristic	Fluticasone (n = 13)	Placebo (n = 12)	P value†
Mixed/obstructive apnea/hypopnea index			
No. per hour	-5.0 ± 1.0	2.2 ± 3.3	.04
No. with a decrease from baseline	12	6	.03
Desaturation index (No./h)	-4.1 ± 1.3	-0.3 ± 1.0	.03
Respiratory movement/arousal index (No./h)	-3.4 ± 1.1	-0.2 ± 1.1	.05
Sleep time with paradoxical movement of chest and abdomen (%)	-6.1 ± 2.6	0.5 ± 4.5	.29
Respiratory rate (breaths/min)	0.8 ± 0.6	-0.5 ± 0.6	.12
Heart rate (beats/min)	-0.9 ± 2.1	-6.7 ± 3.5	.16
SaO ₂ mean (%)	0.6 ± 0.4	0.1 ± 0.4	.35
SaO ₂ minimum (%)	-2.5 ± 1.7	-1.3 ± 1.0	.55
Sleep efficiency (%)	-0.2 ± 1.1	3.3 ± 1.6	.08
Adenoidal/nasopharyngeal ratio	-0.03 ± 0.01	-0.05 ± 0.02	.46
Minimal airway size (mm)	1.3 ± 0.5	1.9 ± 0.8	.51
Tonsillar size (increase/no change/decrease)	1/4/8	1/7/4	.24
Symptom score	-4.3 (0.0, -7.4)	-1.4 (0.0, -4.3)	.30

*Values given as mean \pm SE or, if data were not normally distributed, as median (interquartile range).

†P values are for comparison of the changes from baseline in each characteristic between the fluticasone group and the placebo group.

the fluticasone group than in the placebo group, $P = .03$ (Fig 2). The frequency of movement/arousals terminating apneas and hypopneas decreased more in the fluticasone group than in the placebo group, $P = .05$. During the treatment period, 5 of 13 subjects in the fluticasone group and 2 of 12 subjects in the placebo group received antibiotics for otitis media (6) or sinusitis (1), $P = .20$; with stepwise multiple regression, antibiotic use did not affect group differences for the previously described outcomes. Changes in respiratory rate, heart rate, lowest hemoglobin saturation, percentage of sleep time with paradoxical movement of the chest and abdomen, and sleep efficiency were not statistically significant.

Other Outcomes

Differences across groups for radiographic and clinical outcomes were not statistically significant (Table II). Tonsillar size decreased in 62% of subjects in the fluticasone group and in 33% of subjects in the placebo group,

$P = .24$. The OSA symptom score decreased in 69% of the subjects in the fluticasone group and in 50% of the placebo group, $P = .43$.

Follow-up

Post-study treatment choices did not differ significantly by study group. Parents and the otolaryngologist decided to proceed to adenotonsillectomy after study completion for 46% of the subjects in the fluticasone group and for 75% of the subjects in the placebo group. Open-label treatment with nasal fluticasone propionate was chosen after study completion by parents of 62% and 33% of the fluticasone group and placebo group, respectively.

DISCUSSION

This study investigated the effect of nasal corticosteroids on OSA in children. We found that a 6-week course of nasal fluticasone decreased the severity of pediatric OSA, as demon-

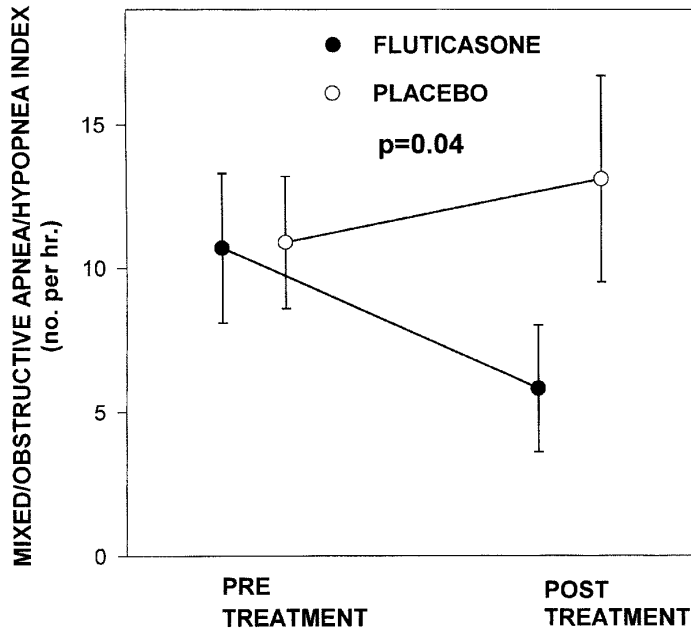


Fig 1. Mixed/obstructive apnea/hypopnea index decreased from 10.7 ± 2.6 to 5.8 ± 2.2 (SE) in fluticasone group but increased from 10.9 ± 2.3 to 13.1 ± 3.6 in placebo group, $P = .04$.

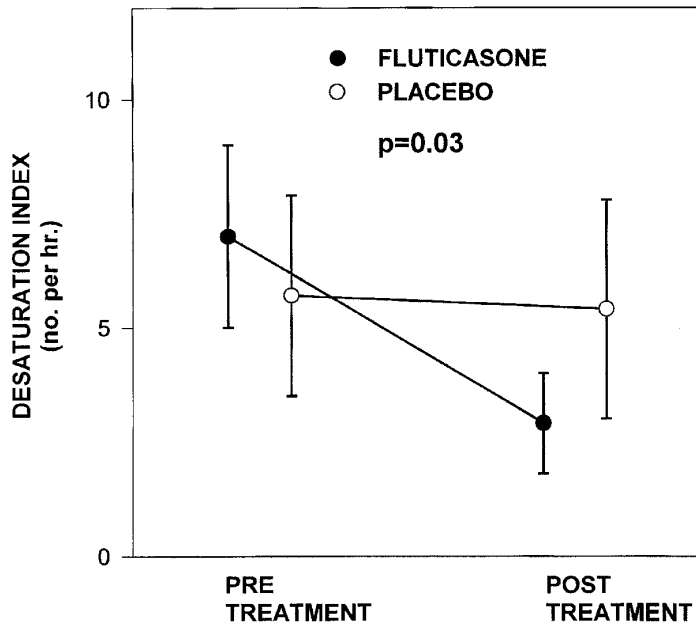


Fig 2. Frequency of desaturation events decreased from 7.0 ± 2.0 to 2.9 ± 1.1 in fluticasone group and decreased from 5.6 ± 2.0 to 5.4 ± 2.4 in placebo group, $P = .03$.

strated by reduced frequencies of obstructive airway events, hemoglobin desaturation episodes, and movement/arousals terminating apneas and hypopneas. The frequency of obstructive airway events decreased in 12 of 13 subjects treated with fluticasone. This study did not demonstrate statis-

tically significant reductions in adenotonsillar hypertrophy or the symptom score. However, parental reports may not be a sensitive marker for severity of OSA, because several previous studies have shown that parents are not able to differentiate reliably between OSA and simple snoring.²⁶

The pathogenesis of OSA is thought to involve both anatomic and neuromuscular factors that predispose to inspiratory collapse of the pharyngeal airway.¹⁵ Marcus¹³ has shown that pharyngeal airway closing pressure is higher in children with OSA than in a control group. The importance of neuromuscular maintenance of upper airway patency is supported by animal models and clinical studies and by the clustering of obstructive events in rapid eye movement sleep, when pharyngeal muscular tone decreases.^{23,27,28} The importance of the anatomic component is supported by the generally beneficial response to adenotonsillectomy.^{4,5,29} Furthermore, Isono et al³⁰ showed that the difference in closing pressure of the pharyngeal airway between children with and without OSA is maintained during anesthesia and muscular paralysis.

Topical nasal steroids most likely affect the anatomic component by decreasing inspiratory upper airway resistance at the nasal, adenoidal, or tonsillar levels. McColley et al³¹ demonstrated a high prevalence of allergic rhinitis in children with OSA. However, in patients with rhinitis, snoring and other nasal symptoms improved in both allergic and nonallergic children treated with nasal beclomethasone.¹⁵ Corticosteroids, by their lympholytic or anti-inflammatory effects, might reduce adenotonsillar hypertrophy. Demain and Goetz¹⁵ found that the adenoidal to choanal ratio, as assessed by rhinoscopy, decreased by 29% over a 24-week treatment course. Because our study used a shorter treatment duration and assessed the adenoids by lateral neck radiographs, it remains possible that nasal steroids reduced the severity of pediatric OSA by diminishing adenoidal tissue. The possibility that nasal steroids might reduce tonsillar size had not been previously tested. Although tonsillar size decreased in 62% of subjects in the fluticasone group, the sample size in this study was too small to demonstrate a statistically significant effect.

It is important to acknowledge other limitations of our study. The number of subjects studied was small, and all came from a single center. Children with severe OSA requiring urgent surgery (n = 10) were excluded. In such cases topical nasal steroids should not be used, because this would delay proven, effective treatment: adenotonsillectomy. Most of our polysomnography studies were performed in a home setting without airflow, CO₂ measurement, or sleep state staging. Because our study was a blinded, randomized, controlled trial, there is no reason to suspect that group differences are due to these measurement limitations. Furthermore we have shown that our technique of home polysomnography results in equivalent apnea and desaturation indexes and improved sleep efficiency compared with conventional laboratory polysomnography.²⁰

Our study was not designed to compare nasal corticosteroids with adenotonsillectomy or to determine the optimal drug, dose, or duration for treatment. This study does not prove that pediatric OSA can be cured by nasal corticosteroid treatment. We chose doses of 200 µg/d for the first week and 100 µg/d for the next 5 weeks. In a study using 336 µg/d of nasal beclomethasone for 8 weeks followed by 168 µg/d for 16 additional weeks, both adenoidal size and symptom score continued to decrease over the 24-week treatment period.¹⁵ It therefore seems likely that the optimal duration of treatment for pediatric OSA is longer than the 6-week period used in our study. Whether corticosteroid-induced improvements in OSA frequency, adenoidal size, and symptoms are maintained after the treatment is discontinued is unknown.

The possibility of managing pediatric OSA with topical nasal steroids is an attractive one, because this treatment has been found safe for children and adults with seasonal and perennial rhinitis.^{21,32-34} If topical corticosteroids are used for a prolonged peri-

od, however, careful monitoring for side effects may be necessary. Systemic effects on growth, bone metabolism, and the adrenocortical axis are potentially important problems but seem unlikely for three reasons. First, the low daily doses needed, 100 to 200 µg/d of fluticasone, are below those found to have systemic side effects.^{35,36} Second, because the area of nasal mucosa is much less than the area of pulmonary mucosa, topical nasal corticosteroids result in much less systemic absorption than when corticosteroids are inhaled to manage asthma.³⁷ Less than 2% of nasal fluticasone becomes systemically available.³⁸ Third, newer topical steroids such as fluticasone are poorly absorbed after being swallowed and are rapidly metabolized in the liver, thereby decreasing systemic availability.³⁹

This trial suggests that topical nasal corticosteroids may reduce the severity of pediatric OSA. With these positive findings, further work will be required to replicate the current results, to demonstrate the mechanism by which topical corticosteroids ameliorate obstructive apnea, and to establish the place of corticosteroids within the therapeutic armamentarium. For children with obstruction too mild to justify surgery, topical corticosteroid treatment may prove to be the treatment of choice. For others, as in this protocol, nasal corticosteroids may provide some relief until adenotonsillectomy can be performed. Significant cost savings would accrue if it could be shown that nasal corticosteroid treatment could substitute for many of the 300,000 adenotonsillectomies performed in the United States and Canada yearly.⁴⁰ Long-term follow-up will be required to determine whether improvements are maintained after nasal corticosteroids are discontinued.

REFERENCES

1. Ali NJ, Pitson DJ, Stradling JR. Snoring, sleep disturbance, and behaviour in 4-5 year olds. *Arch Dis Child* 1993;68:360-6.

2. Gislason T, Benediktsdottir B. Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. An epidemiologic study of lower limit of prevalence. *Chest* 1995; 107:963-6.
3. Fujioka M, Young LW, Girdany BR. Radiographic evaluation of adenoidal size in children: adenoidal-nasopharyngeal ratio. *Am J Roentgenol* 1979; 133:401-4.
4. Guilleminault C, Korobkin R, Winkle R. A review of 50 children with obstructive sleep apnea syndrome. *Lung* 1981;159:275-87.
5. Brouillette RT, Fernbach SK, Hunt CE. Obstructive sleep apnea in infants and children. *J Pediatr* 1982;100:31-40.
6. Menashe V, Farrehi F, Miller M. Hypoventilation and cor pulmonale due to chronic upper airway obstruction. *J Pediatr* 1965;67:198-203.
7. Gozal D. Sleep-disordered breathing and school performance in children. *Pediatrics* 1998;102:616-20.
8. Pratt LW. Tonsillectomy and adenoidectomy: mortality and morbidity. *Trans Am Acad Ophthalmol Otolaryngol* 1970;74:1146-54.
9. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;310:674-83.
10. Crysedale WS, Russel D. Complications of tonsillectomy and adenoidectomy in 9409 children observed overnight. *CMAJ* 1986;135:1139-42.
11. McColley SA, April MM, Carroll JL, Naclerio RM, Loughlin GM. Respiratory compromise after adenotonsillectomy in children with obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 1992;118:940-5.
12. Rosen GM, Muckle RP, Mahowald MW, Goding GS, Ullevig C. Postoperative respiratory compromise in children with obstructive sleep apnea syndrome: can it be anticipated? *Pediatrics* 1994;93:784-8.
13. Marcus CL. Management of obstructive sleep apnea in childhood. *Curr Opin Pulm Med* 1997;3:464-9.
14. Al-Ghamdi SA, Manoukian JJ, Morielli A, Oudjhane K, Ducharme FM, Brouillette RT. Do systemic corticosteroids effectively treat obstructive sleep apnea secondary to adenotonsillar hypertrophy? *Laryngoscope* 1997; 107:1382-7.

15. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. *Pediatrics* 1995; 95:355-64.
16. Fernbach SK, Brouillette RT, Riggs TW, Hunt CE. Radiologic evaluation of adenoids and tonsils in children with obstructive sleep apnea: plain films and fluoroscopy. *Pediatr Radiol* 1983;13: 258-65.
17. Brodsky L. Modern assessment of tonsils and adenoids. *Pediatr Clin North Am* 1989;36:1551-69.
18. Brouillette RT, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984;105:10-4.
19. Loughlin GM, Brouillette RT, Brooks LJ, Carroll JL, Chipps BE, England SJ, et al. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med* 1996;153:866-78.
20. Jacob SV, Morielli A, Mograss MA, Ducharme FM, Schloss MD, Brouillette RT. Home testing for pediatric obstructive sleep apnea syndrome secondary to adenotonsillar hypertrophy. *Pediatr Pulmonol* 1995;20:241-52.
21. Fluticasone Propionate Collaborative Pediatric Working Group. Treatment of seasonal allergic rhinitis with once-daily intranasal fluticasone propionate therapy in children. *J Pediatr* 1994; 125:628-34.
22. Brouillette RT, Jacob SV, Morielli A, Mograss M, Lafontaine V, Ducharme F, et al. There's no place like home: evaluation of obstructive sleep apnea in the child's home. *Pediatr Pulmonol Suppl* 1995;11:86-8.
23. Morielli A, Ladan S, Ducharme FM, Brouillette RT. Can sleep and wakefulness be distinguished in children by cardiorespiratory and videotape recordings? *Chest* 1996;109:680-7.
24. Mograss MA, Ducharme FM, Brouillette RT. Movement/arousals. Description, classification, and relationship to sleep apnea in children. *Am J Respir Crit Care Med* 1994;150:1690-6.
25. Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. *Pediatrics* 2000;105:405-12.
26. Carroll JL, McColley SA, Marcus CL, Curtis S, Loughlin GM. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. *Chest* 1995;108: 610-8.
27. Brouillette RT, Thach BT. A neuromuscular mechanism maintaining extrathoracic airway patency. *J Appl Physiol* 1979;46:772-9.
28. Remmers JE, DeGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978;44:931-8.
29. Suen JS, Arnold JE, Brooks LJ. Adenotonsillectomy for treatment of obstructive sleep apnea in children. *Arch Otolaryngol Head Neck Surg* 1995; 121:525-30.
30. Isono S, Shimada A, Utsugi M, Konno A, Nishino T. Comparison of static mechanical properties of the passive pharynx between normal children and children with sleep-disordered breathing. *Am J Respir Crit Care Med* 1998;157: 1204-12.
31. McColley SA, Carroll JL, Curtis S, Loughlin GM, Sampson HA. High prevalence of allergic sensitization in children with habitual snoring and obstructive sleep apnea. *Chest* 1997;111: 170-3.
32. Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999; 104:107-14.
33. Vargas R, Dockhorn RJ, Findlay SR, Korenblat PE, Field EA, Kral KM. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol* 1998; 102:191-7.
34. Agertoft L, Pederson S. Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide. *J Allergy Clin Immunol* 1999;104:948-52.
35. Ferguson AC, Spier S, Manjra A, Versteegh FGA, Mark S, Zhang P. Efficacy and safety of high-dose inhaled steroids in children with asthma: a comparison of fluticasone propionate with budesonide. *J Pediatr* 1999;134: 422-7.
36. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;159:941-55.
37. Barnes PJ, Pederson S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148: S1-26.
38. McDowall JE, Mackie AE, Ventresca GP, Bye A. Pharmacokinetics and bioavailability of intranasal fluticasone in humans. *Clin Drug Invest* 1997;14: 44-52.
39. Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990;84(Suppl A):25-9.
40. Paradise JL, Bluestone CD, Stool SE, Kenna MA, editors. *Pediatric otolaryngology*. 3rd ed. Tonsillectomy and adenoidectomy. Philadelphia: WB Saunders Co; 1996; p. 1054-65.