

Intramuscular ceftriaxone in comparison with oral amoxicillin-clavulanate for the treatment of acute otitis media in infants and children

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Received: March 14, 2003 Revised: June 11, 2003 Accepted: July 14, 2003

In order to evaluate the clinical efficacy and safety profiles of single-dose ceftriaxone (50 mg/kg, not exceeding 1g) and a 10-day course of amoxicillin-clavulanate (amoxi-clav) [45 mg/kg/day, in 3 divided doses] in children with acute otitis media (AOM), we conducted a prospective, comparative, randomized trial. Between February 2000 and April 2002, 110 children with a mean age of 30.73 ± 20.79 months were enrolled. 109 patients were evaluated for the safety assessment. The intent-to treat population included 96 patients who completed at least 3 days of treatment. The standard analysis population included 73 patients who completed the 10-day treatment period without any major violation. For the standard analysis population, 57 out of 73 patients experienced treatment success; 31 out of 41 patients in the ceftriaxone group were cured compared with 25 out of 32 patients in the amoxi-clav group. The rate of persistence of middle-ear fluid did not differ between the 2 groups at day 11 or day 28. A higher treatment preference rate was observed in the ceftriaxone group (93.9% vs 58.6%). The most common drug-related adverse effects were found in the digestive system, skin and appendages in both treatment groups. A single dose of ceftriaxone is as safe and effective as amoxi-clav for curing patients with acute otitis media. In addition, a substantially higher proportion of patients receiving single-dose ceftriaxone showed a preference for the study medication compared with those treated with amoxi-clav for 10 days.

Key words: Amoxicillin-clavulanate combination, ceftriaxone, infant, preschool child

Acute otitis media (AOM) is a common infection in infants and children. Children experience an average of 1.5 episodes in the first year and spend approximately 2.5 months with middle-ear effusions related to AOM [1]. Despite 30% of cases having a non-bacterial etiology [2], AOM is the leading cause for use of antibiotics in children [3]. Because of the non-specific nature of the diagnostic criteria, a small proportion of children who are diagnosed with otitis media may not have the illness. However, since serious sequelae such as hearing loss or mastoiditis may result from persistent infections, it is common to use antibiotic treatment in those children who meet the clinical diagnostic criteria for otitis media.

The most common pathogens responsible for AOM are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* [4,5]. Amoxicillin, amoxicillin-clavulanate (amoxi-clav), trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole are the most frequently prescribed oral antibiotics for the

treatment of AOM. Compliance when administering oral antibiotics to treat pediatric patients, however, is problematic for both the patient and parent. Children often find difficulty in swallowing or may vomit or spit up the medication. The administration of multiple daily doses to children can be especially inconvenient for the working parent. The goal of this study was to compare the effectiveness and the safety profiles of a single intramuscular dose of ceftriaxone with a 10-day course of oral amoxi-clav treatment in infants and children with AOM.

Patients and Methods

Between February 15, 2000 and April 27, 2002, a total of 110 patients newly diagnosed with AOM were recruited into the study. The patients were randomly divided into 2 treatment groups, of 55 patients each. The study population consisted of mainly Chinese children of both genders with age ranging between 3 months and 6 years. The diagnostic criteria for AOM included the following: (1) the presence of 1 or more specific signs or symptoms, such as otalgia, hearing

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loss or non-specific findings such as fever ($\geq 38^{\circ}\text{C}$) or history of fever (within 24 hours), lethargy, irritability, anorexia, vomiting or diarrhea; (2) middle-ear infection of obvious redness as revealed by otoscopy findings and evidence of middle-ear fluid; and (3) an abnormal tympanogram — results consistent with middle-ear effusion. Patients were excluded from the study if they received antibiotic treatment within the last 7 days before enrollment in the study, had a ruptured tympanic membrane, or if they presented with tympanostomy. The study and informed consent document were reviewed and approved by the National Taiwan University Hospital Ethics Committee.

Study design

This was an open-label, single-center, randomized, active-controlled, parallel study trial. Eligible patients received either a single dose of ceftriaxone (50 mg/kg, not exceeding 1 g) or a 10-day treatment of orally administered amoxicillin and clavulanate (45 mg/kg/day) divided into 3 doses. Eligible patients entered a 10-day treatment phase followed by a 17-day follow-up. Children were scheduled to return to the clinic on days 4, 11, and 28 during the trial. Patients requiring systemic antimicrobial therapy for an infection other than otitis media were not allowed to continue in the study. Subjects were instructed to bring their remaining study medication back on every visit. At each visit symptoms and signs related to ear, nose and throat were recorded and tympanogram was performed. The response to therapy was evaluated on days 4, 11 and 28; these evaluations were based on clinical symptoms and signs, otoscopies, and tympanograms. The presence or absence of middle-ear effusion was documented on each visit.

Clinical evaluation

An efficacy analysis was performed separately in the study population and in the intent-to-treat (ITT) population. The treatment outcome was considered successful if the patient's clinical response was assessed as cured at the visit on day 11. Treatment was evaluated as a failure if the symptoms and signs presented at baseline had not improved or had worsened on day 4 or if patients still showed symptoms or signs of otitis media on day 11. Patients were rated as having had clinical cure if signs and symptoms had totally resolved by day 4 and they remained totally resolved through day 11. Patients were rated as having clinical cure if complete resolution of clinical signs and symptoms continued

from day 11 through to day 28. The treatment preference rate was assessed at day 11 and parents or guardians were asked if they would choose the same treatment again.

Each child who received at least 1 dose of antibiotic was evaluated for safety, based on the adverse effects reported by parents or by the physician. The occurrence of symptoms known to be adverse effects of either treatment was rated on inclusion.

Statistical analysis

The statistical analysis was carried out to assess equivalence. The analyzed population included a safety population defined as all enrolled patients; the ITT population was defined as those who were exposed to at least 1 dose of ceftriaxone or 4 days of the oral course of amoxi-clav; the standard analysis population (STD) was defined as those meeting certain predefined inclusion/exclusion criteria without any major protocol violation and those who completed either the single dose ceftriaxone or the 10-day oral course of amoxi-clav. Both the ITT and STD populations were applied to the primary and secondary efficacy variables, respectively, while patients in the safety population were assessed for safety. The null hypothesis was that there was no treatment difference. Where applicable, a p value < 0.05 was considered to be statistically significant.

The primary efficacy rate was the clinical success rate for both STD and ITT populations using the Fisher's exact test. The difference in response rate between the treatment groups and the 95% confidence interval for the difference were presented. The secondary efficacy measurements were the rate of clinical cure maintained, relapse rate, recurrence rate, and persistent middle-ear effusion rates.

Results

Population

A total of 110 patients were randomly recruited into the study. Seventy-eight patients ($n = 43$ in the ceftriaxone group; $n = 35$ in the amoxi-clav group) completed the treatment and 71 of them were followed up to 28 days.

109 patients were eligible for a safety analysis with 1 excluded due to protocol violation. Ninety-six patients were included in the ITT population, and there were 13 patients in the safety population who did not complete the 3-day treatment period. The standard analysis population consisted of 73 patients — 41 in the

Table 1. Summary of patient demographics

Characteristic	Ceftriaxone n = 54 (%)	Amoxi-clav n = 55 (%)	<i>p</i>
Age (months) ^a	31.74 ± 21.34	29.75 ± 20.39	0.619
Body weight (kg) ^a	14.33 ± 5.67	13.45 ± 4.46	0.365
Sex ratio (M/F)	1.7	2.2	0.547
Primary diagnosis of AOM			0.300
Bilateral	31 (57.4)	30 (54.6)	
Unilateral	23 (42.6)	25 (45.4)	
Left ear	16 (29.6)	12 (21.8)	
Right ear	7 (13.0)	13 (23.6)	
First episode of AOM enrolled			0.154
No	21 (38.9)	14 (25.5)	
Yes	33 (61.1)	41 (74.6)	

Abbreviations: AOM = acute otitis media, Amoxi-clav = amoxicillin-clavulanate

^aMean ± SD.

ceftriaxone group and 32 in the amoxi-clav group. A total of 23 patients in the ITT population were excluded from the standard analysis population. Fifteen of them were excluded due to premature withdrawal from the study while 6 of them violated the protocol. Two patients withdrew from the study and violated the protocol as well. Demographic data, clinical findings, and concomitant symptomatic treatments were similar in the 2 treatment groups (Table 1). No significant differences were found between the distribution of demographics and clinical characteristics in the 2 treatment groups, or between the distributions in the per-protocol and the ITT analyses.

Clinical efficacy

Among the 73 patients in the standard population, 16 patients experienced treatment failure (9 in the ceftriaxone group, 7 in the amoxi-clav group) while 56 patients were cured. The cure rate was 75.6% in the ceftriaxone group compared with 78.1% in the amoxi-clav group. The difference in clinical success rate between the 2 treatment groups was 2.5% ($p=1.000$) with a 95% confidence interval of -21.9% to 16.9%. For the ITT population, 19 out of the 96 patients experienced treatment failure, while 63% and 60% of patients were cured in the ceftriaxone and the amoxi-clav groups, respectively. The difference in clinical success rates between the 2 treatment groups was 2.8% ($p=0.84$) with a 95% confidence interval of -16.8% to 22.3%. No statistically significant differences were found between treatment groups in both populations.

For the standard analysis population, 74.2% compared with 84% in the ceftriaxone and amoxi-clav groups, respectively, had maintained the clinical cure

($p=0.52$). Recurrence was observed in 6 patients, 3 in each group. No relapse was found. Among the clinically cured patients, 32 (16 in each treatment group) had persistent middle-ear effusion on day 11, compared with 18 patients (7 in ceftriaxone group and 11 in the amoxi-clav group) on day 28 for both populations. Table 2 presents the clinical outcomes of patients in both treatment groups. Of the 96 patients in the ITT population, 73 patients were included in the standard analysis population.

Treatment preference

Patient treatment preferences were assessed by the site staff on day 11. Among the 73 patients in the standard analysis population, 62 patients had valid treatment preference recorded. Thirty-one out of 33 patients (93.9%) in the ceftriaxone group would choose the same treatment again compared with 17 out of 29 patients (58.6%) in the amoxi-clav group ($p=0.0016$). Thus, a higher treatment preference rate was observed in the ceftriaxone group.

Safety

A total of 46 drug-related adverse effects was reported in 33 patients. At least 1 drug-related adverse effect was experienced by 13 subjects in the ceftriaxone group compared with 20 subjects in the amoxi-clav group. The most frequently observed drug-related adverse effects were in the digestive system (22.2% with ceftriaxone, 34.6% with amoxi-clav) and skin and appendages (7.4% for ceftriaxone, 10.9% for amoxi-clav) in both treatment groups. Diarrhea and rash were the most commonly reported drug-related adverse effects among the amoxi-clav group were diarrhea (30.9% and 10.9%,

Table 2. Summary of clinical outcomes

	No. of cases (%)		
	Total	Ceftriaxone	Amoxi-clav
Population: standard analysis	n = 73	n = 41	n = 32
Overall			
Cure	56 (76.7)	31 (75.6)	25 (78.1)
Failure	16 (21.9)	9 (21.9)	7 (21.9)
Unknown	1 (1.4)	1 (2.4)	0 (0.0)
Maintained rate	n = 56	n = 31	n = 25
Maintained	44 (78.8)	23 (74.2)	21 (84)
Recurrence	6 (10.7)	3 (9.7)	3 (12)
Unknown	6 (10.7)	5 (16.1)	1 (4)
Clinical cure rate	56 (76.7)	31 (75.6)	25 (78.3)
Population: intent-to-treat	n = 96	n = 51	n = 45
Overall			
Cure	59 (61.5)	32 (62.8)	27 (60)
Failure	19 (19.8)	11 (21.6)	8 (17.8)
Unknown	18 (18.8)	8 (15.7)	10 (22.2)
Maintained rate	n = 59	n = 32	n = 27
Maintained	47 (79.7)	24 (75)	23 (85.2)
Recurrence	6 (10.2)	3 (9.4)	3 (11.1)
Unknown	6 (10.2)	5 (15.6)	1 (3.7)
Clinical cure rate	59 (61.5)	32 (62.8)	27 (60.0)

Abbreviation: Amoxi-clav = amoxicillin-clavulanate

respectively) and the ceftriaxone group (16.7% and 7.4%, respectively). Eight patients in the amoxi-clav group discontinued treatment due to drug-related adverse effects.

Discussion

The increasing resistance rate of pneumococci to penicillin and beta-lactamase-producing *H. influenzae* and *M. catarrhalis* raises additional difficulties in the choice of an appropriate therapy for AOM [6]. The efficacy of high-dose amoxicillin or amoxi-clav is considered appropriate for treating AOM due to possible coverage of some penicillin-resistant pneumococci [7]. Amoxicillin, however, cannot cover beta-lactamase-producing *H. influenzae* and *M. catarrhalis*. Furthermore, a long-term oral antibiotic course is often inconvenient to parents [8].

Ceftriaxone is a broad-spectrum, parenterally administered third-generation cephalosporin characterized by good antibacterial activity against most pathogens causing AOM [7]. Ceftriaxone is absorbed rapidly following intramuscular administration and achieves high mean peak serum levels 2 hours after administration [9]. Because of its prolonged half-life, the drug is ideally suited to single-dose therapy and has been documented to be effective in treating gonorrhoea

and incubating syphilis [10,11]. Ceftriaxone reaches middle-ear fluid concentrations of 10% of its serum concentration [7]; these exceed the MICs of the typical AOM pathogens for approximately 56 hours after a single intramuscular injection of 50 mg/kg [12-14].

This study demonstrates the clinical equivalence for a single intramuscular dose of ceftriaxone (50 mg/kg) and a 10-day regimen of amoxi-clav for the treatment of AOM. Several studies have shown the effectiveness of 1 intramuscular dose of ceftriaxone for treating AOM [5,7,15]. Green and Rothrock demonstrated that a single injection of ceftriaxone had similar efficacy to a 10-day course of oral amoxicillin in the treatment of AOM in 1993 [16]. Similar results had also been reported by Barnett et al [17] after a 4-week follow-up, using oral trimethoprim-sulfamethoxazole as a comparative drug and by Varsano et al [15] using oral amoxi-clav as a comparative drug.

Ceftriaxone was approved by the US Food and Drug Administration (FDA) for the treatment of AOM in December 1997 and became the first single-dose, injectable antibiotic for the treatment of AOM. Preparations that could be given parenterally would provide an advantage to children who might have poor absorption of an oral drug, who refuse to take oral medications, or who have decreased compliance due to family circumstances [17].

Through this trial, we have demonstrated similar efficacy and safety results to previous studies. For the efficacy profiles based on the standard analysis population, the clinical success rate of patients treated with ceftriaxone is comparable to the rate of those treated with amoxi-clav, based on the primary diagnosed AOM ear (75.6% in the ceftriaxone group vs 78.1% in the amoxi-clav group). Persistence of middle-ear fluid did not differ between the 2 groups at day 11 (51.6% of ceftriaxone recipients vs 64% of amoxi-clav recipients) or day 28 (22.6% vs 40%, respectively). Recurrence was observed in 6 patients (3 in each treatment group) and no relapse was found. The most commonly reported drug-related adverse events were diarrhea and skin rashes in both treatment groups. We also showed, in common with a study by Bauchner et al [18], that a single intramuscular dose was felt by parents to be preferable to a 10-day treatment course of oral antibiotics.

The study had some limitations: middle-ear fluid cultures were not obtained and only 73 cases completed the treatment course, which may have affected the results. Indeed, many cases were ruled out due to study violations and they were only available for safety evaluation. Evaluation of efficacy of antibiotics for treatment of AOM is complicated by the difficulty in defining the clinical signs of AOM and outcome measures, a high spontaneous resolution rate, discrepancies between microbiologic and clinical outcomes, and the necessity for large sample sizes in clinical studies [17]. In addition, otoscopy and tympanogram examinations are not always objective. However, studies using the physical signs of abnormal tympanic membranes plus abnormal tympanometry have demonstrated yields of bacterial pathogens from middle-ear effusion ranging from 65% to 92% [19]. Diagnostic tympanocentesis was not routinely performed mainly for ethical reasons; it is unnecessary for uncomplicated AOM and did not influence the outcome of the disease [20]. However, it greatly aids understanding of the microbiology and drug sensitivities of AOM pathogens, and may be valuable in complicated cases.

Rates of persistence of middle-ear fluid did not differ significantly between the 2 groups. A significantly higher rate of persistence of middle-ear fluid in children treated with ceftriaxone compared with those treated with amoxicillin was reported by Varsano et al [15], but was attributed to differences in follow-up rates between the groups or a potential effect of ceftriaxone

on inflammatory response. Adverse events were infrequent during our study. The major encountered problems were diarrhea and rash. There were no significant differences in drug-related adverse events between the 2 groups.

Although there is some concern that the use of such a broad-spectrum agent may hasten the emergence of antibiotic-resistant organisms [21], the chance of carrying penicillin-resistant *S. pneumoniae* did not increase after ceftriaxone treatment from nasopharyngeal cultures [5]. Also there was no evidence that a single dose of ceftriaxone contributed to more resistance than 10 days of treatment with amoxi-clav [5]. However, more studies are needed to clarify this issue.

From the clinical efficiency and economic viewpoints, use of ceftriaxone can be justified in the management of AOM under special circumstances, particularly in cases when the patient's ability to tolerate or absorb oral drugs is compromised, in children with treatment failure with oral amoxicillin [15]. This study demonstrated that a single intramuscular dose of ceftriaxone had similar efficacy and safety profiles to 10 days of therapy with oral amoxi-clav in patients with AOM. Furthermore, single-dose ceftriaxone therapy offers increased compliance, and greater convenience for patients and parents.

References

1. Faden H. The microbiologic and immunologic basis for recurrent otitis media in children. *Eur J Pediatr* 2001;160: 407-13.
2. Heikkinen T, Ghaffar F, Okorodudu AO, Chonmaitree T. Serum interleukin-6 in bacterial and nonbacterial acute otitis media. *Pediatrics* 1998;102:296-9.
3. Cohen R. The antibiotic treatment of acute otitis media and sinusitis in children. *Diagn Microbiol Infect Dis* 1997;27: 35-9.
4. Block SL, Hedrick JA, Tyler RD, Smith RA, Harrison CJ. Microbiology of acute otitis media recently treated with aminopenicillins. *Pediatr Infect Dis J* 2001;20:1017-21.
5. Cohen R, Navel M, Grunberg J, Boucherat M, Geslin P, Derriennic M, et al. One dose of ceftriaxone vs. ten days of amoxicillin/clavulanate therapy for acute otitis media: clinical efficacy and change in nasopharyngeal flora. *Pediatr Infect Dis J* 1999;18:403-9.
6. Bradley J. Oral vs. intramuscular antibiotic therapy for acute otitis media: which is best? *Pediatr Infect Dis J* 1999;18: 1147-51.
7. Leibovitz E, Piglansky L, Raiz S, Press J, Leiberman A, Dagan

- R. Bacteriologic and clinical efficacy of one day vs. three day intramuscular ceftriaxone for treatment of nonresponsive acute otitis media in children. *Pediatr Infect Dis J* 2000;19:1040-5.
8. Becker MH, Drachman RH, Kirscht JP. Predicting mothers' compliance with pediatric medicine regimens. *J Pediatr* 1972; 81:843-54.
9. Frascini F, Braga PC, Scarpazza G, Scaglione F, Pignataro O, Sambataro G, et al. Human pharmacokinetics and distribution in various tissues of ceftriaxone. *Chemotherapy* 1986;32:192-9.
10. Laga M, Naamara W, Brunham RC, D'Costa LJ, Nsanze H, Piot P, et al. Single-dose therapy of gonococcal ophthalmia neonatorum with ceftriaxone. *N Engl J Med* 1986;315:1382-5.
11. Rawstron SA, Hammerschlag MR, Gullans C, Cummings M, Sierra M. Ceftriaxone treatment of penicillinase-producing *Neisseria gonorrhoea* infections in children. *Pediatr Infect Dis J* 1989;8:445-8.
12. Block SL. Causative pathogens, antibiotic resistance and therapeutic considerations in acute otitis media. *Pediatr Infect Dis J* 1997;16:449-56.
13. Frascini F, Braga PC, Scarpazza G, Scaglione F, Pignataro O, Sambataro G, et al. Human pharmacokinetics and distribution in various tissues of ceftriaxone. *Chemotherapy* 1986;32:192-9.
14. Schaad UB, Stoeckel K. Single dose pharmacokinetics of ceftriaxone in infants and young children. *Antimicrob Agents Chemother* 1982;21:248-53.
15. Varsano I, Volovitz B, Horev Z, Robinson J, Laks Y, Rosenbaum I, et al. Intramuscular ceftriaxone with oral amoxicillin-clavulanate for treatment of acute otitis media in children. *Eur J Pediatr* 1997;156:858-63.
16. Green SM, Rothrock SG. Single dose intramuscular ceftriaxone for acute otitis media in children. *Pediatrics* 1993;91:23-30.
17. Barnett ED, Teele DW, Klein JD, Cabral HJ, Kharasch SJ. Comparison of ceftriaxone and trimethoprim-sulfamethoxazole. *Pediatrics* 1997;99:23-8.
18. Bauchner H, Adams W, Barnett E, Klein J. Therapy for acute otitis media. *Arch Pediatr Adolesc Med* 1996;150:396-9.
19. Del Beccaro MA, Mendelman PM, Inglis AF, Richardson MA, Duncan NO, Clausen CR, et al. Bacteriology of acute otitis media: a new perspective. *J Pediatr* 1992;120:81-4.
20. Engelhard D, Cohen D, Strauss N, Sacks TG, Jorzack-Sarni L, Shapiro M. Randomized study of myringotomy, amoxicillin/clavulanate or both for acute otitis media in infants. *Lancet* 1989;II:141-3.
21. Infectious diseases and immunization committee, Canadian pediatric society. Antibiotic management of acute otitis media. *Pediatr Child Health* 1998;3:265-7.