Are Antihistamine-Decongestants of Value in the Treatment of Acute Otitis Media in Children?

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Acute otitis media is the most common bacterial infection of childhood. The effectiveness of oral antihistamine-decongestant mixtures in the treatment of this illness remains controversial in clinical practice. In a double-blind randomized study, 82 children (aged under 15 years) with acute otitis media were treated with amoxicillin and either a decongestant-antihistamine mixture (Dimetapp) or placebo. All diagnoses required agreement between a family practice resident and the supervising family physician. Clinical course was assessed by symptom diaries completed by parents and by follow-up examination at approximately two weeks, which included pneumatic otoscopy. No statistically significant benefit of the antihistamine-decongestant mixture was shown in terms of resolution of the symptoms or prevention of the complications of acute otitis media. It is recommended that antihistamine-decongestants not be routinely added to an antibiotic in the treatment of acute otitis media in children.

Acute otitis media has been called the most common bacterial infection of childhood.[1,2] Eighty-five to 90 percent of all children will have at least one attack of otitis media before they reach the age of 6 years.[1] Resultant persistent middle ear effusion with accompanying significant hearing loss has been shown to occur in up to 20 percent of children following an episode of acute otitis media.[3] Hearing loss, if prolonged, has been shown to have a significantly deleterious effect on the development of cognitive speech and language skills.[4,5] Despite the high incidence and significant morbidity associated with acute otitis media and its sequelae, variation still exists regarding its treatment in clinical practice with respect to the use of antihistamines and decongestants.[4-9]

The pathogenesis of acute otitis media is thought to be based on an underlying abnormality of eustachian tube function, which results in the development of a middle ear effusion that becomes secondarily infected by bacteria.[1] Logically treatment should consist of an antibiotic, as bacteria may be expected to be cultured from middle ear fluid in 70 to 75 percent of cases,[10,11] plus agents directed at normalizing the underlying defect in eustachian tube function. The pharmacological effects of antihistamines and decongestants on eustachian tube function as outlined by Peerles and Noiman[12] theoretically would make these agents effective adjuncts to antibiotics in the treatment of this disease.

Several studies have assessed this approach to the treatment of acute otitis media. While general agreement exists in North America regarding the effectiveness of antibiotics,[1,8-11,13,14] studies assess-

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TABLE 1. COMPARABILITY OF ANTIHISTAMINE-DECONGESTANT AND PLACEBO GROUPS

	Antihistamine-Decongestant (N=38) Percentage	Placebo (N=44) Percentage	P Value
Sex (male)	66	75	.50*
Age (<4 years)	79	61	.14*
Past history of otitis media			
0 episodes	34	23	.45*
1 to 3 episodes	37	43	
>3 episodes	29	34	
Mean number of symptoms at presentation (range 1-7)	5.2	4.2	.03**

*Chi-square test with Yates' correction
**Student's t test of independent means t=2.20

ing the concomitant use of antihistamine-decongestant preparations have found conflicting results, with some showing benefit[6,8,13,15] while others have shown no clinical benefit.[7,9,16-18]

This randomized, double-blind study was designed to evaluate the effectiveness of an oral antihistamine-decongestant mixture in children with acute otitis media for early resolution of symptoms and for prevention of complications.

METHODS

The study sample was drawn from patients attending a family medical teaching center in London, Ontario, between September 1982 and March 1983. All children younger than 15 years who were seen during office hours with a diagnosis of acute otitis media were further assessed by one of two experienced family physicians. For admission into the study, patients required at least one of the following symptoms: (1) earache, (2) ear pulling, (3) fever, (4) irritability, (5) draining ear, (6) anorexia, and (7) "cold" symptoms; and at least two of the following otoscopic findings of the tympanic membrane: (1) red, (2) absent light reflex, (3) bulging, or (4) perforated.

Children were excluded if they had (1) myringotomy tubes, (2) previously undergone tonsillectomy or adenoidectomy, (3) otitis media within one month, and (4) a medical contraindication or allergy to any of the study medications.

All children in the study aged between 1 and 4 years received oral amoxicillin in a dosage of 125 mg three times a day; older children received a dosage of 250 mg three times a day. All children also received a coded bottle of purple liquid, which contained either the active treatment drug or placebo.

The active treatment group received a commonly used drug, Dimetapp, a mixture containing brompheniramine maleate 4 mg/5 mL, phenylephrine hydrochloride 5 mg/5 mL, and phenylpropanolamine hydrochloride 5 mg/5 mL in a 2.3 percent alcohol solution. The placebo group received identically tasting and appearing liquid that consisted of the nonactive flavoring and vehicle constituents of Dimetapp. Only the pharmacist who had randomized the bottles knew the code. The antihistamine-decongestant or placebo dosage for 1 to 2 years of age was 2.5 mL three times a day, 2 to 3 years of age was 2.5 mL four times a day, 4 to 8 years of age was 5 mL three times a day, and 9 to 14 years of age was 5 mL four times a day.

Parents were requested to complete a ten-day record of medications given and a daily assessment of five symptoms: ear pain and tugging, runny nose, cough, irritability, and fever or as being either absent, mild, or moderate to severe on a three-point scale. Parents were told to expect significant improvement in the condition of their children within 48 hours, and if this did not occur, to return to the office for reassessment. If no clinical improvement was detected, the case was judged an "early treatment failure." In the event that parents felt their child required medication in addition to acetylsalicylic acid or acetaminophen, they were instructed to call the office.

Patients in the study were given return appointments 11 to 14 days after treatment was initiated, at which time diary records and medication bottles were collected. Residual volumes were measured as an indicator of compliance. Compliance was considered high if more than 86 percent of the prescribed medicine had been consumed. At the time of reassessment, the persistence of symptoms was questioned, otoscopy was repeated, and pneumatic otoscopy was performed.

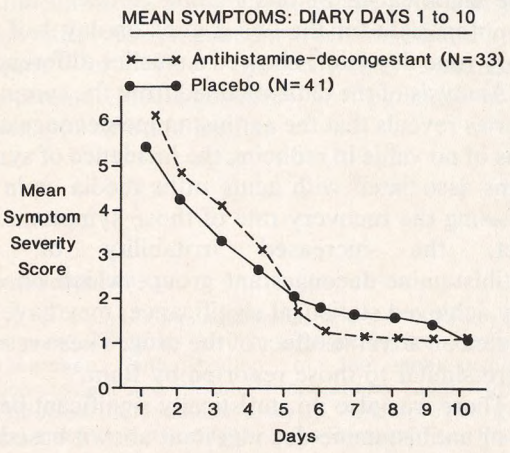

Figure 1. Mean symptoms: diary days 1 through 10

Abnormal tympanic membranes were defined as those with persistent injection, bulging or loss of light reflex, or visible evidence of middle ear effusion.

Statistical significance was assessed at the $P < .05$ level. Categorical data were analyzed using the chi-square test with Yates' correction. Differences in means between the antihistamine-decongestant and placebo groups were assessed by Student's *t* test for independent means.

RESULTS

Eighty-two patients were enrolled in the study. Thirty-eight of these patients received the antihistamine-decongestant mixture, while 44 received the placebo mixture. Of these 82 patients, four patients from the Dimetapp group and three from the placebo group failed to return for follow-up. There was only one "early treatment failure"—a 4-year-old girl who had received the antihistamine-decongestant. Following a change in antibiotic, her symptoms resolved uneventfully.

The two groups at entry were comparable (Table 1) for sex, age, and past history of otitis media. The antihistamine-decongestant group had significantly more symptoms at presentation than the placebo group.

TABLE 2. PERCENTAGE IMPROVEMENT IN SYMPTOM SEVERITY SCORES*

	Mean Percentage Improvement	
	Antihistamine-Decongestant (N=33)	Placebo (N=41)
Score Improvement		
At day 5	68.0	60.0
At day 10	83.0	80.0

*All results $P > .2$ by t test

Note: Score improvement = $\frac{\text{day 1} - \text{day 5 (or 10)}}{\text{day 1}}$

Active Drug and Symptoms Reduction

In Figure 1 the mean symptom scores from the diary reports are plotted. The two groups run a very similar course with no significant difference in number of symptoms on any day. When individual symptoms are considered, there were no differences between the groups in the course of ear pain, runny nose, cough, or fever. Patients in the antihistamine-decongestant group recorded higher ($P=.03$) irritability scores on day 3, but subsequent scores were similar between the groups. This finding could be due to chance alone with the high number of comparisons being undertaken.

Because of the higher number of initial symptoms in the drug group, the percentage improvement in diary symptoms has been reported at day 5 and day 10 in Table 2. Both groups showed similar improvement.

Active Drug and Outcome

In Table 3 the two groups are compared, first on medications taken during the illness episode and then on clinical outcomes at follow-up. Compliance to the prescribed regime was not significantly higher in the active drug group ($P = .07$, $\chi^2 = 3.20$). The use of acetylsalicylic acid and acetaminophen were similar ($P = 0.3$, $\chi^2 = 1.05$). Otoscopic examinations were similar at the follow-up examination for both groups ($P = 1.0$, $\chi^2 = 0.05$). Pneumatic otoscopy results were not significantly different between the groups ($P = 0.3$, $\chi^2 = 1.08$).

TABLE 3. PERFORMANCE OF ANTIHISTAMINE-DECONGESTANT AND PLACEBO GROUPS

	Antihistamine Decongestant (N=33)		Placebo (N=41)	
	Number	%	Number	%
Compliant*		82		63
Mean number of times aspirin/acetaminophen given in 10 days	3.3		2.4	
Abnormal otoscopy	4	12.1	6	14.6
Abnormal pneumatic otoscopy	4	12.1	10	24.4

Greater than 86% of prescribed liquid taken

DISCUSSION

This double-blind randomized trial found no benefit to those children receiving the antihistamine-decongestant preparation.

That there were no statistically significant differences between the study and control groups in terms of age, sex, or past history of otitis media suggests that randomization was successful.

The male predominance of the study sample is striking. Rubenstein et al[9] and Stickler et al[13] have suggested in the past that the sex ratio for acute otitis media in children aged 5 years or less (a group that made up 84 percent of the study sample) is approximately three boys to two girls. The age-sex register of the practice from which the study sample was obtained reveals a ratio in this age group of 1.3 boys to 1.0 girls. These two factors may explain the male predominance of the sample.

There was only one "early treatment failure" among the 82 cases in the study, which in addition to the diary record data suggests that children with acute otitis media treated with amoxicillin generally are significantly improved after 48 hours of treatment.

There is no explanation for the statistically significantly greater number of symptoms noted at intake for the antihistamine-decongestant group. The significance of this finding is uncertain, as symptom data for the two groups on day 1 of the diary (one day later) showed a smaller difference.

Analysis of the data obtained from the symptom diaries reveals that the antihistamine-decongestant was of no value in reducing the incidence of symptoms associated with acute otitis media or in increasing the recovery rate of those symptoms. In fact, the increased irritability of the antihistamine-decongestant group, which on one day achieved statistical significance, may have reflected an adverse effect of the drug. These results were similar to those reported by Bain.[18]

There was also no statistically significant benefit of antihistamine-decongestant shown based on the rates of abnormal otoscopy and abnormal pneumatic otoscopy performed at follow-up. The overall rate of abnormal pneumatic otoscopy of 19 percent is between the 13 percent found by Lampe et al[8] and the 33 percent found by Olson et al.[7] Olson et al suggested that their data may have been influenced by the relatively high numbers of allergic children and children with previous episodes of serous otitis media included in his sample, as these are recognized risk factors for the development of serous otitis media.[1]

Although the rates of abnormal pneumatic otoscopy in the antihistamine-decongestant group and control group were not statistically significantly different, the rate for the antihistamine-decongestant group was 12 percent lower. The power of this sample size to detect a difference of 20 percent was only 57 percent.

In any study showing failure of the study drug to achieve a desired result, one must ensure that the drug was actually taken and that it was prescribed in an adequate dose. The antihistamine-decongestant in this study was prescribed according to the manufacturer's recommended dosage schedule. Compliance, as measured by residual volumes in medical bottles at follow-up, was high.

The results of this study would therefore support those of Olson et al,[7] Bhambhani et al,[16] Bain,[18] and Rubenstein et al[9] in suggesting that antihistamine-decongestant preparations apparently are of no benefit as adjuncts to antibiotic therapy in the treatment of childhood acute otitis media.

These results, together with those of the re-

cently published study of Cantekin et al[19] in patients with serous (secondary) otitis media, do not support any role for currently available antihistamine-decongestants in patients with either type of otitis media.

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