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Pediatric Adenoidal Hypertrophy and Nasal Airway Obstruction: Reduction With Aqueous Nasal Beclomethasone
Jeffrey G. Demain and David W. Goetz
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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ABSTRACT. Objective. Pediatric adenoidal obstruction of the nasal airway is associated with significant morbidity and is a frequent indication for surgery. Because efficacious medical alternatives to adenoidectomy are lacking, we assessed the potency of standard-dose topical nasal beclomethasone in reduction of adenoidal obstruction of the nasal airway.

Methods. Seventeen children, 5 to 11 years of age, exhibiting chronic obstructive nasal symptoms and a group mean (±SE) adenoid/choana ratio of 91 ± 1% on rhinoscopic examination, completed an 8-week, double-blind, placebo-controlled crossover study of standard-dose aqueous nasal beclomethasone (total 336 µg/day) in the treatment of adenoidal hypertrophy. In a 16-week, open-label, follow-on study, subjects received beclomethasone 1 spray in each nostril twice daily (168 µg/day).

Results. Over the initial 4 weeks, improvements in the mean adenoidal obstruction of the choanae were significantly greater in the group receiving beclomethasone than in the group receiving placebo (right, −14.0% vs. +0.4%, P = .0002) (left, −15.0% vs. −2.0%, P = .0006). In the subsequent crossover 4 weeks, a significant beclomethasone carryover effect resulted in further adenoidal size reduction in both treatment groups. All patients demonstrated a decrease in adenoid size with beclomethasone treatment, compared with a mixed response to placebo. Over the full 8-week crossover study, the mean (±SE) obstructive symptom score after beclomethasone treatment (20.5 ± 3.0) was significantly improved compared to patients’ initial (43.1 ± 2.9) and placebo scores (31.1 ± 4.2, P ≤ .05), despite the active drug carryover effect into the placebo treatment period. Significant improvements in adenoidal obstruction and symptom scores over the 8-week crossover study were enhanced in the subsequent 16-week open-label period (P = .0001). By 24 weeks, an 82% reduction in group mean nasal obstruction symptom score accompanied a 29% mean reduction in adenoid/choana ratio. No clinical or demographic characteristic predicted a patient’s degree of response to treatment.


Adenoidal hypertrophy producing nasal airway obstruction remains one of the most frequent indications for surgery in children.1 While prolonged adenoidal upper airway obstruction resulting in obstructive sleep apnea or cardiorespiratory syndrome may elicit prompt surgical intervention, lesser degrees of obstruction also may produce significant pediatric morbidity but less aggressive intervention.2–4 Chronic sinusitis, recurrent otitis media with effusion, and chronic serous otitis media associated with pediatric adenoidal hypertrophy are common indications for surgical removal of the adenoid.5,7 As adjunctive treatments of chronic sinusitis and chronic otitis media, nonsurgical alternatives for reduction of adenoid size are limited. Several days of oral steroids will produce a prompt, but temporary, reduction in adenoid size. More commonly, medical management is indirect, treating concurrent infections and the complications of adenoidal enlargement.9

In an 8-week, double-blind, placebo-controlled crossover study of children 5 to 11 years of age, we evaluated the efficacy of standard-dose topical nasal beclomethasone in reducing adenoidal obstruction of the nasal airway. Topical beclomethasone treatment significantly reduced both adenoid size and patient obstructive symptom scores compared to placebo. This relief of adenoidal obstruction of the nasal airway was maintained and enhanced during a 16-week, follow-on, open study of topical beclomethasone in reduced doses.

METHODS

Study Population
Twenty children, ages 5 to 11 years old, were recruited from a military-dependent population presenting to the Wilford Hall Medical Center Allergy and Immunology Clinic with the complaint of chronic nasal obstruction. Most subjects had been treated and followed previously in either the pediatric or allergy/immunology clinic with both chronic nasal obstruction and symptoms of chronic otitis media, serous otitis media, or chronic sinusitis. Inclusion criteria for the study required that each patient have an estimated 90% or greater adenoidal obstruction of the nasal airway on initial rhinoscopic examination. Subjects were excluded if they had used intranasal, topical, or systemic steroids within the last year; had used any intranasal medication within 2 weeks of entering the study; had an active upper respiratory infection within 2 weeks of entering the study; or had a history of chronic epistaxis, immunodeficiency, or hypersensitivity to beclomethasone.
Study Design

The study was double-blind, placebo-controlled, and crossover in design. All patients enrolled in the study were individually randomized to receive either 4 weeks of intranasal aqueous beclomethasone nasal spray followed by 4 weeks of placebo or the two drugs in the reverse order. Both the active drug and placebo were dispensed in the same commercially available pump spray bottle. At the end of the first 4-week period, the patient returned the initial spray bottle and received the bottle containing the crossover treatment. Compounded from normal saline and rose water, the placebo had a consistency and floral scent similar to the active drug. Preparation and dispensing of drugs, as well as randomization, were performed by each arm of the study, was accomplished independently by a clinical pharmacologist.

Informed consent for participation in this study was obtained from the parent or legal guardian of each patient enrolled. The study design and consent form were approved by the Wilford Hall Medical Center Institutional Review Committee. While scientifically preferable, ethical concern for the length of time during which pediatric patients would have been without active treatment precluded acceptance by the Institutional Review Committee of a study design with a washout period between the two arms of the study.

During the 8-week crossover study, patients dispensed two sprays of the study drug in each nostril twice daily (placebo or 336 µg/day). At their initial visit and subsequent follow-ups, all patients were instructed in the technique of neck flexion while dispensing from a vertically held bottle in order to direct the spray toward the posterior nasal cavity. At the completion of the 8-week, double-blind, placebo-controlled crossover study, subjects continued in a 16-week open assessment of intranasal aqueous beclomethasone nasal spray dispensed as 1 spray (42 µg) in each nostril twice daily (168 µg/day).

Evaluations and Patient Management

Initial assessment of each patient upon entering the study included the following: history and physical examination, parental questionnaire, sinus roentgenogram, pulmonary spirometry, prick skin testing to aeroallergens, nasal cytology for eosinophils, tympanogram, audiogram, and fiberoptic rhinoscopy to evaluate adenoid tissue as well as to assess nasal and sinus disease. Initial patient history was reviewed for study inclusion criteria, age, race, sex, chronic or intermittent medications, history of atopy, and family history of atopy. Subsequent assessments during the cross-over portion of the study were made at 4 and 8 weeks, while assessments during the open follow-on were accomplished at 16 and 24 weeks. Assessments at these times included the following: interim history, physical examination, parental questionnaire, tympanogram, audiogram, and rhinoscopy. Tympanometry and audiology examinations were performed by a certified audiologist. All other examinations and assessments were completed by a single investigator (J. G. D.).

The symptom questionnaire accomplished at enrollment and at each subsequent visit used visual analog scales to measure parental assessment of the patient’s nasal congestion, nasal voice, snoring, daytime drowsiness, restless sleep, nasal discharge, ear popping/pain, and bad breath. The parent indicated the degree of each symptom by placing a mark on a 100-mm ungraduated line. The distance from the left edge of the line to the mark was converted to a symptom score of 0.0 (never has the symptom) to 10.0 (constantly has the symptom). Parents did not have access to scores from previous visits. Scores from all eight assessments at a single visit were added together to provide a total symptom score of the patient (range 0.0 to 80.0). At each visit parents also reported the patient’s bed wetting frequency on a similar analog scale (range 0.0 to 10.0). On the same questionnaire, parents estimated the number of drug doses missed per week and reported any side effects (stinging, nose bleeds, or sneezing) related to the use of the nasal spray during the preceding treatment period.

Routine four-view sinus roentgenograms were read by the investigator and subsequently reviewed in the radiology department. A MultiSpirio-SX spirometry system (MultiSpirio, Inc., Irvine, CA) was used to assess pulmonary function. Prick skin tests to tree, grass, weed, and mold extract mixes as well as Dermatophagoides pteronyssinus and Dermatophagoides farinae dust mites (Hollister-Stier, Spokane, WA) were graded as follows: 0, no erythema or wheal; 1+, erythema ≤ 20 mm; 2+, erythema ≥ 20 mm; 3+, erythema with wheal ≥ 3 mm; and a pseudopod. Prick skin tests ≥ 3+ were considered positive. The patient was considered atopic if one or more of the five skin tests was positive. Eosinophils in freshly collected, Hansel stained nasal secretion (Hollister-Stier, Spokane, WA) were counted as a percentage of all leukocytes identified on light microscopy.

Adenoid size was assessed during rhinolaryngoscopic examination with an Olympus flexible P-2 Rhinolaryngoscope (Olympus Corporation, Lake Success, NY). Patients were pretreated with 0.05% oxymetazoline hydrochloride and 4% lidocaine nasal sprays. Rhinoscopy was well tolerated, and only one prospective study patient failed to be enrolled because of intolerance of the rhinoscopic examination. During initial evaluation and at each subsequent assessment, color 35-mm transparencies were taken of both left and right posterior choanae and adenoid using an Olympus OM-2 camera adapted to the rhinoscope. Photographs were taken with the patient in quiet nasal respiration. At completion of the study, before the disclosure of patient assignment to crossover treatment groups, the transparencies from each patient were presented in a random sequence for analysis by one investigator (D. W. G.) who was blinded to patient identity and photograph sequence. The two-dimensional areas of the adenoid and choana were measured on the projected transparency by planimetry, tracing the perimeter of the image on a Zeiss Interactive Digital Analysis System (Carl Zeiss, Inc., Thornwood, NY). Reproducibility of area measurements by this technique was ± 0.6%. Adenoidal obstruction was calculated as the ratio of the two-dimensional area of the adenoid relative to the area of the posterior choana.

Middle ear pressures and tympanic membrane mobility were measured on a GMI-33 Middle Ear Analyzer (Grason-Stadler, Inc., Littleton, MA) at each assessment. Ascending and descending peak pressures (mmH2O) were averaged to achieve a more reproducible measure of the middle ear pressure in each ear. Audiology examination was accomplished on a GSI-10 or GSI-12 Audiometer (Grason-Stadler, Inc.). Speech thresholds and pure-tone thresholds (250 to 6000 dB) were recorded for each ear. For statistical comparisons, a pure-tone average threshold was calculated for each ear as the mean of the 500-, 1000-, and 2000-dB pure-tone thresholds. At all initial and subsequent evaluations, tympanometry and audiology examinations were accomplished by an American Speech, Language, and Hearing Association certified audiologist.

Compliance with medications was assessed both by the parent questionnaire and by measurement of drug weight administered over each 4-week treatment period. Spray bottles were weighed before dispensing to the patient and again when they were returned at the end of the treatment period. The total drug administered by the patient was calculated as the difference in bottle weights.

At each visit any illness (eg, otitis media, sinusitis, pharyngitis) in the intervening period since the patient was last seen was recorded, along with any treatments the patient received for the illness. Whether given at interval study visits or as part of intervening acute management, patients received routine medical care for all intercurrent illness. Any use of systemic steroids resulted in removal of the patient from the study.

Statistical Analysis

Statistical analyses were performed using the appropriate non-parametric test for nominal or ordinal data: the McNemar chi-square, Wilcoxon signed-rank, or Friedman test. Statistical analysis of all quantitative data employed the appropriate paired or unpaired t test, or a one- or two-factor repeated measures analysis of variance (ANOVA). When ANOVA showed significant differences, specific comparisons among means were made using the Scheffe F test. Correlations were calculated using the Pearson correlation coefficient. Two-tailed tests with significance level α = 0.05 were used in all comparisons.

RESULTS

Subjects

Twenty patients, 10 male and 10 female, aged 5 to 11 years were enrolled in the study. Presenting complaints were chronic nasal obstruction alone (12 subjects), chronic nasal obstruction plus chronic otitis media (6 subjects), and chronic nasal obstruction...
plus chronic sinusitis (2 subjects). Duration of symptoms had been from 2 to 6 years.

Seventeen patients completed the 8-week double-blind, placebo-controlled crossover study. One patient from the placebo/beclomethasone group was withdrawn from the study because he received systemic steroids for an acute exacerbation of asthma. The other two patients (one from each treatment group) were lost to follow-up, in one case because of parental deployment during the Persian Gulf War.

The 8-week crossover study included seven subjects in the beclomethasone/placebo treatment arm and 10 subjects in the placebo/beclomethasone arm. All were Caucasian, 8 male and 9 female, 5 to 11 years of age (7.77 ± 0.46 years (mean ± SE)). Nine were atopic by skin test criteria. Nasal cytology identified >5% nasal eosinophils in two of the atopic and none of the nonatopic subjects. Spirometry demonstrated a mild obstructive pattern in 2 subjects, with 1 being atopic and 1 nonatopic. Roentgenograms demonstrated sinusitis in 3 subjects, who were treated appropriately with antibiotics before entry into the study.

Of the 17 subjects, 7 had a personal history of atopy (asthma, allergic rhinitis, or atopic dermatitis); 12 had a family history of atopy; 6 had a history of chronic otitis media; 3 had a history of chronic sinusitis; and 4 had previously received tympanostomy tubes. No patient had tympanostomy tubes in place at the time of the study. One subject, 11 years of age, had undergone adenoidectomy 5 years before. At entry into the study, 2 subjects were using medications for asthma (inhaled β agonists and cromolyn sodium only), and 5 used antihistamine/decongestants intermittently. No patient had received nasal steroids before the study.

Fifteen subjects completed the study through week 16, and 14 patients completed the full 24-week period of blinded plus open treatment. Subjects not returning for follow-up were commonly unable to do so because of parental reassignment or deployment out of the area. Rhinoscopy was well tolerated by all study patients, without complications, during the initial and subsequent rhinoscopic examinations. On rhinoscopic examination, no subject demonstrated anatomical obstruction of the nasal airway other than adenoidal hypertrophy.

Treatment Compliance and Side Effects

Compliance with twice daily nasal spray was comparable between treatment periods as assessed by parental report and total weight of drug dispensed during each 4-week treatment period. Parents reported between 0 and 4 missed doses/week in either period, with 0.89 ± 0.25 (mean ± SE) missed doses/week during beclomethasone treatment and 1.05 ± 0.31 missed doses/week during placebo (P = .58). The average total drug dispensed by each subject during active treatment with beclomethasone (19.59 ± 1.04 grams) was similar to that dispensed during placebo administration (19.24 ± 1.18 grams, P = .81).

Side effects associated with use of an intranasal aqueous spray were similar for subjects when receiving beclomethasone or placebo. During the crossover study, stinging was reported by 6 subjects while taking beclomethasone and 1 subject while receiving placebo (P = .06); epistaxis was recorded by 2 subjects on beclomethasone and 1 on placebo (P = 1.00); and 1 subject reported sneezing while receiving beclomethasone compared to 4 receiving placebo (P = .25).

Illnesses During the Study

During the study, patients received routine medical care for all intercurrent illnesses. In the first 4 weeks of the crossover study, 5 subjects received antibiotics: 3 for sinusitis, 1 for bilateral otitis media, and 1 for streptococcal pharyngitis. Three of these subjects were receiving beclomethasone, and 2 were receiving placebo. During the second 4 weeks of the crossover study, 2 additional subjects, both of whom had received placebo during the first 4 weeks, required initiation of antibiotics for otitis media and sinusitis, respectively. No subject who had received beclomethasone in the initial 4 weeks of the study required initiation of treatment with antibiotics during the subsequent 4 weeks. The frequency of antibiotic usage during the beclomethasone and placebo treatment periods was not significantly different (P = .26).

During the 16-week open study period, one subject required initiation of antibiotic treatment for sinusitis in each of the 8-week periods.

Adenoid Size

Comparisons of the adenoidal obstruction of the choanae for the two treatment groups in the double-blind placebo-controlled 8-week crossover study are shown chronologically in Fig 1 for the right and Fig 2 for the left choana. Figs 1A and 2A display the mean adenoid/choana ratios for placebo/beclomethasone and beclomethasone/placebo treatment groups at 0, 4, and 8 weeks. A drug carryover effect following active beclomethasone treatment was seen in the beclomethasone/placebo treatment group during placebo administration. For both right and left choana examinations, this carryover effect was evident as a continued improvement in the mean adenoid/choana ratio after the crossover from beclomethasone to placebo. In two-factor ANOVA of the 8-week study, the drug carryover effect was manifested by significant differences in the two treatment groups (right, P = .01) (left, P = .03); and a significant drug order-of-administration (right, P = .003) (left, P = .03).

At entry into the study, the mean adenoidal obstruction of the choanae for all subjects was 0.91 ± 0.01 (mean ± SE). Between 0 and 4 weeks, the improvements in mean adenoidal obstruction in the treatment group receiving beclomethasone were statistically greater than in the group receiving placebo (right, −0.14 vs +0.004, P = .0002) (left, −0.15 vs −0.02, P = .0006). Subsequent changes in adenoidal obstruction for the two drug treatment groups were not statistically different between 4 and 8 weeks due to the active drug carryover effect.

Comparisons of the mean adenoidal obstructions in the two treatment groups at the initiation of the study.
study demonstrated no difference between groups in either the right or left adenoidal/choana ratios (right, \( P = .44 \)) (left, \( P = .78 \)). In contrast to the drug order-dependent changes during placebo administrations, significant improvements in mean adenoidal obstruction were similar for both treatment groups during active beclomethasone treatments (placebo/beclomethasone group, weeks 4 to 8 (right, \( -0.15, P = .0002 \)) (left, \( -0.12, P = .002 \)) and beclomethasone/placebo group, weeks 0 to 4 (right, \( -0.14, P = .001 \)) (left, \( -0.15, P = .0004 \))). For comparison, no significant change in mean adenoidal obstruction was seen with placebo when administered as the first drug in weeks 0 to 4 (placebo/beclomethasone group (right, +0.004, \( P = .83 \)) (left, \( -0.02, P = .25 \))).

Mean adenoidal obstructions for all patients at 0, 4, and 8 weeks demonstrated a significant improvement over the 8-week study period (right and left, \( P = .0001 \)). Further statistical analyses demonstrated that presenting complaint, sex, atopy, family history of atopy, history of chronic illness, use of accessory medications, and intercurrent illness during the study were not significantly related to the changes in adenoidal obstruction during the study.

Individual patient responses (Figs 1B, 1C and 2B, 2C) showed a decrease in the adenoidal obstruction for all patients during the beclomethasone treatment period, contrasted to a mixed response during the 4 weeks of placebo administration. This was true despite the drug carryover effect in the beclomethasone/placebo treatment group.

Figure 3 displays the improvement in adenoidal obstruction of the choanae over the full 24 weeks of blinded plus open treatment. Right and left choanal obstruction improved in parallel fashion. The decrease in adenoidal obstruction was statistically significant over the 24 weeks (right and left, \( P = .0001 \)), as well as between most paired examination times (specific comparisons not shown). The change in slope of adenoidal obstruction improvement after 8 weeks corresponded with the reduction in dose from 2 to only 1 spray in each nostril twice daily.

Tymanometry and Audiology

In the double-blind, placebo-controlled 8-week crossover study, there was a statistical trend toward improvement in mean (±SE) middle ear pressures with beclomethasone treatment (right, \( -23 ± 8 \) mmH\(_2\)O) (left, \( -49 ± 12 \) mmH\(_2\)O) compared to initial (right, \( -51 ± 21 \) mmH\(_2\)O) (left, \( -112 ± 36 \) mmH\(_2\)O) and placebo administration values (right, \( -73 ± 26 \) mmH\(_2\)O, \( P = .06 \)) (left, \( -80 ± 28 \) mmH\(_2\)O, \( P = .07 \)). This trend toward improvement with beclomethasone treatment was maintained for middle ear pressures followed through the open treatment period (24 weeks (right, \( -26 ± 9 \) mmH\(_2\)O) (left, \( -23 ± 8 \) mmH\(_2\)O)).

Pure-tone average thresholds in the 8-week crossover study also demonstrated a statistical trend toward improvement with beclomethasone treatment compared to initial and placebo values (right, \( P = .04 \)) (left, \( P = .21 \)); however changes in the pure-tone average thresholds were <10 dB and
A)

![Graph](image)

**Fig 2.** Adenoidal obstruction of the left choana at weeks 0, 4, and 8. Mean (A) and individual subject data (B and C) for both placebo/beclomethasone (n = 10) and beclomethasone/placebo (n = 7) crossover groups are shown. From 4 to 8 weeks, a drug carryover effect was evident during placebo administration in the beclomethasone/placebo group. From 0 to 4 weeks, improvement in mean adenoidal obstruction in the beclomethasone treatment group was statistically significant compared to the placebo group (P = .0006).

B)

![Graph](image)

C)

![Graph](image)

not considered clinically important differences. Beclomethasone treatment (right, 5.3 ± 0.9 dB) (left, 7.3 ± 1.5 dB), initial (right, 7.2 ± 0.9 dB) (left, 10.4 ± 2.2 dB), and placebo administration (right, 8.1 ± 1.2 dB) (left, 8.1 ± 1.6 dB) values remained within the normal range throughout the study, as did subsequent pure-tone average thresholds during the 16 weeks of open treatment (data not shown).

Patient speech thresholds showed no significant differences or trends during the 24 weeks of study. Average speech thresholds for the study group remained within the normal range (data not shown).

Statistical analyses addressing drug order-of-administration, presenting complaint, sex, atopy, family history of atopy, history of chronic illness, use of accessory medications, and intercurrent illness during the study demonstrated no significant relationships to changes in tympanometry, pure-tone average thresholds, or speech thresholds. Analyses of middle ear pressures, pure-tone average thresholds, and speech thresholds for the subgroup of six patients with a history of chronic otitis media resulted in findings similar to those of the entire study population.

**Symptom Scores**

Figure 4 displays the mean symptom scores of both drug treatment groups during the 8-week crossover study. Improvements in mean symptom scores were significant and similar for both treatment groups during active beclomethasone treatment (placebo/beclomethasone group (weeks 4 to 8), -16.9, P = .006) (beclomethasone/placebo group (weeks 0 to 4), -18.5, P = .01). In contrast, due to the lack of a washout period in the study design, the change in mean symptom score with placebo administration (weeks 4 to 8) in the beclomethasone/placebo group (+1.8, P = .67) was not comparable to that seen with placebo administration (weeks 0 to 4) in the placebo/beclomethasone group (-8.5, P = .03). As described...
for the changes in adenoidal obstruction, there was a significant drug order-of-administration effect for symptom score changes \( (P = .04) \), which accounted for differences in response to placebo administration between the two treatment groups. Subsequent statistical analyses demonstrated that presenting complaint, sex, atopy, family history of atopy, history of chronic illness, use of accessory medications, and intercurrent illness during the study were not significantly related to the changes in symptom scores during the study.

In a repeated measures ANOVA comparison of initial, beclomethasone, and placebo symptom scores of all subjects during the 8-week crossover study, mean symptom scores were significantly different \( (P = .0001) \). Despite a drug order-of-administration effect enhancing the apparent placebo treatment significance, the mean \((±SE)\) symptom score with active beclomethasone treatment \( (20.5 ± 3.0) \) was significantly improved in specific comparisons to symptom scores both initially \( (43.1 ± 2.9) \) and following placebo administration \( (31.1 ± 4.2, P ≤ .05) \).

Displayed in Fig 5, patient mean symptom scores demonstrated a significant improvement over the full 24 weeks of crossover and open treatment \( (P = .0001) \). In parallel with the adenoidal obstruction changes (Fig 3), the rate of improvement in symptom scores decreased after 8 weeks when the dose of beclomethasone was halved during the open treatment period.

Of the individual symptoms making up the total symptom score, all clinical symptoms individually showed significant improvements by ANOVA during the full 24 weeks of study (nasal congestion, nasal voice, snoring, daytime drowsiness, restless sleep, and nasal discharge (each \( P = .0001 \)); ear popping/pain \( (P = .014) \); and bad breath \( (P = .0002) \).

Figure 6 correlates the total symptom score with average adenoidal obstruction for all patients at each examination \( (n = 79) \). A significant relationship between symptom score and adenoidal obstruction was present with a correlation coefficient of 0.65 \( (P = .0001) \). A "floor effect" was evident in the correlation when symptom score values were below approximately 10.

Nine patients, 7 male and 2 female, were identified as having clinically significant enuresis if a bed wetting score \( ≥ 1.0 \) (range 0.0 to 10.0) was reported at any visit. During the 8-week crossover study, the enuresis score of this subgroup improved significantly \( (P = .02) \). Enuresis changes with treatments in the 8-week crossover study (data not shown) were parallel to those of the obstructive symptom scores shown in Fig 4. The mean \((±SE)\) enuresis score during active beclomethasone treatment \( (1.81 ± 0.30) \) was significantly improved compared to the score at entry into the study \( (4.50 ± 0.96, P ≤ .05) \). The enuresis score following placebo treatment was intermediate \( (2.94 ± 1.14) \), due in part to the drug order-of-administration effect. At completion of the blinded crossover and open-label beclomethasone treatment periods, the mean enuresis symptom score of the 8 members of the subgroup completing 24 weeks \( (2.31 ± 1.18) \) remained significantly improved compared to the mean score at entry into the study \( (4.64 ± 1.08, P = .015) \), with all but one subject reporting improvement. The improvement in enuresis was most closely correlated with the patient snoring symptom score (median individual correlation coefficient \( = 0.78 \)).

**DISCUSSION**

Adenoidal hypertrophy which obstructs the nasal airway in children is associated with multiple symp-
fers weeks to months. Further clinical trials are needed to address the ability of chronic nasal steroids to suppress adenoidal hypertrophy for longer periods (months to years). Such chronic use of topical nasal and inhaled steroids in standard doses has proven safe in the treatment of allergic rhinitis and asthma.\(^{11,12}\)

Among the technical aspects of this study, compliance in the administration of active drug or placebo was similar during each arm of the double-blind, placebo-controlled crossover study as measured by both bottle weights and parental questionnaires. The side effects attributed to nasal spray administration were also similar for active and placebo treatments.

Endoscopy was the most accurate and reproducible method for repeated assessments of adenoid size. Rhinoscopic assessment of dynamic nasal airway obstruction by the hypertrophied adenoid correlates with obstructive symptoms more closely than static radiographic assessment methods.\(^{13,14}\) For maximal reproducibility in adenoid measurement, the technical importance of evaluating nasopharyngeal airway patency during quiet nasal breathing has been demonstrated previously using nasopharyngeal radiographic assessment of the palatal airway.\(^{15}\) In agreement with this finding, we noted that quiet nasal breathing provided the most patent nasal airway and most reproducible physiologic state for measurement of adenoid size in our patients during examinations. Rhinoscopy was safe and well tolerated by our pediatric patients, except for one potential study patient who was not enrolled because of inability to cooperate with rhinoscopy. Once enrolled in the current study, even the smallest children tolerated repeated rhinoscopic examinations. During more than 80 rhinoscopic examinations, there were no complications. For comparison, in over 1700 adult and pediatric examinations, Selner\(^{16}\) reported 10 syncopal episodes, 2 coughing spasms, and 1 episode of epistaxis.

Reproducible quantification of the two-dimensional adenoid/choana area ratios allowed comparisons of the adenoid obstruction of the nasal airway among examinations. While the choana is a roughly planar structure and well defined by its area, the enlarged single adenoid is an irregular globular, three-dimensional structure which must protrude through the left and right choana to effectively obstruct them, much like corks stopper bottles. The measured adenoid/choana ratio accurately describes the obstruction at larger values around 90%, but it underrepresents the relative reduction in adenoid size and relief of obstruction when ratios decrease. The volume of the adenoid decreases more rapidly than its measured area; and, like a cork being removed from a bottle, the posterior regression of the treated adenoid can provide relief of airway obstruction even while the planar ratio of the adenoid to choana is substantial. Thus, the modest average 17% reduction in adenoid/choana area ratio for all subjects over the 8-week crossover study was associated with a much more striking reduction in adenoid volume visualized on rhinoscopy (eg, Fig 7) as well as significant and parallel reduction in nasal airway obstruction symptom scores.

During the study, other lymphoid tissues were not sequentially assessed. On routine physical examination, 7 of the 17 subjects completing the study were...
Fig 7. Rhinoscopic views of left choana with obstructing adenoid (patient RL). At entry into the study, the patient’s adenoid/choana ratio was 0.99 (not shown). A, at 4 weeks, after treatment with placebo, adenoid/choana ratio was 0.96; B, at 8 weeks, after crossover treatment with beclomethasone, adenoid/choana ratio was 0.75.

noted to have moderate-sized palatine tonsils at entry into the study, while no subjects were described as having extreme enlargement. This lack of palatine tonsillar hyperplasia is consistent with Stearns’17 demonstration that there is no correlation between adenoid and palatine tonsillar sizes. No clinically notable change in tonsillar size was recorded on physical examination of these 7 patients during the study, suggesting little or no effect of the topical steroids on the palatine tonsils. The demonstration of topical steroid modification of lymphoid tissues other than the adenoid would require additional study.

During the 8-week crossover study, all subjects responded to beclomethasone treatment with a decrease in adenoid size, compared to a mixed response to placebo. The significant drug carryover effect evident for adenoid/choana ratios from 4 to 8 weeks in the beclomethasone/placebo group necessitated a statistical comparison of beclomethasone to placebo other than a simple repeated measures ANOVA. In the statistical comparison of the two treatment groups from 0 to 4 weeks, before crossover, adenoidal obstruction was significantly reduced by active beclomethasone treatment compared to placebo (Figs 1 and 2). Group mean improvements in adenoidal obstruction were significant and similar during beclomethasone treatment in both crossover groups. The strong beclomethasone carryover effect into placebo administration in the beclomethasone/placebo group suggested that, if the study had been allowed by the Institutional Review Committee to include a washout period, the time required to allow adenoidal obstruction to return to baseline levels (if it did return) would have been much longer than 4 weeks. During the first 4 weeks of the study, placebo nasal spray alone effected no change in mean adenoid size.

A drug order effect was evident also in comparisons of symptom scores during active and placebo crossover treatments (Fig 4). However, despite this drug order-of-administration effect which enhanced the apparent placebo treatment significance, the mean symptom score with active beclomethasone treatment was shown to be significantly improved compared to symptom scores both initially and following placebo administration.

Over the 24 weeks of study, adenoidal obstruction and total symptom score were correlated significantly (Fig 6), and each demonstrated clinically significant parallel improvements (Figs 3 and 5). During the 8-week crossover study in which patients received 4 weeks of beclomethasone treatment, a 17% reduction in mean adenoid/choana ratio was accompanied by a 51% reduction (from 43.1 to 21.2) in mean nasal obstruction score. By 24 weeks, a 29% reduction in mean adenoid/choana ratio was paralleled by an 82% reduction in mean nasal obstruction score to 7.9, less than the “floor” symptom score level noted in Fig 6 (ie, a minimum mean symptom score had been achieved). The correlation between rhinoscopically assessed adenoidal obstruction and symptom score is consistent with previous studies showing that patient clinical evaluations correlate well with endoscopic assessments of obstruction.6'13'14 The rates of improvement in adenoidal obstruction and symptom scores, as evidenced by the slopes of the curves, decreased after 8 weeks, coincident with the reduction in beclomethasone dosing to one puff in each nostril twice a day during the open-label portion of the study. While this change may be coincidental or a function of the degree of improvement over the first 8 weeks, it is probable that halving the dose produced the reduction in clinical response. Confirming the response of adenoidal hypertrophy to various nasal steroid doses will require further study.

Although the rate of improvement varied over the 24 weeks of blinded and open study, all subjects demonstrated both an objective decrease in adenoid
size and decreased symptom scores with topical beclomethasone treatment. No clinical or demographic characteristic predicted a patient’s degree of response to treatment with nasal aqueous beclomethasone. Even atopy, which was found in approximately half of the subjects (9/17 by skin test and 7/17 by history), did not differentiate between subjects in degree of response to treatment. While this study was limited to 24-week duration, it is possible that similar clinical improvement can be maintained over longer intervals. Two patients who had subsequent evaluations at 1 year demonstrated continued control of adenoidal obstruction, symptom score, and enuresis on chronic beclomethasone, one spray in each nostril twice a day (data not shown). While similar results might be expected with topical nasal steroid preparations other than beclomethasone, their efficacy can only be inferred and would require confirmation through further studies.

For most patients with adenoidal hypertrophy and enuresis, beclomethasone treatment was accompanied by reduction in reported enuresis episodes. Enuresis may be secondary to nocturnal respiratory disturbances caused by upper airway obstruction. In a study of 115 children, 3 to 19 years of age, 76% had fewer enuresis episodes after surgical removal of an upper airway obstruction. In that study, improvement in enuresis was most pronounced in subjects with secondary enuresis and was attributed to improved quality and quantity of sleep. In a similar manner, the improvement in enuresis seen in 8 of 9 subjects in this study accompanied reduction in adenoid size and an improvement in upper airway obstructive symptoms with beclomethasone treatment.

In concert with the improvements seen in adenoid size and symptom scores, the frequency of intercurrent illnesses requiring antibiotic treatment decreased with beclomethasone treatment during both the initial 8-week crossover and subsequent 16-week open-label study. The initiation of antibiotics in 7 subjects during the first 8 weeks was followed by an antibiotic requirement in only 1 additional patient in each of the subsequent 8-week periods.

While both middle ear pressures and pure-tone average thresholds demonstrated a trend toward improvement with beclomethasone compared to placebo, both these measures of middle ear pathology, as well as speech thresholds, were insensitive measures for objective improvement in this study. This insensitivity is understandable since the study patients were not selected for middle ear disease and most did not have more than mild middle ear pathology associated with their adenoidal hypertrophy. Group average tympanic and auditory measures were all within the normal range. Only 6 patients had a past history of chronic ear disease. The two subjects treated for otitis media during the study period were among those history-positive patients and were treated during the first 8 weeks. No cases of otitis media were treated during the 16-week open-labeled study.

Several mechanical and/or immunological mechanisms may be postulated for the reduction of adenoid size and symptoms of nasal airway obstruction with topical beclomethasone. Reduction in adenoid size may be due to a direct lympholytic action of topical steroids on adenoid tissue and, secondarily, to a general corticosteroid inhibition of inflammation in the respiratory tissues. Relief of nasal airway obstructive symptoms would then follow through a combination of mechanical increase in airway caliber and reduction in tissue inflammation. An additional mechanism may involve topical steroid alteration of adenoid bacterial flora. While direct adenoidectomy relieves upper airway obstructive symptoms and complications of adenoidal hyperplasia, the efficacy of adenoidectomy in the specific treatment of chronic otitis media is considered to be independent of adenoid size and a result of removal of a pharyngeal nidus of infection supplied by the enlarged adenoid. Other studies have supported both the lack of correlation of adenoid size with presence of chronic otitis media and the importance of the adenoid as a reservoir of pathologic bacteria that may potentiate airway and ear disease. Fujiyoshi et al demonstrated adenoidal tissue histological changes and immunologic activation consistent with chronic inflammation of the enlarged adenoid in a group of 100 patients undergoing adenoidectomy for severe upper airway obstruction. Considering these previous observations, we may speculate that improved symptoms of nasal airway obstruction with topical nasal beclomethasone may be a result of one or more of the following mechanisms: direct reduction of adenoid size, reduction in adenoid and nasopharyngeal inflammation, and/or decreased significance of the adenoid as a nidus for infection. Definitive mechanisms by which topical nasal steroids reduce adenoid size and nasal airway obstructive symptoms will require further research with direct tissue examination during treatment.

In summary, an 8-week double-blind, placebo-controlled crossover study of 17 children, 5 to 11 years of age, demonstrated the efficacy of standard-dose topical nasal beclomethasone in reducing adenoidal obstruction of the nasal airway. Patients used a flexed neck position when administering the intranasal aqueous beclomethasone. Treatment significantly reduced both adenoid size and patient obstructive symptom scores compared to placebo. This relief of adenoidal obstruction of the nasal airway was maintained and enhanced during a 16-week follow-on open study of topical beclomethasone in reduced doses. By 24 weeks, an 82% reduction in mean nasal obstruction symptom score accompanied a 29% mean reduction in adenoid/choana ratio. No clinical or demographic characteristic predicted a patient’s degree of response to treatment. Over the full 24 weeks of blinded and open study, the study group experienced a reduction in frequency of treated upper airway and ear infections. In the subset of patients with enuresis, improvement in enuresis frequency was noted with active beclomethasone treatment.

ACKNOWLEDGMENTS

We are indebted to Cliff Butzin, PhD for his direction in statistical analyses. We also wish to acknowledge the support and
advice of Stephen Davis, PharmD, Lee Burrow, MA, David Parsons, MD, and Theodore Freeman, MD.

REFERENCES

2. Grundfast KM, Wittich DJ. Adenotonsillar hypertrophy and upper airway obstruction in evolutionary perspective. Laryngoscope. 1982;92:650-656

1994 RED BOOK ERRATA

Page 20: In the last sentence on page, delete "pneumococcal polyvalent polysaccharide and meningococcal quadrivalent polysaccharide." Sentence should read:

"However, certain vaccines (eg, Haemophilus influenzae vaccines) recommended for IM injection may be given subcutaneously to persons at risk for hemorrhage after IM injection, such as those with hemophilia."

Page 68: In fourth paragraph, change Energix to Engerix.

Page 229: In Table 3.12, change heading of last column, Energix-B to Engerix-B.

Page 238: In Table 3.17, the second column, under "HBsAg-Positive," the last entry should read:

2. If adequate, (not 2. If inadequate, no treatment no treatment)

Page 319: In Table 3.30, entry for Hepatitis B prophylaxis should have "3" entered in the last column under "Interval (mo)." Line should read:

<table>
<thead>
<tr>
<th>Hepatitis B prophylaxis</th>
<th>IM 0.06 mL/kg</th>
<th>10 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(as HBIG)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Page 382: Under the heading "Recommendations for IPV," in the third paragraph, second sentence, change OPV to IPV. Sentence should read:

If IPV and DTP are given at the same time, they should be given in separate syringes because of possible interference.

Page 476: Under the heading "Treatment" for Trichomonas vaginalis Infections, change (120 g) to (1 g). The fifth sentence should read:

Treatment failures should be retreated with metronidazole (1 g in two divided doses for adolescents and adults) for 7 days.

Page 566: In Table 5.5, the second to last entry, under the first and second columns, "Drugs" and "Strength" should read:

Selenium sulfide 2.5%

(not Selenium sulfide 1%)
Pediatric Adenoidal Hypertrophy and Nasal Airway Obstruction: Reduction With Aqueous Nasal Beclomethasone
Jeffrey G. Demain and David W. Goetz

*Pediatrics* 1995;95:355-364

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