Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion

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Background: Following otitis media, 10% to 50% of children develop residual middle ear effusion with concurrent hearing loss and potential cognitive, behavioral, and language impairment. Prophylactic antibiotics and tympanostomy tubes are currently recommended treatments for chronic middle ear effusion.

Objective: In a double-blind, placebo-controlled, randomized study of chronic middle ear effusion, we assessed the effectiveness of topical intranasal beclomethasone as an adjunct to prophylactic antibiotic therapy.

Methods: Sixty-one children, aged 3 to 11 years with persistent middle ear effusion greater than 3 months, were randomized into three treatment groups: (1) prophylactic antibiotics; (2) prophylactic antibiotics plus intranasal beclomethasone (336 μg/day); and (3) prophylactic antibiotics plus intranasal placebo. Patients were evaluated with aeroallergen skin tests at entry; and tympanogram, otoscopic examination, and symptom questionnaire at 0, 4, 8, and 12 weeks.

Results: While middle ear pressures, otoscopic examinations, and symptom scores were improved for each treatment group over 12 weeks of therapy, the beclomethasone plus antibiotics group improved all three measures more rapidly than the antibiotics-alone and placebo nasal spray plus antibiotics groups over the first 8 weeks. Only the beclomethasone group significantly improved left ($P = .004$) and right ($P = .01$) middle ear pressures over 12 weeks. Resolution of chronic middle ear effusions was more frequent in the beclomethasone group ($P \leq .05$ at 4 and 8 weeks). No difference in response to nasal steroids was observed between atopic and nonatopic subjects.

Conclusions: We conclude that intranasal beclomethasone may be a useful adjunct to prophylactic antibiotic treatment of chronic middle ear effusion.

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INTRODUCTION

Otitis media is one of the most common illnesses seen in a pediatrician's office, accounting for more than 30 million visits each year in the United States.[1] The majority of children with acute otitis media will resolve their infection when treated with appropriate antibiotics; however, approximately 10% to 50% of patients will develop residual asymptomatic effusion.[2,3] Chronic middle ear effusions, defined as effusions persisting longer than 3 months,[2] may be accompanied by hearing loss as well as possible cognitive, behavioral, and language impairment.[3]

Current treatment of chronic middle ear effusions relies upon prophylactic, low-dose antibiotics that have been shown to promote resolution of chronic effusions.[3,4] Antihistamines and both oral and topical decongestants are ineffective in the treatment of chronic middle ear effusion unless there is evidence of contributing allergic rhinitis.[2,5] If medical treatment fails, tympanostomy tube placement (with or without adenoidectomy) is the most frequently performed surgical treatment for chronic middle ear effusion in children.[6–8]

Recently, a potential role for corticosteroids in treatment of chronic middle ear effusion has emerged. A well-controlled 1990 study by Berman et al suggests that combination therapy of trimethoprim-sulfamethoxazole for 4 weeks plus prednisone for seven days promotes the resolution of persistent middle ear effusion and can reduce the need for tympanostomy tube placement by 30% to 40% in children with persistent middle ear effusion.[9] This and other studies support the short-term use of systemic steroids to significantly improve middle ear disease and decrease the need for surgical intervention. While systemic steroids have been extensively studied, the effectiveness of topical nasal steroids as an adjunct in treatment of chronic middle ear effusion has not been adequately evaluated.

In this double-blind, placebo-controlled randomized study of children with chronic middle ear effusion, the efficacy of intranasal aqueous beclomethasone as an adjunct to treatment with antibiotic prophylaxis is compared with both prophylactic antibiotics alone and prophylactic antibiotics plus placebo nasal spray over 12 weeks of therapy.

METHODS

Study Population

Sixty-one children, aged 3 to 11 years old, were recruited from a military-dependent population referred to the

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The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Defense or other Departments of the U.S. Government. The voluntary fully informed consent of the subjects used in this research was obtained as required by AFI 40-403.

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Wilford Hall Medical Center pediatric Chronic Ear Clinic with the complaint of chronic middle ear effusion between October 1991 and June 1992. Inclusion criteria for the study required that each patient have (1) had documented persistent middle ear effusion for a minimum of 3 months at the time of entry into the study as well as average middle ear pressures less than -150 mmH_2 at study entry, and (2) had a minimum of three episodes of acute otitis media within the past 6 months or four episodes within the past year. Subjects were excluded from the study if they had (1) used systemic steroids within the previous 6 months; (2) used any intranasal medication within the previous 2 weeks; (3) had tympanostomy tubes in place; or (4) had a history of chronic epistaxis, immunodeficiency, or hypersensitivity to beclomethasone.

Study Design

The study design utilized a randomized 3-treatment group comparison: prophylactic antibiotics alone versus prophylactic antibiotics with the double-blind, placebo-controlled addition of intranasal aqueous beclomethasone spray. The study therefore contained one active nasal spray treatment group and two control groups. Group 1 received amoxicillin 20 mg/kg divided twice a day to a maximum of 250 mg twice a day for 12 weeks, without a nasal spray. Group 2 received amoxicillin plus intranasal aqueous beclomethasone nasal spray, 2 sprays in each nostril twice a day for 12 weeks (336 μg/day of beclomethasone). Group 3 received amoxicillin plus placebo nasal spray, 2 sprays in each nostril twice a day for 12 weeks. If amoxicillin was contraindicated by the patient's history, sulfisoxazole 75 mg/kg divided twice a day to a maximum of 500 mg twice a day was substituted. Both the beclomethasone and placebo nasal spray were dispensed in the same commercially available pump spray bottle. Compounded from normal saline and rose water, the placebo had a consistency and floral scent similar to the active drug. At their initial visit and subsequent follow-ups, all patients in groups 2 and 3 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 subsequent 4-week and 8-week evaluations, nasal spray bottles were collected from each patient in groups 2 and 3 and a new bottle was dispensed. Preparation and dispensing of drugs as well as randomization of patients to 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. [Although scientifically sound, inclusion of placebo oral suspension/tablet groups were not approved by the institutional review board on ethical grounds.]

Evaluations and Patient Management

Evaluations for all patients were accomplished at 0, 4, 8, and 12 weeks. Initial assessment of each patient upon entering the study included the following: history and physical examination, symptom questionnaire, prick skin testing to aeroallergens, and tympanogram. Initial patient history was reviewed for study inclusion criteria, age, sex, history of atopy (asthma, hayfever, or chronic eczema), history of tympanostomy tube placement, family history of atopy, presence of a smoker in the home, concurrent attendance at school or daycare, and chronic or current medications. Subsequent assessments at 4, 8, and 12 weeks included the following: interim history, physical examination, symptom questionnaire, and tympanogram. Tympanometry was performed by a certified audiologist. All other examinations and assessments were completed by one of three authors, all board-certified pediatricians.

Each otoscopic examination was scored using criteria which had been cross-validated among examiners in order to minimize interexaminer descriptive variability of the three authors who accomplished all examinations. Both ears were examined and scored individually. Tympanic membranes were assessed for mobility by pneumatic otoscopy, for presence of effusion, and for retraction. Each of the three findings were scored separately and given a score of 0 (normal), 1, or 2 (very abnormal). The final otoscopic examination score, which was the composite sum of the scores for mobility, effusion, and retraction, had a range of 0 to 6.

The symptom questionnaire accomplished at enrollment and at each subsequent visit used visual analog scales to measure parental assessment of the patient's ear pain, ear popping, ear pulling, hearing loss, nasal congestion, nasal discharge, nosebleeds, snoring, bad breath, and fever. 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 ten assessments at a single visit were added together to provide a total symptom score for the patient (range 0.0 to 100.0). On the same questionnaire, parents estimated the number of drug doses missed per week during the preceding treatment period.

Middle ear pressures and tympanic membrane mobility were measured on a GMI-33 Middle-Ear Analyzer (Grason-Stradler, Inc, Littleton, MA) at each assessment. Ascending and descending peak pressures (mmH_2O) were averaged to achieve a more reproducible measure of the middle ear pressure in each ear. At all initial and subsequent evaluations, tympanometry examinations were accomplished by an American Speech, Language, and Hearing Association certified audiologist.

Prick skin tests to tree, grass, weed, and mold extract mixes as well as *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* dust mites (Hollister-Stier, Spokan, WA) were graded as follows: 0, no erythema or

wheal; 1+, erythema ≤20 mm; 2+, erythema ≥20 mm; 3+, erythema with wheal ≥3 mm; 4+, 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 were positive.

Compliance with nasal spray 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 each 4-week 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. Use of decongestant medications and initiation of allergy immunotherapy was not allowed during the study. Any use of systemic steroids resulted in removal of the patient from the study.

Statistical Analysis

Statistical analyses were performed using the appropriate nonparametric test for nominal or ordinal data: contingency table analysis, Mann-Whitney U test, Kruskal-Wallis test, or Friedman test. Statistical analysis of all quantitative data employed the appropriate paired or unpaired *t* test, factorial (nonrepeated measures) analysis of variance (ANOVA), or a one-factor or two-factor repeated measures ANOVA. When ANOVA showed significant differences, specific comparisons among means were made using the Scheffe F-test. Two-tailed tests with significant level alpha = .05 were used in all comparisons.

RESULTS

Subjects

Of 61 patients enrolled, fifty-nine (40 males and 19 females) aged 3 to 11 years [5.03 ± 0.26 years (mean ± SEM)] completed the study. Two patients were lost to follow-up when families were transferred out of the immediate area.

Table 1 summarizes the patient characteristics of each of the three treatment groups. The three treatment groups were not statistically different in any characteristic (age, sex, atopy by history or skin test, family history of allergy, history of tympanostomy tubes, presence of a smoker in the home, concurrent school or daycare, antibiotic treatment at entry into the study, or history of amoxicillin allergy). The frequency of atopy in the patient population was 24% (14/59). Of the 14 subjects on antibiotics at entry into the study, 12 were receiving or had just completed a course of amoxicillin (prescribed for acute or chronic otitis media), one was receiving penicillin (pharyngitis), and one patient was being treated with cefixime (acute otitis media). Of the four patients who received sulfisoxazole prophylaxis because amoxicillin was contraindicated by history, two were in group 1 and one each in groups 2 and 3. At entry into the study, six patients were routinely using medications for asthma [inhaled beta agonists (6), theophylline (1), and inhaled beclomethasone (1 in Group 3)], and one patient was receiving methylphenidate.

Treatment Compliance

Compliance with twice daily nasal spray was comparable between groups 2 and 3 as assessed by parental report and total weight of drug dispensed during each 4-week treatment period. Parents reported between 0 and 8 missed doses/week, with 1.37 ± 0.33 (mean ± SEM) missed doses/week in the beclomethasone group 2 versus 2.05 ± 0.44 the placebo group 3 during the first 4 weeks; 1.21 ± 0.28 versus 1.10 ± 0.28 missed doses/week during the second 4 weeks; and 1.68 ± 0.44 versus 1.70 ± 0.42 missed doses/week during the third 4 weeks ($P >$ .05 for all comparisons). The average total drug dispensed by patients during active treatment with beclomethasone

Table 1. Patient Characteristics According to Treatment Group

Characteristic	Group 1 Antibiotics Alone (n = 20)	Group 2 Antibiotics Plus Beclomethasone (n = 19)	Group 3 Antibiotics Plus Placebo Nasal Spray(n = 20)	*P* Value
Age (mean ± SEM in years)	5.90 ± 0.62	4.63 ± 0.31	4.55 ± 0.32	0.36
Sex				
Male	14	12	14	0.97
Female	6	7	6	
Atopic patient history	25%	21%	30%	0.81
Atopic by skin testing	25%	26%	20%	0.88
Family history of allergy	55%	58%	55%	0.98
History of tympanostomy tubes	20%	21%	35%	0.48
Smoker present in home	45%	16%	45%	0.09
Concurrent school or daycare	75%	84%	75%	0.93
Receiving antibiotic at entry	25%	21%	25%	0.95
History of amoxicillin allergy	10%	5%	5%	0.78

in group 2 during each of the three sequential 4-week periods (17.76 ± 1.29, 18.91 ± 1.09, and 17.96 ± 1.53 grams) was similar to that dispensed by patients receiving placebo in group 3 (18.74 ± 1.03, 16.88 ± 1.36, and 16.37 ± 1.28 grams, $P > .05$ for all comparisons).

Illnesses During the Study

During the study, patients received routine medical care for all intercurrent illnesses. Over the 12 weeks of the study, five patients received antibiotic treatment for intercurrent acute otitis media (1-trimethoprim/sulfamethoxazole, 2-erythromycin/sulfisoxazole, 1-cefixime, and 1-amoxicillin/clavulanate), and one patient received cefixime for acute sinusitis. Of these six patients, none were in group 1 (antibiotics-alone), two in group 2 (antibiotics plus beclomethasone), and four were in group 3 (antibiotics plus placebo nasal spray). The frequency of antibiotic usage for intercurrent illnesses during the 12-week study was not significantly different among the three treatment groups ($P = .11$).

Tympanometry

During the 12-week study, mean middle ear pressures improved for all three treatment groups. The mean (±SEM) mean middle ear pressure for the full cohort of 59 patients improved sequentially and significantly from the initial (right, -240 ± 13 mmH_2O) (left, -250 ± 15 mmH_2O) through the 4-week, 8-week, and 12-week (right, -164 ± 17 mmH_2O, $P = .0002$) (left, -174 ± 17 mmH_2O, $P = .0001$) evaluations.

Figures 1 and 2 display the right and left mean middle ear pressures for each of the three treatment groups. At the initiation of the study, all three treatment groups had similar right and left mean middle ear pressures. During the first 4 weeks of the study, however, the antibiotics plus beclomethasone nasal spray group 2 demonstrated a significantly greater reduction in negative middle ear pressures than the other two groups (right, $P = .010$) (left, $P = .009$). Compared with the other two groups at 4 weeks, the beclomethasone group mean middle ear pressures were significantly better than those of the antibiotics plus placebo nasal spray group (right, $P = .008$) (left, $P = .018$). Over the subsequent and final 8 weeks of the study, mean middle ear pressures improved in all three groups, with groups 1 and 3 only partially "catching-up" to group 2. At 12 weeks, the differences among groups was no longer significant.

Over the entire 12 weeks of the study, only the antibiotics plus beclomethasone nasal spray group 2 significantly improved both right and left mean middle ear pressures (right, $P = .010$) (left, $P = .004$). Over the same 12 weeks the improvements in the two control groups (groups 1 and 3) were similar in magnitude, but reached significance only for group 3 on the left ($P = .03$).

Further statistical analyses addressing sex, atopy, family history of allergy, history of tympanostomy tubes, presence of a smoker in the home, concurrent school or daycare, and antibiotic treatment at entry into the study demonstrated no significant relationships to changes in tympanometry through the course of the study.

Otoscopic Examination Scores

During the 12-week study, the median otoscopic examination score for the full cohort of 59 patients improved significantly during sequential evaluations at 0, 4, 8, and 12 weeks. Over the 12 weeks, each of the three treatment groups demonstrated individual significant improvement in right and left otoscopic examination scores ($P \leq .01$).

Figures 3 and 4 display the right and left median otoscopic examination scores for each of the three treatment groups. At the initiation of the study, all three treatment groups had similar right and left median otoscopic examination scores. In analogy to the middle ear pressure results, the improvements in otoscopic examination scores over the first 8 weeks of the study were numerically greatest for the antibiotics plus beclomethasone nasal spray group 2. The superior improvement in group 2 otoscopic examination scores was significant at 4 weeks compared with

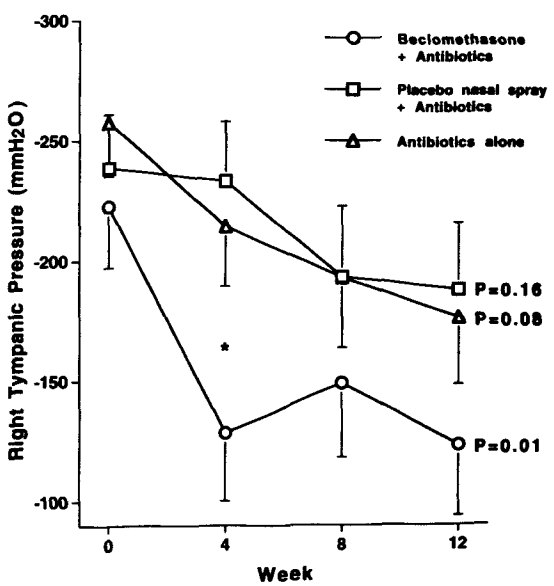

Figure 1. Right mean tympanic membrane pressures for the three treatment groups over twelve weeks of study. *P* values are shown for the repeated-measures ANOVA evaluation of each individual treatment group over 0, 4, 8, and 12 weeks. *$P = .03$ in the factorial ANOVA comparison of the three treatment groups at 4 weeks. The beclomethasone + antibiotics group had significantly more normal pressures than the placebo nasal spray + antibiotics group at 4 weeks (t-test, $P = .008$).

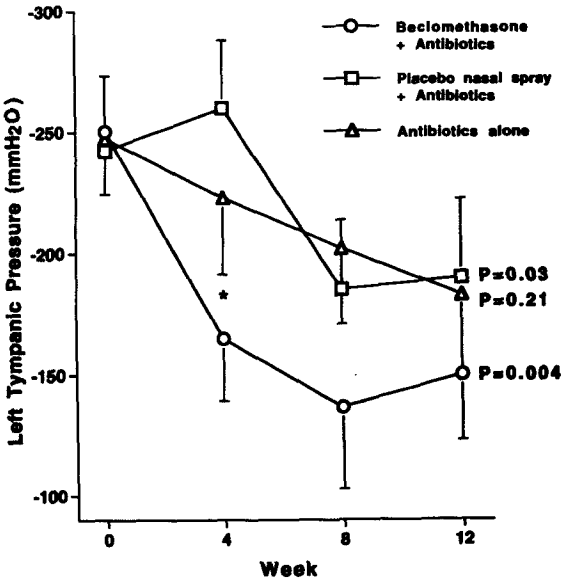

Figure 2. Left mean tympanic membrane pressures for the three treatment groups over 12 weeks of study. *P* values are shown for the repeated-measures ANOVA evaluation of each individual treatment group over 0, 4, 8, and 12 weeks. *The beclomethasone + antibiotics group had significantly more normal pressures than the placebo nasal spray + antibiotics group at 4 weeks (t-test, $P = .018$).

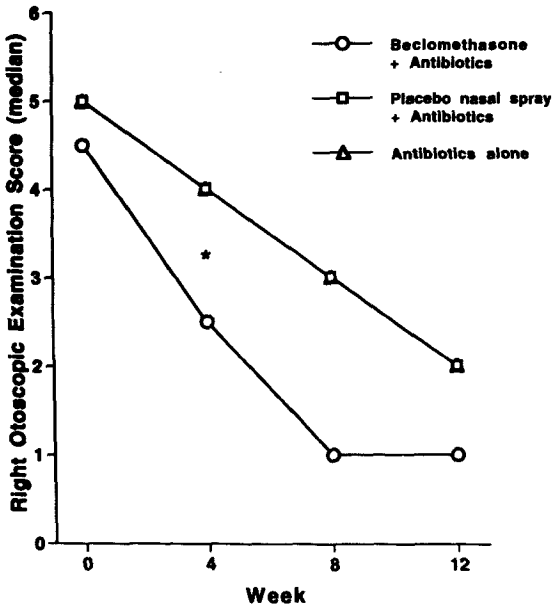

Figure 3. Right median otoscopic examination scores for the three treatment groups over the 12 weeks of study. Each individual group significantly improved otoscopic examination scores over 0, 4, 8, and 12 weeks ($P < .01$ in each group). *In paired comparison at 4 weeks, the beclomethasone + antibiotics group had achieved significantly lower scores than the placebo nasal spray + antibiotics group ($P = .03$).

the antibiotics plus placebo nasal spray group 3 (right, $P = .03$), and at 8 weeks compared with the antibiotics-alone group 1 (left, $P = .05$). Over the final 4 weeks of the study, otoscopic examination score improvement in groups 1 and 3 partially "caught-up" to group 2. By 12 weeks the difference in otoscopic examination scores among the three groups was not significant.

Further statistical analyses demonstrated that patient sex, atopy, family history of allergy, history of tympanostomy tubes, presence of a smoker in the home, concurrent school or day-care, and antibiotic treatment at entry into the study were not significantly related to the changes in otoscopic examination scores during the study.

Symptom Scores

During the 12-week study, the mean (±SEM) patient symptom score for the full cohort of 59 patients improved sequentially and significantly from the initial (35.89 ± 1.80) through the 4-week, 8-week, and 12-week (12.11 ± 1.48, $P = .0001$) evaluations. Over the 12 weeks, each of the three treatment groups demonstrated individual significant improvement in mean patient symptom scores ($P = .0001$).

For each of the three treatment groups and four evaluation times, Table 2 displays the mean total symptom score as well as a mean symptom score composed of the four ear-associated symptoms. At the initiation of the study, the symptom scores were similar for all three groups. Symptom score improvement was similar in all three treatment groups through 4 weeks. After 4 weeks, however, the improvement in the antibiotics plus beclomethasone nasal spray group 2 exceeded that of the two control groups, of which the antibiotics plus placebo nasal spray group demonstrated more improvement than the antibiotic-alone group for both total and ear-associated symptoms. By 12 weeks, the difference in symptom scores between the antibiotics plus beclomethasone nasal spray group 2 and the antibiotics-alone group 1 was significant ($P = .015$ and .008).

Subsequent statistical analyses demonstrated that sex, atopy, family history of allergy, history of tympanostomy tubes, presence of a smoker in the home, concurrent school or day-

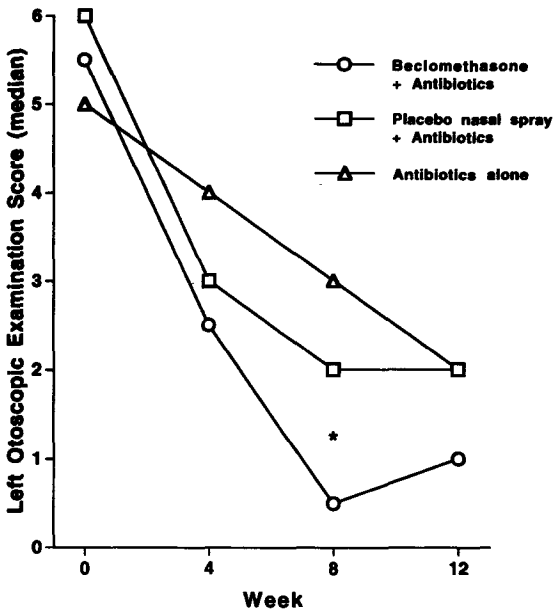

Figure 4. Left median otoscopic examination scores for the three treatment groups over the 12 weeks of study. Each individual group significantly improved otoscopic examination scores over 0, 4, 8, and 12 weeks ($P < .004$ in each group). *In paired comparison at 8 weeks, the beclomethasone + antibiotics group had achieved significantly lower scores than the antibiotics-alone group ($P = .05$).

care, and antibiotic treatment at entry into the study were not significantly related to the changes in symptom scores during the study.

Resolution of Chronic Middle Ear Effusion

For a composite clinical comparison of treatments groups, resolution of chronic middle ear effusions was compared among groups. Resolution by middle ear pressure criteria was defined as a middle ear pressure ≥ -100 mmH_2O. Resolution by ear examination score criteria was defined as a score ≤ 2 (of a maximum score of 6). Using these criteria, disease resolution by subject and by individual ear are displayed in Table 3. Because results for each measure were similar for the antibiotics-alone and the antibiotics plus placebo nasal spray groups over the 12 weeks (Figs 1 to 4), the two control groups were combined for this comparison.

Within each group, chronic middle ear effusion demonstrated significant resolution over 12 weeks. At 4, 8, and 12 weeks, the resolution of disease was greatest in the antibiotics plus beclomethasone nasal spray group for both comparisons by ears and by subjects. For the comparison by ears, this difference was statistically significant at 4 and 8 weeks, but not at 12 weeks, in concert with the previously noted "catch-up" of the control groups by the end of the study.

DISCUSSION

Otitis media is the most common medical problem in children less than 15 years of age and accounts for significant morbidity.[10] Although most children with acute otitis media resolve their effusion with antibiotic therapy, approximately 10% to 50% continue to have middle ear effusion lasting longer than 3 months.[2] Chronic middle ear effusion following otitis media has been implicated in the etiology of functional impairments in speech and language acquisition as well as decreases in hearing and attention. The extent to which chronic middle ear effusion plays a role in these long-term morbidity's continues to be debated.[12,13]

The pathogenesis of otitis media with effusion is multifactorial with eustachian tube dysfunction, infection, and inflammation among the important contributing factors.[14–16] In addition, environmental factors including day-care enrollment, passive smoking, and infant feeding practices have all been implicated as contributors to the pathogenesis of persistent middle ear effusion.[11] When avoidance of environmental risk factors fails to clear recalcitrant effusion, effective medical and surgical treatments have become the mainstay of therapy in promoting the resolution of persistent middle ear effusion. Prophylactic antibiotics are commonly employed because approximately 50% of asymptomatic chronic middle ear effusions have associated bacterial colonization, with β-lactamase activity noted in up to 79% of isolates of middle ear effusion.[4] In contrast, antihistamines and decongestants have proven ineffective in the treatment of chronic middle ear effusion in the absence of concurrent allergic rhinitis.[2,5] When middle ear effusion persists despite prophylactic antibiotics and avoidance of environmental risk factors, tympanostomy tubes are effective in promoting resolution of chronic middle ear effusion.[17]

In recent years, a potential role for corticosteroids in the treatment of chronic middle ear effusion has emerged. Several reports have analyzed the value of oral corticosteroids or the combination of oral corticosteroids with antibiotics in treatment of chronic middle ear effusion. In separate studies, Macknin and later Giebink reported 15% and 45% cure rates respectively with the use of oral steroids alone.[18,19] In other studies using combinations of prednisone and antibiotics, cure rates have ranged between 40% and 77%.[9,20–25] Berman and co-workers demonstrated that combination therapy with prednisone for seven days plus trimethoprim-sulfamethoxazole for 4 weeks promotes more rapid resolution of persistent middle ear effusion than trimethoprim-sulfa-

Table 2. Symptom Scores (mean ± SEM)

	Treatment Duration, wk			
	0	4	8	12
Total symptom score by treatment group				
Beclomethasone nasal spray + antibiotics	36.0 ± 3.0	21.0 ± 3.7	12.1 ± 2.3	7.9 ± 1.4*
Antibiotics + placebo nasal spray	34.7 ± 3.0	21.0 ± 3.3	13.4 ± 2.2	12.4 ± 2.6
Antibiotics alone	35.7 ± 3.3	21.4 ± 3.8	19.9 ± 3.3	16.7 ± 3.1*
Ear pain + ear popping + ear pulling + hearing loss symptom scores by treatment group				
Beclomethasone nasal spray + antibiotics	10.7 ± 1.5	5.7 ± 1.4	2.6 ± 1.0‡	1.6 ± 0.7#
Antibiotics + placebo nasal spray	10.4 ± 1.4	5.8 ± 1.3	4.2 ± 0.9	3.0 ± 0.7
Antibiotics alone	11.9 ± 1.6	7.3 ± 1.5	6.0 ± 1.2‡	5.8 ± 1.4#

* $P = .015$, ‡$P = .034$, and #$P = .008$; For every group, repeated measures comparison over 12 weeks demonstrated significant improvement ($P < .0001$).

Table 3. Resolution of Chronic Middle Ear Effusion in Group 2 Subjects Treated with Intranasal Beclomethasone Nasal Spray + Antibiotics Compared with Combined Controls (Groups 1 and 3)*

	Initial Number	Treatment Duration, wk		
		4	8	12
Resolution by middle ear pressure criteria				
Ears: beclomethasone nasal spray + antibiotics	28	21%†	43%†	43%
Ears: antibiotics ± placebo nasal spray	65	6%†	18%†	25%
Subjects: beclomethasone nasal spray + antibiotics	19	22%	42%†	32%
Subjects: antibiotics ± placebo nasal spray	40	18%	18%†	25%
Resolution by otoscopic examination score criteria				
Ears: beclomethasone nasal spray + antibiotics	33	39%†	61%†	64%
Ears: antibiotics ± placebo nasal spray	71	13%†	37%†	51%
Subjects: beclomethasone nasal spray + antibiotics	19	37%	47%	53%
Subjects: antibiotics ± placebo nasal spray	40	15%	28%	38%

* Resolution was defined as an ear examination score of ≤2 (maximum 6), or a middle ear pressure ≥ −100 mmH_2O. Resolution by subject required resolution in both ears, whether initial disease was unilateral or bilateral.
† $P \leq .05$ (beclomethasone nasal spray + antibiotics versus antibiotics ± placebo nasal spray).

methoxazole alone.[9] Daly and co-workers employed a 6-week trimethoprim-sulfamethoxazole stepped treatment regimen, which also included 2 weeks of prednisone, resulting in a 48% cure rate with active treatment compared to 14% with placebo.[25]

In addition to studies of oral steroids, three studies have addressed topical nasal steroid use in the treatment of persistent middle ear effusion. In each of these studies the topical nasal steroid was used as a single drug therapy. In 1980, Schwartz and co-workers reported a 48% cure rate in an uncontrolled trial of beclomethasone metered dose inhaler nasal spray in 25 children after 5 weeks of treatment without concurrent antibiotics.[26] Children at entry into this study had been followed with an effusion for a mean duration of 5 weeks. Lindholdt and Kortholm in 1982 reported no difference between active and placebo groups in a blinded, placebo-controlled study of beclomethasone metered dose inhaler nasal spray administered for 1 month in 70 children.[27] Children, however, were entered into this study based upon current clinical findings, apparently without regard for the duration or chronicity of the middle ear effusion. Potentially, a high percentage of study subjects with limited, self-resolving disease may account for the lack of efficacy seen by Lindholdt and Kortholm for nasal steroids compared with placebo. In the third study, Shapiro et al in 1982 compared dexamethasone nasal spray to placebo in a blinded study of 45 children with effusions for a minimum of 4 weeks duration.[28] Over 3 weeks of therapy, the dexamethasone group showed greater efficacy than placebo at the end of week 1 and 2; but by the third week, there was no difference between treatment and control groups. The study of Shapiro et al is distinguished by its use of dexamethasone, a steroid with significantly different pharmacology than beclomethasone. Unlike dexamethasone, beclomethasone does not suppress adrenal function in commonly used clinical doses and is generally well tolerated.[29,30]

In contrast to these three previous reports, our double-blind, placebo-controlled randomized study (1) used aqueous beclomethasone or placebo nasal spray, (2) included prophylactic antibiotic treatment commonly employed in clinical practice in all three study subgroups, (3) required a duration of middle ear effusion of at least 3

months for entry into the study in order to ensure subjects characterized chronic disease and met the definition for chronic middle ear effusion, and (4) was of a longer 12-week treatment duration. Over the first 8 weeks of the study, we noted that aqueous beclomethasone significantly hastened the 4-week improvements in middle ear pressures and the 4-week and 8-week improvements in otoscopic examination scores in the active treatment group compared with the placebo and antibiotics-alone groups (Figs 1–4). Resolution of chronic middle ear effusion occurred with significantly greater frequently for ears treated with beclomethasone at 4 and 8 weeks (Table 3). From 8 to 12 weeks, improvements in middle ear pressures, otoscopic examination scores, and disease resolution plateaued for the beclomethasone group. By 12 weeks, the differences among the three study groups were no longer statistically significant. Unlike the objective outcome measurements, group differences in subjective parental symptom scores were not evident until 8 to 12 weeks, when the active treatment group demonstrated a significantly lower symptom score than the antibiotics-alone group (Table 2).

Over the full 12 weeks of the study, only the antibiotics plus beclomethasone nasal spray group significantly improved middle ear pressures in both left and right ears. Over the same 12 weeks, all groups made significant improvement in their otoscopic examination scores, symptom scores, and resolution of chronic middle ear effusion. Since all three groups were on antibiotic therapy, it was not surprising that all groups improved in each parameter. The active beclomethasone treatment group demonstrated the greatest overall improvement.

Oral steroids are hypothesized to aid middle ear effusion resolution by stabilizing membrane phospholipid breakdown and preventing the formation of inflammatory mediators.[19] Additionally they may promote shrinkage of peritubular lymphoid tissue,[20] enhance secretion of eustachian tube surfactant, and reduce viscosity of middle ear fluid.[31] Compared with systemic steroids, topical nasal steroids have limited systemic effects and would be expected to exert their anti-inflammatory effects more locally on the nose, nasal pharynx, and eustachian tube.[30,32]

For the treatment of chronic middle ear effusion, the relative safety of topical intranasal steroids makes them a more attractive adjunct to therapy than systemic steroids, for which concurrent disseminated viral infections, especially varicella, are a major concern.[33,34] Intranasal beclomethasone is approved for use in children 6 years and older and for the treatment of allergic and non-allergic rhinitis. Effective delivery of the aqueous spray to the nasal cavity and pharynx requires the patient to flex the neck forward while dispensing from a vertically held bottle in order to direct the spray toward the posterior nasal cavity. In children 4 years of age and older, short-term and chronic topically inhaled and intranasal steroids in standard doses have proven safe and effective in treatment of pediatric allergic rhinitis and asthma.[29,30,35–39] The glucocorticoid is rapidly degraded enzymatically in the nasal mucosa to less active metabolites. Any unchanged drug that is absorbed in metabolized in the first pass through the liver.[29,30,40] Other than transient nasal stinging and epistaxis, no significant side effects requiring the discontinuation of beclomethasone or placebo nasal spray were reported in our study. Adrenal function was not monitored because the total daily doses in the beclomethasone treatment group did not exceed standard doses of 336 μg/day. Further study is needed to assess the benefit of short courses of nasal steroids on long-term outcome parameters of chronic middle ear effusions, including the duration of effusion resolution and incidence of tympanostomy tube placement.

In summary, this 12-week study of intranasal aqueous beclomethasone as an adjunct to therapy in chronic middle ear effusion of greater than 3 months duration compared three active treatment groups: prophylactic antibiotics alone, antibiotics plus intranasal beclomethasone, and antibiotics plus intranasal placebo. The beclomethasone treatment group improved middle ear pressures, otoscopic examination scores, symptom scores, and disease resolution more rapidly than either control group over the first 8 weeks of therapy. Atopic individual were no more likely to respond to therapy than nonatopics. We conclude that intranasal beclomethasone aqueous may be a useful adjunct to prophylactic antibiotic treatment of pediatric chronic middle ear effusion. With safety and side-effect profiles superior to oral steroids, nasal steroid preparations deserve further study as adjuncts in the treatment of chronic middle ear disease.

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