

ORIGINAL ARTICLE

Ceftriaxone Therapy of Bacterial Meningitis in Children

by

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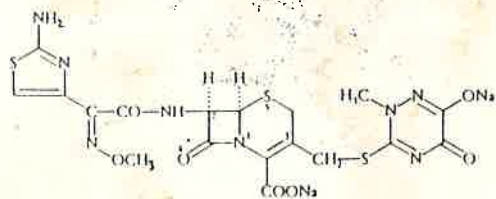
Abstract

Twenty-nine children, age 3 months to 11 years, admitted with the clinical diagnosis of bacterial meningitis to the Department of Child Health, were included in a prospective treatment study of ceftriaxone (Rocephin Hoffmann - La Roche AG Basle, Switzerland). Ceftriaxone was used as the only antibiotic agent in single daily dose of 100 mg/kg body weight given intravenously for a minimum of 10 days. Of these 29 patients, 25 (86.2%) recovered, 3 (10.3%) died and 1 (3.4%) no respond to treatment. Among fatal cases, two patients had subdural empyema and one had a cerebral abscess. The microorganisms isolated from cerebrospinal fluid were: *Streptococcus pneumoniae* (5), *Pseudomonas sp.* (4), *Proteus sp.* (2), *Salmonella typhi* (1), *Escherichia coli* (1), *Clostridium sp.* (1), *Pseudomonas aeruginosa* (1), *Staphylococcus aureus* (1), and *Streptococcus haemolyticus* (1). In 12 patients (41.4%), organisms were not identified. The diagnosis was made based on clinical symptoms, Gram staining, cell count, glucose, and protein in the CSF. In all patients, repeated spinal fluid cultures had no bacterial growth at 24 hours after initiation of intravenous therapy. No evidence of clinical important drug toxicity was observed. Three patients, however, had slightly elevated hepatic transaminase levels, and one patient had mild neutropenia. These clinical and bacteriological results suggested that ceftriaxone is reasonably safe and effective in the treatment of bacterial meningitis caused by the most common pediatric pathogens in Indonesian children over one month of age.

Introduction

Ceftriaxone - a third generation cephalosporin, has been shown to successfully eradicate most Gram-negative bacteria, *Neisseria gonorrhoea*, *H. influenzae*, *Staph. aureus*, *Streptococcus pyogenes* and group B *Streptococcus* (Lolekha et al., 1983).

Rocephin (ceftriaxone developed by Hoffman-La Roche Basle/Switzerland) has the following structural formula:



Its pharmacokinetic properties are as follows: (1) It possesses a long biological half-life relative to other cephalosporins

Materials and methods

The clinical efficacy of ceftriaxone in treating bacterial meningitis was prospectively studied in 29 children ranging in age from 3 months to 11 years. No neonates were included in this study. In 17 of the patients the diagnosis of bacterial meningitis was confirmed by culturing the causal agents. Diagnosis in 12 patients without positive cultures, however, were made by the cell count, level of glucose and protein in cerebrospinal fluid and clinical symptoms.

Rocephin (ceftriaxone developed by Hoffman-La Roche Basle/Switzerland), was used as the sole antibiotic agent with a single dose of 100 mg/kg body weight given intravenously for 10 days or longer.

due to its lower systemic clearance because of insignificant renal tubular clearance and extensive plasma protein binding; (2) The aminothiazolyl group (7-acyl side chain) increases its activity against Gram-negative bacteria, and the methoxyamino component contributes to its stability against B-lactamase enzymes; (3) The heterocyclic thiomethyl group (at the 3-position) influences the pharmacokinetics of ceftriaxone, resulting in a higher serum peak level and a prolonged serum half-life; (4) The hydroxyl group on the triazine ring may account for the improved pharmacokinetics of ceftriaxone.

This prospective study was designed to test the efficacy and safety of ceftriaxone for the treatment of bacterial meningitis in children suspected of having bacterial meningitis on the basis of clinical signs and microscopic examination of the CSF.

Multiple laboratory studies were obtained on all patients at the time of admission to the study. Cerebrospinal fluid was obtained for culture, Gram staining, cell count, protein and glucose determinations. Blood was obtained for culture. A complete blood count with differential WBC count and platelet count were done on admission and once a week during treatment. Determinations of serum levels of hepatic enzymes and renal function tests were done before and after treatment. An EEG was performed on all patients with clinical evidence of seizure activity. This study was based on clinical and bacteriological findings; no pharmacological studies were performed.

Several criteria were used to evaluate the improvement of neurologic status and clinical improvement including the disappearance of fever and irritability, the improvement of the level of consciousness, weight gain, and the normalization of the cell count, level of protein and glucose in the cerebrospinal fluid.

Results

Table 1 : Ceftriaxone in the treatment of Gram-positive bacillary meningitis in children (100 mg/kg/day, single dose therapy) RSCM Jakarta 1985 - 1986

Case No.	Age (Yrs)	Sex	Culture result		Duration of treatment (days)	Complications	Side effects	Patient outcome
			Blood	CSF				
1	1 2/12	M	-	Clostridium sp.	Neg	21	None	↑transaminase* Failure***
2	10/12	F	-	Staphylococcus aureus	Neg	14	None	(R)**
3	5/12	F	-	Streptococcus pneumoniae	Neg	12	None	diarrhea (R)**
4	8/12	F	-	Streptococcus pneumoniae	Neg	15	None	(R)**
5	2	M	-	Streptococcus pneumoniae	Neg	12	None	diarrhea (R)**
6	8/12	F	-	Streptococcus pneumoniae	Neg	12	Subdural effusion	(R)
7	4/12	M	-	Strep. haemolyticus group B	Neg	14	Hemiparesis	(R)
8	5/12	F	-	Streptococcus pneumoniae	Neg	12	None	(R)**

* Transaminase: SGOT and SGPT

** Recovered - No sequelae

*** Change to conventional therapy

(R) : Recovered

Table 1 shows baseline data for patients with Gram-positive organisms isolated from the CSF. All patients recovered, and all patients had sterile repeated CSF cultures 24 hours after starting treatment. The average time to defervescence was 3.1 days (range one to seven days). Mild diarrhea was observed in 2 patients. Patient No. 1

was considered as a failure because there was no improvement in laboratory parameters after 21 days of treatment. Patient No. 6 had a subdural effusion and patient No. 7 had hemiparesis as sequelae. One patient had slightly elevated hepatic transaminase levels, which later returned to normal.

Discussion

Because of the changing susceptibilities of infecting organisms and the difficulties in maintaining intravenous access, there is great need for alternatives to the current standard therapy of bacterial meningitis with ampicillin and chloramphenicol.

The reasons for choosing ceftriaxone in this study were: (1) Ceftriaxone possesses a long biological half-life relative to other cephalosporins, (2) Ceftriaxone reaches bactericidal concentrations far in excess of the minimum inhibitory concentrations for the usual causative organisms of meningitis, (3) Ceftriaxone diffuses readily into the cerebrospinal fluid (Stoeckel et al., 1981; Stoeckel, 1986).

Because Del Rio et al. (1983) found that 8 of 16 patients with ceftriaxone (75 mg/kg) had positive CSF cultures on repeated lumbar punctures 4 to 12 hours after the first done, the authors were concerned about the use of once daily therapy on the first day of treatment for bacterial meningitis. Therefore, we used an initial dose of 100 mg/kg i.v. and continued therapy with this dosage once daily. All patients with cultures positive of Gram-positive or Gram-negative bacteria had sterile CSF cultures 24 hours after initiation of therapy.

Stoeckel et al. (1981) reported that the protein binding of ceftriaxone is non linear, i.e. an increase in its free fraction in plasma was found when a higher dose was given. As a result, higher CSF levels are expected after once a day dosing as compared to twice daily dosing (with the same total dose). Havlick et al. (1981) documented excellent ceftriaxone CSF levels at 24 hours following injection of 80-100 mg/kg.

This observation led us to continue therapy with a once daily dose of 100 mg/kg.

In this study ceftriaxone appeared effective in the treatment of bacterial meningitis due to one of the most commonly encountered pathogens, *S.pneumoniae*. Of particular interest is the fact that ceftriaxone also proved to be effective in treatment of bacterial meningitis caused by *Salmonella typhi*. In 1976-1979 *Salmonella sp.* appeared to be the most common pathogen causing bacterial meningitis in newborns and young infants in Jakarta (Sumarmo et al., 1982).

Ceftriaxone was well tolerated in this study. Diarrhea was noted in five patients (17%). This rate is similar to that seen in a previously published study on the use of once daily ceftriaxone for the treatment of bacterial meningitis (Congeni et al., 1986). A slightly elevated hepatic transaminase level was observed in three patients, and one patient had mild neutropenia. However, abnormal values returned to normal at the end of therapy, and side effects did not lead to withdrawal of therapy in any patient.

In conclusion, this limited clinical and bacteriological study suggests that once daily ceftriaxone appears to be safe and effective in the treatment of bacterial meningitis caused by the most common pediatric pathogens in Indonesia for children over one month of age. The drug was well tolerated and the only clinically significant side effect was diarrhea which was self-limited. The fact that ceftriaxone can be given as a single daily dose lessens the burden on patients and nursing staff alike.

Acknowledgement

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