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Comparison of Cefuroxime Axetil and Amoxicillin-Clavulanate Suspensions in Treatment of Acute Otitis Media with Effusion in Children

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Two hundred sixty-three pediatric patients from the ages of 3 months to 11 years were enrolled in a randomized, investigator-blinded, multicenter study comparing the clinical and bacteriological efficacies and safety of cefuroxime axetil suspension (CAE) with those of amoxicillin-clavulanate suspension (AMX-CL) in the treatment of acute otitis media with effusion. Patients received CAE at 30 mg/kg of body weight per day (n = 165) in two divided doses or AMX-CL at 40 mg/kg/day (n = 98) in three divided doses for 10 days. The primary pathogens among 200 isolates from pretreatment cultures of middle ear fluid were identified as follows: *Haemophilus influenzae* (39%), over a third of which were β-lactamase positive; *Streptococcus pneumoniae* (34%); and *Moraxella catarrhalis* (16%). Pathogens were eradicated or presumed to be eradicated from 81% (95 of 118) and 76% (50 of 66) of bacteriologically evaluable patients in the CAE and AMX-CL groups, respectively. A satisfactory clinical response (cure or improvement with or without resolution of effusion) occurred in 113 (77%) of 146 clinically evaluable patients in the CAE group and in 66 (74%) of 89 evaluable patients in the AMX-CL group. Clinical failure or recurrence (within 2 weeks following the completion of treatment) occurred in 22 and 26% of CAE- and AMX-CL-treated patients, respectively. Drug-related adverse events occurred in 18% of CAE-treated patients, whereas they occurred in 39% of AMX-CL-treated patients ($P < 0.001$); diarrhea or loose stools was the most commonly reported adverse event (CAE, 12%; AMX-CL, 31%; $P < 0.001$). These results indicate that CAE given twice daily is as effective as AMX-CL given three times daily in the treatment of acute otitis media with effusion in pediatric patients, but CAE was associated with significantly fewer drug-related adverse events.

Acute otitis media is an extremely common and frustrating medical problem, a fact only too familiar to pediatricians who attend youngsters with this condition on nearly a daily basis and to the children's caretakers, whose normal routine is so often disrupted as a result. Prompt treatment of acute otitis media is desirable in order to relieve the child's immediate discomfort. In addition, effective therapy should lessen the likelihood of long-term sequelae, such as hearing loss or permanent middle ear damage (3, 8, 12).

Successful management of acute otitis media depends on many factors, including knowledge of the etiologic organisms, primarily *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (2, 4), and their particular susceptibilities to antimicrobial agents. Regional antimicrobial resistance patterns may also influence treatment, as may host factors, such as recent history of treatment for acute otitis media. The choice of antibiotic therapy remains controversial, however, and is subject to change as new information both about the disease and about treatment modalities becomes available.

We present data comparing the efficacy and safety of the suspension formulation of cefuroxime axetil (CAE), the ester prodrug of cefuroxime, with that of amoxicillin-clavulanate suspension (AMX-CL). Both compounds have broad spectra of activity against those pathogens implicated most frequently in otitis media, including β-lactamase-producing organisms (12).

MATERIALS AND METHODS

Study design and patient population. The present randomized, evaluator-blinded study comparing CAE with AMX-CL in the treatment of acute otitis media with effusion (AOME) was conducted at 12 centers located throughout the United States. Outpatients between the ages of 3 months and 12 years with AOME were eligible for enrollment. The diagnosis of AOME was based on the usual signs and symptoms (i.e., otalgia, irritability, fever), as well as pneumatic otoscopic evidence of erythema or opacity and impaired mobility of the tympanic membrane.

Patients were ineligible for inclusion if they had any of the following: ruptured tympanic membrane; a history of hypersensitivity to cephalosporins or penicillin; use of a systemic antibiotic within 7 days prior to the study (in any patient from whom a middle ear pathogen was not isolated); a gastrointestinal disorder that could interfere with absorption of orally administered antibiotics; or serious medical problems, concurrent illness, or factors that could preclude completion of treatment or follow-up. Written informed consent was obtained from each patient's parent or legal guardian, and the protocol was approved by an institutional review board for each study center.

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Procedures. Prior to the initiation of antibiotic therapy, the ear canal was cleansed with an antiseptic and tympanocentesis was performed to obtain middle ear fluid for isolation of bacterial pathogens and determination of antibiotic susceptibilities. Clinical evaluations (including pneumatic otoscopy) were conducted at the time of enrollment, 3 to 5 days after the initiation of therapy, and 1 to 4 and 12 to 16 days after the completion of treatment. When possible, tympanocentesis was repeated if there was no clinical improvement after 72 h of treatment or as clinically indicated. Patients were also evaluated at any time if the progression or recurrence of symptoms warranted an examination.

Treatment. Patients were randomly assigned to receive a 10-day course of either CAE at 30 mg/kg of body weight per day (maximum, 500 mg/day) in two divided doses (every 12 h with meals) or AMX-CL at 40 mg/kg/day (maximum, 750 mg/day) in three divided doses (every 8 h without regard to meals) according to a computer-generated randomization schedule. Randomization of treatment began on a 1:1 schedule but was changed early in the study to a 2:1 schedule (CAE: AMX-CL) to increase the number of patients receiving CAE. A graduated dosing syringe was given to parents for accurate medication administration.

Assessment of outcome. Bacteriological outcomes were classified as follows: cure (pathogen eradicated from posttreatment cultures), presumed cure (no subsequent culture but no signs or symptoms of acute infection with or without persistence of middle ear effusion), cure with reinfection (new pathogen isolated following cure, requiring continued or alternate therapy), failure (no clearance of initial pathogen following ≥3 days of treatment), presumed failure (no subsequent culture and clinical signs and symptoms of AOME still present after ≥3 days of therapy), and recurrence (eradication and then reisolation of the initial pathogen).

Clinical outcomes were classified as follows: cure (resolution of signs and symptoms of AOME lasting through the 2-week posttreatment period, with resolution of middle ear effusion by at least the 2-week posttreatment visit), improvement (cure but without resolution of middle ear effusion at the 2-week posttreatment visit), failure (no improvement in clinical signs and symptoms after ≥3 days of treatment or discontinuation of therapy because of an adverse event), recurrence (resolution of signs and symptoms of AOME during treatment with subsequent recurrence of clinical signs of acute infection within the 2-week posttreatment period).

Safety evaluations. Clinical laboratory tests (complete blood count, blood chemistry, and urinalysis) performed at the initial visit were repeated at 1 to 4 days posttreatment. At each visit, any adverse event observed by the parents, patient, or investigator was recorded.

Compliance. Urine specimens were assayed during treatment as described previously (5) to assess the presence or absence of antibiotic in each patient and to monitor compliance. Compliance was also evaluated by measuring the amount of unused drug returned by the parents at the end of treatment.

Statistical analyses. All statistical comparisons used two-sided significance tests. Analyses of demographic characteristics and clinical and bacteriological outcomes were conducted by using the Van Elteren (16) or Mantel-Haenszel tests (11), controlling for investigational site. The incidence rates of the adverse events were compared between groups by Fisher's exact test. Differences were considered statistically significant at $P \leq 0.05$.

The null hypothesis in the present study was that CAE and AMX-CL were equally effective clinically. A retrospective power evaluation indicated that this study had sufficient power to detect a clinically relevant difference of 10% between treatment groups in the proportion of patients with a satisfactory clinical outcome (i.e., cure or improvement). In the analysis, we assumed that the comparator treatment (AMX-CL) would yield a satisfactory clinical response in 85% of evaluable patients. In computing the power of the study, a one-sided test was used, because the study did not attempt to establish that CAE was more effective than AMX-CL. Setting the significance level at 0.10, the probability of failing to detect a real difference in treatments (β or type II error) was 0.30, resulting in a power of 70%.

TABLE 1. Demographic characteristics of patients

Characteristic	CAE	AMX-CL
No. of patients	165	98
Sex (no. [%])		
Male	90 (55)	66 (67)
Female	75 (45)	32 (33)
Mean age (yr) [range])	2 (<1–11)	2 (<1–9)
Ethnic origin (no. [%])		
White	122 (74)	77 (79)
Black	40 (24)	19 (19)
Other	3 (2)	2 (2)
History of otitis media (no. [%])		
Previous episode	117 (71)	81 (83)
Recurrent episodes	76 (46)	54 (55)
Episode in previous 3 months	64 (39)	49 (50)

RESULTS

A total of 263 children were enrolled in the study; 165 of the children were treated with CAE and 98 were treated with AMX-CL. There were no statistically significant differences between the two treatment groups with respect to demographic characteristics (Table 1).

Bacteriological outcome. Bacteriological data from 184 of 263 patients (70%) were evaluable for efficacy analyses (i.e., a pretreatment pathogen was cultured and identified, the patient received treatment for ≥3 days, and follow-up visits were completed). A "satisfactory" bacteriological outcome (i.e., cure, presumed cure, and cure plus reinfection with a different pathogen) was achieved in 81% of patients who received CAE and 76% who received AMX-CL ($P > 0.05$) (Table 2). Bacteriological outcome on a per organism basis for the primary pathogens isolated (*H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*) is given in Table 3.

Clinical outcome. Of the 263 patients assigned to treatment, 235 (89%) were judged to be clinically evaluable (i.e., the patient received therapy for ≥3 days, follow-up visits were completed, and the patient did not withdraw from the study for reasons other than an adverse event). Satisfactory clinical outcomes (cure and improvement) were achieved by 77% of patients in the CAE group and 74% of patients in the AMX-CL group ($P = 0.7$) (Table 4). Compliance with each of the prescribed regimens was similar between treatment groups. Of those tested, antibiotic activity was detected in the urine of 148 of 150 (99%) CAE-treated patients and 89 of 89 (100%) AMX-CL-treated patients.

An intent-to-treat analysis was performed to provide supportive evidence for the primary efficacy analysis. Of the 263 patients initially enrolled in the study, a pretreatment patho-

TABLE 2. Bacteriological efficacy[a]

Outcome	CAE	AMX-CL
Cure	5	1
Presumed cure	88	49
Cure with reinfection	2	0
Satisfactory	95 (81)	50 (76)
Failure	1	2
Presumed failure	2	1
Recurrence	1	0
Presumed recurrence[b]	19	13
Unsatisfactory	23 (19)	16 (24)
Subtotal (bacteriologically evaluable)	118 (100)	66 (100)
Unevaluable	47	32
Inability to culture and identify pretreatment pathogen	35	21
Lost to follow-up	5	6
Resistant pretreatment pathogen or susceptibility not tested	3	2
Concurrent nonstudy antimicrobial agent	1	2
Noncompliant	2	0
Received drug for <3 days	1	0
Enrollment violation	0	1
Total	165	98

[a] Data are number (percent) of patients.
[b] Clinical recurrence without documented bacteriological outcome.

TABLE 4. Clinical efficacy[a]

Outcome	CAE	AMX-CL
Cure	91	51
Improvement	22	15
Satisfactory	113 (77)	66 (74)
Failure, persistence	2	2
Failure, adverse event	1	3
Recurrence	30	18
Unsatisfactory	33 (23)	23 (26)
Subtotal (clinically evaluable)	146 (100)	89 (100)
Unevaluable	19	9
Lost to follow-up	10	3
Resistant pretreatment pathogen or susceptibility not tested	3	2
Concurrent nonstudy antimicrobial agent	1	2
Noncompliant	2	0
Received drug for <3 days	2	0
Withdrawal (other than for adverse event)	1	1
Enrollment violation	0	1
Total	165	98

[a] Data are number (percent) of patients.

gen was identified in 207 patients (79%) (Table 2); in these 207 patients, the pretreatment pathogen was eradicated from 95 of 130 (73%) the CAE-treated patients and 50 of 77 (65%) the AMX-CL-treated patients ($P = 0.2$). Similarly, complete resolution of the signs and symptoms present at the time diagnosis was achieved in 113 of 165 (69%) CAE-treated patients and 66 of 98 (67%) AMX-CL-treated patients ($P = 0.9$).

Adverse events. All 263 patients enrolled in the study received one of the study drugs and were included in the safety analyses. Eighteen percent of the CAE-treated patients and 39% of the AMX-CL-treated patients experienced at least one adverse event that was judged by the investigator to be drug related ($P < 0.001$). A significant difference in drug-related adverse events affecting the gastrointestinal tract was seen between treatment groups (CAE, 15%; AMX-CL, 32%; $P < 0.01$). The most common individual adverse events were diarrhea or loose stools (CAE, 12%; AMX-CL, 31%; $P < 0.001$) and diaper rash (CAE, 3%; AMX-CL, 12%; $P < 0.01$). Five patients withdrew from the study because of an adverse event, two in the CAE group (one with abdominal pain and the other with vomiting that began prior to treatment) and three in the AMX-CL group (two with diarrhea and one with bronchitis); all adverse events except the vomiting and bronchitis were assessed by the investigator as being drug related.

TABLE 3. Bacteriological outcome by organism[a]

Isolate	No. (%) of patients			
	CAE		AMX-CL	
	Satisfactory	Unsatisfactory	Satisfactory	Unsatisfactory
H. influenzae				
β-Lactamase negative	31	4	10	2
β-Lactamase positive	12	6	8	4
Total	43 (81)	10 (19)	18 (75)	6 (25)
M. catarrhalis				
β-Lactamase negative	1	1	5	0
β-Lactamase positive	12	4	5	4
Total	13 (72)	5 (28)	10 (71)	4 (29)
S. pneumoniae	33 (83)	7 (18)	20 (74)	7 (26)
Other	16 (80)	4 (20)	24 (77)	7 (23)

[a] More than one pathogen was isolated from some patients.

DISCUSSION

We report the results of a comparison between two oral antibiotic suspensions, CAE and AMX-CL, in the treatment of AOME in infants and children. These findings parallel the results of an earlier clinical trial (15) which also compared CAE and AMX-CL in the treatment of acute otitis media. Those investigators concluded that the clinical efficacy of CAE was equivalent to that of AMX-CL, although AMX-CL was associated with significantly more adverse events (primarily of the gastrointestinal system) than was CAE. In contrast to the previous study (15), in which problems with the acceptability of the taste of CAE were noted, only two patients in the CAE group in the present study withdrew because of refusal to take medication.

The present study extends the earlier clinical trial (15) by including the use of tympanocentesis to obtain middle ear aspirates for bacterial culture, a procedure not routinely performed in clinical practice but considered the "gold standard" by which success of the antibiotic in the treatment of patients with AOME can best be measured. Other investigators (13) have also suggested that bacteriological outcome is a more sensitive measure than clinical outcome.

The results of our pretreatment bacteriological evaluations reinforce the importance of understanding the patterns of bacterial resistance before initiating antibiotic therapy for AOME. More than a quarter of all the organisms isolated in our study were found to be β-lactamase-positive, with 34% of the *H. influenzae* isolates and 78% of the *M. catarrhalis* isolates falling into this category. Other studies have also cited an increased incidence of β-lactamase-producing strains, particularly *M. catarrhalis*, in the etiology of AOME (3, 10). The prevalence of β-lactamase-producing organisms may also vary with geographic location. Thus, in areas known to have a high incidence of such organisms, β-lactamase-stable antibiotics should be considered as initial therapy. In addition to β-lactamase-producing organisms, the emergence of penicillin- and multi-drug-resistant *S. pneumoniae* (1, 9) highlights the importance of understanding the susceptibility patterns of the bacterial pathogens responsible for AOME in a particular geographic location prior to selecting an appropriate antimicrobial agent.

In the present study, neither the bacteriological nor clinical responses demonstrated significant differences between the two treatment groups. However, the adverse events profiles of these two drugs were significantly different. In previous studies, the incidence of diarrhea in children treated with AMX-CL for AOME was approximately 20% (7, 13, 14), although it was somewhat higher in the present study (31% for AMX-CL versus 12% for CAE).

In addition to treatment efficacy, spectrum of antibiotic activity, and the adverse events profile, patient (and, in many cases, parent) compliance with treatment regimens is an important factor in antimicrobial therapy. Hussar (6) reports that only 40% of children given a drug on a three-times-a-day dosing schedule will complete a 10-day course of treatment, whereas 70% of children will finish a twice-a-day regimen. Since a twice-daily dosing schedule eliminates the need for an afternoon dose during day-care or school attendance, adherence to therapy becomes easier.

In summary, in the present study twice-daily dosing with CAE was as effective, by both clinical and bacteriological parameters, as three-times-daily dosing with AMX-CL in the treatment of AOME in pediatric patients. CAE, however, was associated with significantly fewer adverse events.

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