

Treatment of Acute Otitis Media in Children with Tympanostomy Tubes: A Caregiver's Perspective

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ABSTRACT

We compared the duration of otorrhea (a discharge from the ear) and caregiver satisfaction in children with otitis media who were treated with a combination drug containing ciprofloxacin/dexamethasone versus ofloxacin. Otorrhea was cured sooner and patients improved more rapidly after administration of ciprofloxacin and dexamethasone. Consequently, caregivers of children with acute otitis media with tympanostomy tubes were more satisfied with ciprofloxacin/dexamethasone.

INTRODUCTION

Acute otitis media is an inflammation of the middle ear that usually results from infection. When fluid accompanies the inflammation, the condition is known as otitis media with effusion. Tympanostomy tubes are commonly inserted to treat recurrent otitis media with effusion.¹ In the U.S., approximately two million tympanostomy tubes are inserted annually. The estimated incidence of acute otitis media accompanied by otorrhea (drainage from the ear) in patients with tympanostomy tubes ranges from 15% to 74%.² Many practitioners use topical antibiotics to treat children who have acute otitis media with tympanostomy tubes (AOMT).

Topical rather than oral antibiotics are often preferred. The topical agents exert a direct action at the site of infection or inflammation. Oral antibiotics are more likely to cause systemic side effects and antimicrobial resistance.³ When possible, topical antibiotic preparations free of potential ototoxicity should be used instead of otological preparations that have the potential for otological injury if the middle ear or mastoid is open.⁴ Some topical otic preparations also contain steroids, which may lessen symptoms and hasten the resolution of AOMT.⁵ Both ciprofloxacin/dexamethasone (Ciprodex® Otic Suspension, Bayer, licensed to Alcon) and ofloxacin (Floxin® Otic Solution, Johnson & Johnson/Daiichi), broad-spectrum fluoroquinolones, have been approved in the U.S. for the topical otic treatment of patients with AOMT.

Patient and caregiver satisfaction with particular treatment regimens is increasingly important in pharmaceutical research. Researchers commonly use diaries and questionnaires to assess the course of a disease and its symptoms, compliance with drug

regimens, and treatment satisfaction. Diaries and questionnaires also provide information on how patient and caregiver activities are affected by a disease and its treatment. The goals of this study were to assess caregiver satisfaction with AOMT therapy and to examine the relationship between satisfaction and the time necessary to achieve cessation of otorrhea.

Alcon Research, Ltd., completed a large, pivotal, FDA-approved clinical trial comparing ciprofloxacin 0.3% and dexamethasone 0.1% to ofloxacin 0.3% for the treatment of patients with AOMT. This study established that more ciprofloxacin/dexamethasone (Cdex) than ofloxacin (Ofx) patients were cured on the 11th day.⁵

In addition to assessing efficacy in that study, we investigated the relationship between the duration of otorrhea and caregiver satisfaction with treatment. We collected diary data that documented changes in AOMT symptoms and patient activities occurring during the treatment period.

METHODS

We conducted a multicenter, observer-masked, randomized, active-control, parallel-group trial to compare Cdex and Ofx. Children six months to 12 years of age with acute otitis media, a patent tympanostomy tube, and otorrhea of three weeks' duration or less were enrolled. Before starting treatment, patients observed a washout period for therapies, including antibiotics that might interfere with the trial. The concomitant use of topical or oral anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, was prohibited. Patients were permitted to use acetaminophen for pain.

The patients were randomly assigned to receive either Cdex, four drops twice daily into the ear canal of infected ears for seven days, or Ofx, five drops twice daily for 10 days.

A total of 599 patients were enrolled in the clinical trial. Of this total, 485 of the patients' caregivers completed the satisfaction questionnaire. Because our goal was to determine the relationship between caregiver satisfaction and the time necessary to achieve a cure (otorrhea cessation), another 56 caregivers (25 from the Cdex group and 31 from the Ofx group) of children whose otorrhea extended past the administration of the survey were excluded from the survey analysis. Thus, we established a sample of 429 caregivers whose satisfaction responses were directly correlated with the onset of cure for the two therapeutic alternatives.

Caregivers kept daily diaries to record symptoms and to document compliance with the treatment regimen. The presence or absence of otorrhea was recorded twice daily, once each morn-



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Table 1 Caregiver Questionnaire Items and Subscales for Children with Acute Otitis Media and Tympanostomy Tubes

Subscale	Item
Duration of therapy	Number of days the patient had to take the study medication
Onset of action	Time it took for ear drops to take effect Time needed to decrease amount of ear drainage
Control of symptoms	Time necessary to stop drainage Control of ear pain Control of ear discomfort Control of ear discharge Control of patient's fever Control of patient's balance
Patient functioning	Irritability of patient Mood or sadness of patient Restlessness of patient Appetite of patient Level of patient's playing Effect on patient's sleeping Effect on patient in relation to family activities Effect on patient attending school or day care
Comfort	Overall comfort of ear drops
Overall satisfaction	Overall satisfaction of ear drops

nique to examine the reliability of the caregiver satisfaction questionnaire. This instrument demonstrated a high degree of internal consistency, with an overall Cronbach's alpha score of 0.97.

Statistical Methods

We used a Kaplan-Meier Log-Rank test to analyze differences in the duration of otorrhea between the Cdex and Oflox treatment groups. This type of analysis revealed differences in the proportion of patients cured over time. The use of a survival technique allows the examination of cure rates in a longitudinal fashion (over time), as opposed to a single, cross-sectional measure in time.

We used Student's *t*-test to analyze differences in caregiver satisfaction and patients' ages between the Cdex and Oflox treatment groups, and we evaluated sex differences between the treatment groups using a *chi*-square test of homogeneity.

Ordinary least-squares linear regression was used to analyze the relationship between caregiver satisfaction with treatment and the duration of otorrhea. "Overall satisfaction with ear drops" (from the caregiver survey) was used as the dependent measure, and "duration of otorrhea" (from the caregiver diary) was used as the independent measure. All tests were two-sided, with alpha fixed at 5%. We analyzed the parameters using SAS Software Version 8.0 and JMP version 5.0 (SAS Institute, North Carolina).

RESULTS

Demographic Comparisons

Sex. There were no statistical sex differences between the treatment groups. Table 2 presents the demographics of each treatment group.

Age. There were no statistical differences in age between the two treatment groups. The overall (pooled) mean age for all of the AOMT patients was 2.72 years (with a standard deviation [SD] of 2.47). The mean age of the Cdex treatment group was 2.77 years (SD, 2.53), with a 95% confidence interval (CI) of 2.43 to 3.10 years. In contrast, the mean age of the Oflox group was 2.68 years (SD, 2.42), with a 95% CI of 2.35 to 3.00 years.

Duration of Otorrhea

Otic drainage stopped approximately 1.5 days sooner in the Cdex children than in those treated with Oflox (Table 3). The median time to cure was 2.5 days for the Cdex patients (CI, 95% in 2–3 days) compared with 4 days (CI, 95% in 3.5–4.5 days) for the Oflox patients. The 25th and 75th percentile time-to-cure figures are also consistent. The 25th percentile column is the number of days

ing and evening. The time to cessation of otorrhea was defined as the first day the caregiver noted that otorrhea was absent and subsequently remained absent for the remainder of the study. Daily phone calls, periodic reviews by the coordinator, and other efforts were made to ensure the proper maintenance and completion of the diary.

Specific Methods for Caregiver Treatment Satisfaction

Because the patients were children, the treatment satisfaction results reflected the responses of the caregivers and not the patients themselves. A caregiver survey administered on the 11th day of the clinical trial was used to collect data pertaining to satisfaction with treatment.

A 19-item, disease-specific questionnaire for caregivers was developed to assess, in a valid and reliable manner, their satisfaction with therapy for the following subscales: (1) duration of therapy, (2) onset of action, (3) control of symptoms, (4) comfort, (5) patient functioning, and (6) overall satisfaction. The 19 items were based on an extensive review of the literature and discussions with patient caregivers and otolaryngologists.⁵ These 19 items and their associated subscales are presented in Table 1.

Caregivers responded to each item on a seven-point scale ranging from 0 (very dissatisfied) to 6 (very satisfied). The scale generated scores that were positively correlated with caregiver satisfaction; that is, higher scores indicated greater satisfaction. Caregivers had the option of responding "not applicable" to any or all scale items. Items recorded as "not applicable" were excluded from the satisfaction analysis.

We used the Cronbach alpha internal consistency tech-

Table 2 A Comparison of Gender Demographics Between Two Pediatric AOMT Treatment Groups

Subscale	Ciprodex®		Floxin®		P Value*
	No.	%	No.	%	
Boys	125	57%	136	65%	.0613
Girls	96	43%	72	35%	
Total	221	52%	208	48%	

*Pearson's *chi*-square.

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Table 3 Cure Rate for Children with AOMT

Treatment Group	Mean Days to Cure	Median Days to Cure	Confidence Intervals (Median)		Percentile Time to Cure	
			Lower 95%	Upper 95%	25% Success	75% Success
Ciprodex®	3.65	2.5	2	3	1.5	4.5
Floxin®	4.88	4	3.5	4.5	2.5	7

required for 25% of the patients to experience cessation of drainage.

According to the caregivers, 25% of Cdex patients were otorrhea-free after 1.5 days, whereas 2.5 days were required for 25% of the Oflox patients to achieve an otorrhea-free state. The time to cure was even more pronounced at the 75th percentile. Only 4.5 days were required for drainage to cease in 75% of the Cdex-treated patients, compared with seven days for the Oflox-treated patients. There was a statistical difference ($P < .001$) in the cure rates between the Cdex and Oflox treatment groups. The mean time to cessation of otorrhea for the Cdex group of patients was 3.65 days (standard error [SE], 0.19) and 4.88 days (SE, 0.19) for the Oflox patients.

In Figure 1, the Kaplan–Meier survival curves depict the contrasting cure rates for the Cdex and Oflox groups. Cessation of otorrhea was faster with Cdex, and the proportion of otorrhea-free patients over time was significantly greater in the Cdex group. The area between the curves in Figure 1 represents the differences between the two cure rates. Stated another way, this region signifies the proportion of patients who experienced the added benefit of treatment with Cdex rather than with Oflox. The difference in cure rates represents the alleviation of suffering resulting from the more rapid curing action of Cdex.

Satisfaction of Caregivers with Treatment

Table 4 compares caregiver satisfaction scores between the Cdex and Oflox treatment groups and provides the resultant statistical significance levels. Cdex caregivers were significantly more satisfied than Oflox caregivers on 13 of the 19 satisfaction items. There were no statistically significant differences on the remaining six satisfaction items.

Relationship Between Duration of Otorrhea and Caregiver Satisfaction

The relationship between the duration of otorrhea and caregivers' overall satisfaction with the ear drops was statistically significant ($P < .001$). Caregivers' satisfaction for both Cdex and Oflox was inversely related to the duration of otorrhea (Figure 2). The longer the otorrhea lasted, the less satisfied caregivers were with treatment. All 19 caregiver satisfaction items, except the questions concerning the "appetite of the patient" and the "effect on patient attending school or day care," demonstrated a statistically significant correlation with the duration of otorrhea.

DISCUSSION

AOMT primarily affects young children. Caregivers of children with AOMT are usually parents, family members, or the legal guardians of the sick child. The initial decision to seek treatment usually rests solely with the caregiver.

After the patient with AOMT has seen the physician and begins

treatment, it is again the caregiver who assesses the effectiveness of therapy. Our caregiver satisfaction survey showed that using Cdex for a child with AOMT rather than Oflox resulted in higher overall caregiver satisfaction. Our results agree with those of Shikiar et al.,⁶ who found that satisfaction with a drug was highly correlated with relief of symptoms. Compared with Oflox, better caregiver satisfaction results were obtained with Cdex for most of the questionnaire items, including satisfaction with the time needed to stop ear drainage, control of ear pain, and the number of days for which the patient had to take the antibiotic.

Some researchers may dispute the use of linear regression on a satisfaction scale with an ordinal nature. To address this issue, we also analyzed the satisfaction–duration of otorrhea relationship using two different logistic regression approaches.

First, we analyzed the relationship between the raw "overall satisfaction with ear drops" ordinal scores in relation to the duration of otorrhea. Second, we transformed the raw satisfaction scores into the nominal categories ("satisfied" or "unsatisfied") and analyzed the relationship of the transformed scores relative to the duration of otorrhea. In both instances, the logistic models and

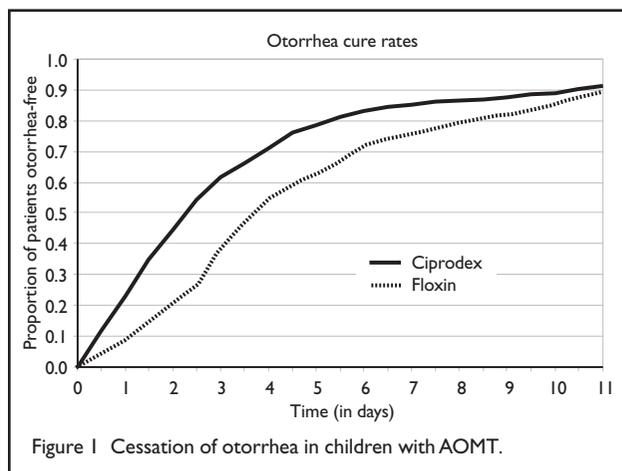


Figure 1 Cessation of otorrhea in children with AOMT.

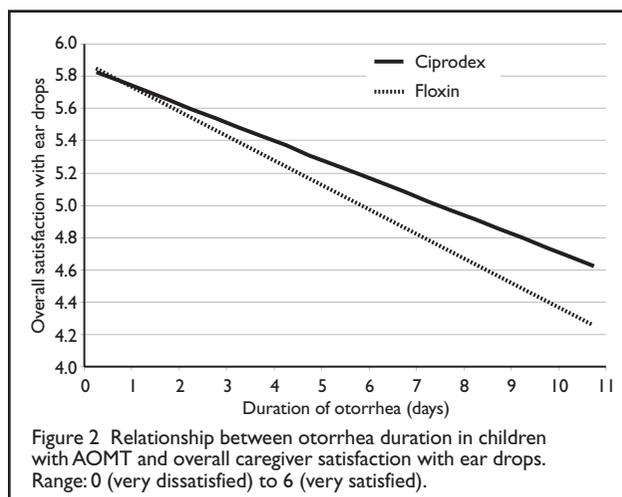


Figure 2 Relationship between otorrhea duration in children with AOMT and overall caregiver satisfaction with ear drops. Range: 0 (very dissatisfied) to 6 (very satisfied).

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Table 4 Caregiver Satisfaction with AOMT Treatment

Satisfaction Item	Treatment Group						P Value*
	Ciprodex®			Floxin®			
	Mean	SD	No.	Mean	SD	No.	
Overall satisfaction with ear drops†	5.54	0.94	220	5.25	1.11	207	.004
Time necessary to stop drainage†	5.41	1.12	220	4.93	1.53	205	<.001
No. of days the patient had to take the study medication†	5.47	0.92	216	5.06	1.27	206	<.001
Time needed for ear drop to take effect†	5.39	1.09	220	4.98	1.34	205	<.001
Time needed to decrease amount of ear drainage†	5.35	1.16	221	4.98	1.34	204	.002
Control of ear pain†	5.31	1.14	180	5.02	1.34	147	.04
Control of ear discomfort†	5.24	1.13	191	4.92	1.33	153	.02
Control of ear discharge†	5.45	1.06	221	4.97	1.37	205	<.001
Irritability†	5.20	1.00	161	4.78	1.31	138	.002
Mood or sadness†	5.27	1.11	139	4.80	1.29	121	.002
Restlessness†	5.16	1.13	144	4.84	1.31	129	.03
Effect on sleeping†	5.35	1.09	168	5.03	1.30	145	.02
Effect on patient in relation to family activities†	5.47	0.84	155	5.09	1.19	145	.001
Control of fever	5.60	0.98	73	5.26	1.33	58	.09
Control of balance	5.58	0.83	69	5.33	1.09	66	.14
Appetite	5.18	1.20	121	5.10	1.21	111	.60
Level of playing	5.45	0.98	148	5.36	1.04	129	.50
Effect on patient attending at school or day care	5.48	1.02	117	5.33	0.96	107	.26
Overall comfort of ear drops	5.12	1.25	218	4.92	1.46	207	.13

* Student's t-test, assuming equal variances.
 † Statistically significant difference.
 Note: Each scale ranges from 0 (very dissatisfied) to 6 (very satisfied) on an ordinal scale.

their associated parameters were statistically significant. As with the linear regression model, the logistic models indicated that the probability of caregiver satisfaction declined as the duration of otorrhea increased; that is, caregiver satisfaction was inversely related to the duration of otorrhea.

One limitation of our study was the use of caregiver satisfaction as a proxy for patient satisfaction. It is always more prudent to assess treatment satisfaction by using the patients themselves when possible. However, in certain patient populations such as our cohort of young children, the only practical way to judge treatment satisfaction is through caregiver assessment of patient behavior and easily observable therapeutic endpoints. Caregivers are probably the most appropriate surrogates for satisfaction with pediatric AOMT therapy assessment because they are responsible for initiating treatment, determining treatment success or failure, and seeking re-treatment if required.

In our study, caregiver satisfaction was assessed for 19 items, but the questionnaire did not identify their relative importance. Future research might focus on the items most important to the caregiver. For example, is caregiver satisfaction more dependent on the "time necessary to stop drainage" or with the "number of days the patient had to take the study medication?" In addition, pain is not a common symptom of patients with AOMT. We believe that caregivers might have interpreted pain in some aspect of therapy comfort. A better understanding of such caregiver impressions and preferences might eventually lead to the development of instruments that further describe caregiver satisfaction.

CONCLUSION

In children with AOMT, the combination drug ciprofloxacin/dexamethasone cured more patients more rapidly than did ofloxacin. As a direct result of this superior efficacy, the Cdex patients experienced faster symptomatic improvement. Consequently, the Cdex caregivers were more satisfied with AOMT treatment than their Ofx counterparts.

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