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OPEN LABELED, NON-COMPARATIVE TRIAL : SINGLE-DOSE INTRAMUSCULAR CEFTRIAXONE FOR UNCOMPLICATED ACUTE OTITIS MEDIA IN CHILDREN

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Abstract

Recently, several therapeutics options have been recommended in the management of otitis media. Compliance and efficacy have been the major concerns in children in the choice of antibiotics. This study evaluated the efficacy and safety of a 50 mg/kg single-dose of intramuscular ceftriaxone for acute uncomplicated otitis media in children. In an open drug trial, 14 children, 7 males and 7 females with a mean age of 1.95 years of age range 5 months to 5 years, 50% of whom are less than 1 year of age seen at the Philippine General Hospital were included.

All patients had previous history of ear infections, 71% occurring during the first three months of life. Colds/rhinitis (85%) were the most common clinical manifestations followed by fever (78%) and cough (71%). Irritability, otalgia, and ear pulling were seen in 50% of cases. Tympanic membrane discoloration (92%) was the most common otoscopic finding. Other findings were opacified tympanic membrane, bulging tympanic membrane, impaired mobility and air fluid level. Tympanometric studies were compatible with otoscopic findings except in 3 in which type A tympanogram was noted with discoloration on otoscopy. All fever resolved within 3 days after therapy while abnormal otoscopic findings dissappeared after 10 days on all successful treatment except for 2 patients with persistent tympanic membrane discoloration and 1 with opacification, which resolved on the 30th day. Treatment was successful in 12 out of 14 cases (86%). Relapse was noted in 1 patient (7%) after 12 days of therapy and reinfection in 2 patients (14%) on day 35 and 90. The only adverse effect noted was pain in the injection site in 1 patient. It is concluded that 50 mg/kg single-dose Ceftriaxone may be used effectively and safely in uncomplicated acute otitis media in children.[1]

[1] Keywords: acute Otitis Media (AOM) Therapy: Single –Dose Ceftriaxone
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Introduction

Conventional antimicrobial therapy for acute otitis media requires anywhere from 5 to 10 days of oral antibiotics given on a twice or thrice-a-day regimen [1-4] The disadvantages of such regimen may include problems regarding compliance, as parents may prematurely terminate therapy based on apparent clinical improvement. In others, the daily compliance may not be adhered to probably because of lack of supervision and poor tolerability to the suspension or syrup. Thus, the preferred antimicrobial agents regimen for acute otitis media should be individualized after consideration of factors relating to compliance and cost.[3] A single-dose regimen may be able to circumvent such problems and prevent complications or treatment failures secondary to poor drug compliance.

Ceftriaxone is a third-generation parenteral antibiotic that has been shown to achieve therapeutic levels in the middle ear. After a single IM injection, serum levels exceed the mean inhibitory concentration for approximately 74 hours, and it is expected to sterilize the middle ear. It has excellent activity over the common etiologies for acute otitis media (*Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis*). It may also be given as a second-line drug for penicillin-resistant *Streptococcus pneumoniae*.[2]

In a study by Green and Rothrock, a single intramuscular dose of ceftriaxone at 50 mg/kg/dose proved to be as effective as the standard 10-day therapy with oral amoxicillin.[1] Furthermore, the total regimen cost of a 10-day course of amoxicillin or a 5-day course of Cefaclor is comparable to a single dose of ceftriaxone. Because of the comparable costing of a single dose of ceftriaxone efficacy and assured compliance, such regimen may be offered by physicians as an alternative to a daily dose regimen to parents in selected clinical situations. No such study has yet been done in the Philippines.

Objective

This study determines the efficacy and tolerability of a single 50 mg/kg dose of intramuscular ceftriaxone therapy in acute uncomplicated otitis media among Filipino pediatric patients (five months to five years of age).

Methodology

This is an open-labeled non-comparative drug trial among pediatric patients of both sexes aged 5 months to less than 5 years old seen at the Outpatient Department of the Philippine General Hospital ENT and Pediatric Section with clinical signs and symptoms of uncomplicated acute otitis media (AOM) and/ or tympanometric studies of acute otitis media. Patients who satisfied the inclusion and exclusion criteria (Table 1 and 2) were enrolled and given single intramuscular dose of ceftriaxone at 50 mg/kg. A medical history, physical examination, tympanometry and nasopharyngeal cultures were done on all patients. Only paracetamol was given for fever. Patients were observed for thirty minutes after IM injection for any untoward reactions. In all patients , a thorough history and physical examination including otoscopy were done. On Day 3, adverse experiences were noted and if the patient worsens clinically on Day 3, a 100 mg/kg IM single-dose of ceftriaxone was given. Patients who otherwise improved or did not clinically deteriorate were instructed to follow-up on Day 10. On Day 10, adverse experiences were again noted and repeat tympanometric studies were done. Patients who had no improvement were given 100 mg/kg/day and tympanocentesis was done with parents or guardians' consent. On Day 30, adverse experiences were again noted and a repeat tympanometry were done. On Day 90, a final complete history and physical examination as well as otoscopy were done. To check relapse and recurrences, patients were followed up on Days 30 and 90.

Table 1: Inclusion Criteria

Inclusion Criteria
1. Patients 5 months to 5 years with at least two of the following: a. a history of fever or irritability or otalgia b. at least one of the following otoscopic findings: i) middle ear fluid ii) tympanic membrane discoloration iii) bulging tympanic membrane iv) impaired mobility v) opacity other than scarring without perforation of tympanic membrane c. abnormal tympanometric showing a type B (flat) or type C curve 2. Written informed consent has been obtained from the parents or guardian of the child.

Table 2: Exclusion Criteria

Exclusion Criteria
1. Antibiotic use within the past 14 days 2. History of acute otitis media within the past month or chronic otitis Media 3. Presence of myringotomy tubes 4. Any serious underlying illness, concurrent infection (pneumonia, meningitis, cellulitis) 5. Allergy to penicillins, cephalosporins, or lidocaine 6. Immunodeficiency states

Patients outcome was classified as follows:

Successful treatment was defined as resolution of AOM symptoms and no return to these symptoms within 10 days of the initiation of ceftriaxone. Subjects who did not meet these criteria were classified unsuccesful.

- Successful treatment was subdivided into:
  - Non-recurrence
    Resolution of AOM symptoms and no recurrence of symptoms within 90 days of initiating treatment
  - Re-infection
    Initial resolution of AOM symptoms with recurrence in 31-90 days
  - Relapse
    Initial resolution of symptoms with recurrence in 11-30 days
- Unsuccessful treatment was subdivided into:
  - Failure
    Persistence or recurrence of symptoms and occurrence of new symptoms within 10 days of initiating treatment
  - Complications
    Appearance of a condition significant enough to require discontinuation of the study protocol.

Results

Clinical Profile

A total of 14 patients were included in the study with 1:1 male to female ratio. Children less than 12 months comprise 50% (7) of patients. The rest of the baseline characteristics are presented in Table 3. Bilateral involvement was seen in 50% of cases. Of the 7 patients who had unilateral involvement, the right ear was affected in 4. All patients had previous history of ear infection: 10 had their first ear infection during the first 3 months of age, 2 at 3 to 6 months, 1 at 6 to 12 months and 1 at more than 1 year of age. Rhinitis was the most common accompanying clinical manifestation which was seen in 85% (12/14) while fever and cough were seen in 78% (11/14) and 71% (10/14), respectively. Other symptoms included irritability, otalgia and ear pulling.

Table 3: Clinical Profile of Patients with Uncomplicated Acute Otitis Media

Characteristics of Patients (%)	Number
Age:	
5-<12 mos.	7 (50%)
12-<24 mos.	3 (21%)
24-<36 mos.	2 (14%)
3-5 yrs.	2 (14%)
Sex:	
Male	7 (50%)
Female	7 (50%)
Ear involvement:	
Bilateral	7 (50%)
Unilateral	7 (50%)
Right	4 (57%)
Left	3 (43%)
First Episode of Ear Infection (Age):	
Less than 3 months	10 (71%)
3 mos.-<6 mos.	2 (14%)
6 mos.-<1 yr.	1 (7%)
> 1 yr.	1 (7%)
Smoking Exposure:	
No smoking household member	8 (57%)
1 smoking household member	4 (28%)
2 or more smoking household members	2 (14%)
Clinical Manifestations:	
Rhinitis/ colds	12 (85%)
Fever	11 (78%)
Cough	10 (71%)
Irritability	7 (50%)
Otalgia	7 (50%)
Characteristics:	
Ear Pulling	7 (50%)
Otoscopic Findings:	
Discoloration	13 (92%)
Bulging tympanic membrane	7 (50%)
Impaired tympanic membrane mobility	4 (29%)
Opacified tympanic membrane	9 (64%)
Air fluid level	3 (21%)

Tympanic membrane discoloration was the most common otoscopic finding, 13 out of 14 or 92% followed by opacified and bulging tympanic membrane in 64% (9/14) and 50% (7/14), respectively. Impaired tympanic membrane mobility was seen in 29% (4/14) of patients and air fluid level in 21% (3/14), respectively. Tympanometric studies were compatible with otoscopic findings except in 3 wherein type A tympanogram was noted with discoloration on otoscopy.

Table 4: Tympanogram of Patients with Abnormal Otoscopic Findings

Classification of Category	Number of Patients (%)
Type A	3 (14%)
Type B	16 (76%)
Type C	2 (10%)

Microbiologic Examination

Nasopharyngeal swabs were done on all patients. *Klebsiella pneumoniae* grew on 4 and 1 grew *Klebsiella ozanae*. *Acinetobacter anitratum* was seen in 2 cases. Other isolates were *Pseudomonas stutzerii, Pseudomonas cepacia, Streptococcus pneumoniae, M. catarrhalis and H. influenzae*. Two specimens grew 2 different organisms. In 3 (21%) cultures, there were no significant pathogens isolated.

Table 5: Nasopharyngeal Bacterial Isolates

Organisms Isolated	Number
Klebsiella pneumoniae	4
Klebsiella ozanae	1
Acinetobacter anitratum	2
Pseudomonas cepacia	2
Pseudomonas stutzerii	1
Haemophilus influenzae	1
Moraxella catarrhalis	1
Streptococcus pneumoniae	1

Response Treatment

In those with fever, resolution occurred within three days therapy with a mean of 2.4 days, while abnormal otoscopic findings dissappeared after ten days with a mean of 11 days on all successful treatment except for three patients with persistent tympanic membrane discoloration and one with opacification which resolved on the thirtieth day. Among otoscopic findings, bulging tympanic membrane resolved earliest. Its dissappearance was noted on Day 3 in 3 out of 7 patients with a mean of 7 days. Discoloration persisted until Day 10 in 8 out of 13 patients, up to 30 days in 3 of the successful cases with a mean of 13 days.

Treatment was successful in 12 out of 14 (86%) patients. Only 2 patients were unsuccesful. One patient developed pneumonia on the third day of treatment, which required admission and was considered a complication. Another patient had persistent hyperemic tympanic membrane with type B tympanometric findings on the 10th day of treatment (unsuccessful). The parents refused 100 mg/kg dose of ceftriaxone and further work-up. Nasopharyngeal swab grew H. influenzae and Moraxella catarrhalis both sensitive to ceftriaxone. One patient had relapse on Day 12 of treatment. This patient had reappearance of colds and on otoscopy showed hyperemic tympanic membrane. He was given

100mg/kg IM ceftriaxone with resolution after 3 days. Two patients had reinfection. One patient came in on Day 35 from treatment with history of 4 days fever, cough and colds. The patient was already taking chloramphenicol when he came for follow-up. Ceftriaxone 100mg/kg was given and he gradually improved after 10 days. This patient had his first ear infection when he was less than 3 months of age. Initial nasopharyngeal swab showed *Streptococcus pneumoniae*, which was sensitive to ceftriaxone. Another patient had reinfection on day 90 from treatment. The patient only had colds with discoloration of tympanic membrane on otoscopy. The patient was exposed to his mother, who has respiratory tract infection. Nine out of twelve (75%) patients with successful treatment had no recurrence at all.

Table 6: Treatment Outcome

Treatment Outcome	Number (%)	
Successful		12 (86%)
Non-Recurrence	9 (65%)	
Relapse	1 (7%)	
Reinfection	2 (14%)	
Unsuccessful		2 (14%)
Failure	1 (7%)	
Complication	1 (7%)	
Total :	14 (100%)	14 (100%)

Discussion

The most common pathogen in acute otitis media in children are *H. influenzae, Streptococcus pneumoniae and Moraxella catarrhalis* [4,5,6] and less commonly group A Streptococcus [6]. Although 35% of the middle ear fluid in otitis media are noted to be sterile, [14] the early treatment with antibiotic provides modest benefit to prevent pain and discomfort 2-7 days after presentation. [5] The four most common pathogens are responsive to 2nd and 3rd generation cephalosporins. In the United States, there has been an increasing number of penicillin-resistant strains of *S. pneumoniae* as high as 59% [7]. In Asian countries like Korea as high as 60-80% penecillin-resistant *Streptococcus pneumoniae* is being reported. Our local data as seen in the 1997 Antimicrobial Resistance Surveillance Data showed penicillin-resistance of 6-15%[8].

The standard treatment for Acute Otitis Media is a ten-day course of amoxicillin. However, an increase in failure rate and recurrence may be expected due to problems with compliance and resistance. Thus, several treatment options are being investigated such as a 5-day treatment with second generation cephalosporins [9] and 3-day Azithromycin [13]. Other oral medications however, may also present with the problem of acceptance and tolerability, which will significantly affect the compliance especially for pediatric patients. Other problems with adverse effects such as gastritis and diarrhea may be exhibited with use of Amoxicillin and macrolides. Ceftriaxone single IM dose will eliminate all these problems. In a study by Bauchner, it was shown that all parents who were included in the study preferred single-dose IM therapy for AOM to standard 10-day oral therapy[11].

Our study showed that ceftriaxone 50 mg/kg IM was 86% successful in the treatment of acute otitis media. The result was similar to the study done by Green comparing ceftriaxone 50 mg/kg IM single dose with a 10-day amoxicillin with 91% success rate[1] and a study by Barnett comparing it with 10-day cotrimoxazole showed a 92.5% success rate [12].

The patient who developed pneumonia on the third day of treatment could have been developing pneumonia at the time of inclusion. The overt signs of pneumonia such as rales and tachypnea were not present at the time of admission to the study in the patient. The other patient with persistently abnormal otoscopic and tympanometric findings on Day 10 of treatment who grew *M. catarrhalis* and *H. influenzae* on nasopharyngeal culture were both sensitive to ceftriaxone. A trial of 100 mg/kg could have confirmed the need for a high dose in some cases. However, the parents refused a second injection in this case. An MIC of the organism had it been done could show the cause of the failed treatment.

Two patients had reinfection, the first patient was a 7 month old male who had his first episode of ear infection when he was less than 3 months and was breastfeeding until one month prior to this episode of AOM. These factors could have predisposed this child to the reinfection. The second patient who had reinfection was a 2-year-9-month-old female who already had her first episode at >1 year with no history of exposure to any pollutant. He was exposed to his mother with a respiratory tract infection.

The disadvantages of ceftriaxone included pain at the injection site and the initial cost of the treatment[1]. However, if high compliance, high success rate and low morbidity are considered, it will eventually result in lower costs and better quality of life [13].

The nasopharyngeal swab cultures were not consistent with the usual pathogens that we expect. Most of our cultures grew *Klebsiella sp., Acinetobacter anitratum,* and *Pseudomonas*. This study may be due to some possible contamination or the appearance of hospital flora among other patients that are usually hospital colonizers. Ideally, a tympanocentesis would have been done in this study. Its invasiveness and the difficulty in obtaining consent since this has not been a common practice have prevented the performance of this procedure.

Conclusion

A single 50 mg.kg IM dose for the treatment of Uncomplicated Acute Otitis Media in pediatric patients was effective and did not show any significant adverse effects. Comparative clinical trials with other Standard antimicrobials for otitis media can be safely done in future studies.

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