The Turkish Journal of Pediatrics 30:247 - 252, 1988

CEFOTAXIME AND AMIKACIN COMBINATION IN THE TREATMENT OF SALMONELLA INFECTION IN PREMATURE INFANTS*

*Olcay Oran MD***, Murat Yurdakök MD***, Gülsevin Tekinalp MD****, Güler Kanra MD***

Key words: premature infants, Salmonella typhimurium, cefotaxime, amikacin

Cefotaxime is a new cephalosporin derivate for parenteral use. It has been shown in in vivo studies to be several times more active than other cephalosporins against most gram negative bacteria including Salmonella. Although the antibacterial spectrum of third-generation cephalosporins including cefotaxime is quite broad, it should not be used alone for initial therapy of severe neonatal infections. The use of a combination of cefotaxime and an aminoglycoside such as amikacin is recommended[1-6]. We planned to evaluate the clinical efficacy of cefotaxime and amikacin combination in the treatment of Salmonella infections in premature infants and as far as we know this is the first report concerning this subject in the literature.

Material and Methods

Twelve premature infants whose stool cultures yielded *Salmonella typhimurium* were included in this study. The babies were hospitalized for various reasons in the Neonatology Ward of Hacettepe University Children's Hospital from July to September, 1986.

There were five males and seven females. Their gestational ages and body weights ranged from 29 to 36.5 weeks (mean 34.3 ± 0.6 weeks) and from 1200 g to 2900 g (mean 1918 ± 158 g), respectively. The medical records of the patients were examined for clinical and laboratory findings and past treatment. Appropriate throat, stool, urine and blood cultures were obtained simultaneously from all patients prior to, during and after therapy. Stool cultures were taken daily throughout the duration of the study.

* From the Hacettepe University Institute of Child Health, Ankara.

** Professor of Pediatrics, Hacettepe University Institute of Child Health

*** Assistant Professor of Pediatrics, Hacettepe University Institute of Child Health.

**** Associate Professor of Pediatrics, Hacettepe University Institute of Child Health.

Stool cultures were routinely plated on blood agar plates, and Salmonella-Shigella and Selenite F Salmonella species were grouped by Salmonella antisera (Difco, Detroit, MI). Antibiotic sensitivities were determined by Kirby-Baller disc diffusion on Mueller Hinton agar. Blood for culture was inoculated into supplemented peptone broth. The organisms were identified by the same methods used for salmonella isolated from stool specimens.

Before receiving results of stool cultures and taking into consideration the fact that there was a Salmonella epidemic in Ankara concurrently, a combination of cefotaxime and amikacin was administered to patients with diarrhea who produced watery greenish-yellow stools. Ten patients had already received antibiotic therapy in various combinations.

Cefotaxime was administered 25 mg/kg body weight intramuscularly; this dose was repeated every 12 hours for the first seven days of life, and every 8 hours after the first week. Amikacin was administered intramuscularly 7.5 mg/kg body weight twice daily during the first week of life and three times daily afterwards. Cefotaxime and amikacin combination was used until three consecutive stool cultures were negative for Salmonella.

All patients were carefully observed for side-effects, and laboratory tests (hemoglobin, white blood cell count, peripheral blood smear, urinalysis, SGOT, SGPT, BUN, serum creatinine) were done before and after the therapy to detect hematopoietic, hepatic and renal toxicity.

Results

Clinical results are shown in Table I. Of the twelve patients who were admitted to the study, ten were under previous therapy with other antibiotics which included penicillin, netilmycin or amikacin. In all patients throat and urine cultures were normal, but *Salmonella typhimurium* was cultured from the blood in only one patient.

In nine of the patients the clinical response was prompt with disappearance of signs and symptoms and eradication of the pathogen from the stool. The time elapsed between the positive stool culture for *Salmonella typhimurium* and the first negative culture varied from one day to 15 days (mean 5.0 ± 1.4 days). The total duration of therapy ranged from seven to 18 days (mean 12.2 ± 1.6 days).

All *S. typhimurium* strains were susceptible to cefotaxime, but the strains from six patients (Cases 1, 2, 5, 6, 11, 12) were resistant to amikacin in vitro; these patients were receiving amikacin for 4.0 ± 1.5 days before initiation of cefotaxime and amikacin combination.

Nine of twelve (75%) patients improved completely. Of the nine patients who survived, one patient improved, but had cholecystitis which demonstrated

TABLE I: Cefotaxime and Amikacin Combination in the Treatment of Salmonella Infections in Premature Infants

Case No.	Sex	Gestational age (wks)	Body weight (gms)	Previous antibiotic therapy	First positive stool culture	Start of therapy	First negative stool culture	Clinical outcome
1	F	29	1900	P, N, A	24th day* (and blood)	29th day*	–	Exitus
2	M	32	1670	P, A	9th day	14th day	–	Exitus
3	M	33.5	1250	–	9th day	9th day	13th day*	Cured
4	F	33.5	2060	P, N	8th day	8th day	9th day	Cured
5	F	34	1440	P, A	7th day	16th day	22nd day	Cured
6	F	34	1200	P, N, A	18th day	20th day	–	Exitus
7	F	35	1900	P, N	2nd day	3rd day	5th day	Cured
8	M	35.5	2220	–	10th day	10th day	11th day	Cured
9	F	35.5	1540	P, N	9th day	9th day	15th day	Cured
10	M	36.5	2800	P, N	16th day	16th day	21st day	Cured (cholecystitis)
11	F	36.5	2120	P, A	8th day	11th day	12th day	Cured
12	M	36.5	2900	P, A	9th day	10th day	15th day	Cured

P : penicillin
N : netilmycine
A : amikacin
* Day of life

ultrasonographically by the presence of hydrops vesica fellae five cm in diameter. Three (25%) patients (Cases 1, 2, 6) did not respond to treatment. They died 11-16 days after the initiation of the cefotaxime and amikacin combination and in spite of supportive measures.

Cefotaxime was well-tolerated. No toxic effects were noted. Side-effects due to cefotaxime and/or amikacin were not observed.

Discussion

The recent literature contains conflicting information regarding the risks of neonatal Salmonella gastroenteritis. Although it is known that Salmonella gastroenteritis in older children and adults is usually a self-limited disease and antimicrobial therapy may not improve the clinical course of acute gastroenteritis, there is a risk of bacteriemia or sepsis in preterm and full-term neonates. Bacteriemia was seen in 45 percent of neonates with stool culture positive for Salmonella[7]. Therefore, even in the absence of bacteriemia, a clinician would appear to be justified in using antibacterial therapy in neonates with Salmonella gastroenteritis. Since Erdem[8] has reported that the progress of Salmonella gastroenteritis into sepsis is more rapid and fatal in premature infants and early application of trimethoprim with sulfametoxazole might be beneficial in the prevention of the progress of gastroenteritis into sepsis in two-thirds of premature infants, we administered antibiotics to our patients. In addition, our patients had clinical and laboratory findings indicative of sepsis, but a positive blood culture for Salmonella was revealed in only one patient.

The problem was to determine which antibiotics to use. In our hospital, there were two important studies carried out concerning neonatal Salmonella infections.

Tuncer et al[9], reported on the general characretistics and mortality rate of neonatal Salmonella infections whose mortality rate he recorded between 1971-1987 as 29.4 percent and 44.6 percent for full-term and pre-term infants, respectively. It is very difficult to compare the results of that study with ours because the infections might have resulted from different *Salmonella typhimurium* strains. However, the mortality rate in our study was 25 percent.

Ceyhan et al[10] presented 47 cases of *Salmonella typhimurium* meningitis which included neonates and reported a 100 percent mortality rate. It was suggested that the most important reason for the high mortality rate was probably a result of the resistance this organism had to various antibacterial drugs including ampicillin, chloramphenicol, streptomycin, sulphamide, tetracycline, gentamicin and trimethoprim. The plasmid coded for this antibiotic resistance is probably quite common in Turkey and other countries in the Middle East[11]. As used by us in this study, a combination chemotherapy composed of new antibacterial drugs such as

cephalosporins and amikacin was recommended by these authors. Although six patients had been taking amikacin for various reasons before the diagnosed Salmonella infection, we used amikacin in addition to cefotaxime because of its clinical effectiveness[6]. We have demonstrated that the cefotaxime and amikacin combination is very effective in the treatment of Salmonella infections in premature infants as witnessed by the curing of nine out of twelve premature infants with salmonellosis. Although pharmacokinetic properties of cefotaxime are suitable for newborns[12], there are just a few reports concerning the usefulness of cefotaxime in the treatment of neonatal infectious including salmonellosis. Papadatos et al[13] have reported 16 newborn babies with severe infections who were treated with a combination of cefotaxime and an aminoglycoside, chiefly amikacin; in fourteen the clinical response was prompt, with disappearance of symptoms and signs, and eradication of the pathogen[13]. These authors also reported three adult patients with *Salmonella typhi* infection and all of them were treated only with cefotaxime resulting in a clinical and bacteriological response. McKendrick and Gaddes[14] have reported two adult patients with typhoid fever who were treated with cefotaxime. They suggested that the strains were extremely sensitive in vitro; however, no clinical response occurred with cefotaxime which possibly reflects a failure of penetration of cefotaxime into mammalian cells since Salmonella mainly causes an intracellular infection. In this study we have demonstrated the effectiveness of cefotaxime and amikacin combination in the treatment of Salmonella infections in premature infants.

Summary

This study included twelve premature infants with *Salmonella typhimurium* infection in most of whom previous antibacterial therapy had failed. Cefotaxime and amikacin combination cured nine of the patients. One patient improved as a result of this therapy but had cholecystitis. The treatment proved to be unsuccessful in three patients, and they died.

REFERENCES

1. Yogev R. A strategy for evaluating which of the new cephalosporins to use. *Pediatr Ann* 15:470, 1986.
2. Gordon RC, Sorting out the cephems: the role of new cephalosporins in pediatric therapeutics. *Pediatr Ann* 14:278, 1985.
3. Eichenwald HF. Antimicrobial therapy in infants and children: update 1976-1985. Part I. *J Pediatr* 107:161, 1985.
4. Starr SE. Antimicrobial therapy of bacterial sepsis in the newborn infant. *J Pediatr* 106:1043, 1985.
5. Cherubin CE, LeFrock J. Cefotaxime in the treatment of meningitis. *Infection* 13 Suppl 1:S68, 1985.

6. Klastersky J, Gaya H, Zinner SH, et al. Cefotaxime and amikacin: results of in vitro and in vivo studies against Gram-negative bacteria and Staphylococcus aureus. EORTC International Antimicrobial Therapy Project Group. *J Antimicrob Chemother* 6 Suppl A:55, 1980.
7. Nelson SJ, Granoff D. Salmonella gastroenteritis in the first three months of life. A review of management and complications. *Clin Pediatr* (Phila) 21:709, 1982.
8. Erdem G. Trimethoprim-sulphamethoxazole treatment in premature infants with salmonella infection. *Turk J Pediatr* 21:46, 1979.
9. Tunçer M, Ceyhan M, Erdem G, et al. Yenidoğan döneminde salmonella enfeksiyonu. *Çocuk Sağlığı ve Hastalıkları Dergisi* 28:103, 1985.
10. Ceyhan M, Kınık E, Çağlar MK. Salmonella typhimurium meningitis in childhood. *Turk J Pediatr* 27:121, 1985.
11. Berkman E. Bakteriyel menenjit etkeni olarak salmonella cinsi bakterilerin önemi. *Mikrobiyoloji Bülteni* 16:239, 1982.
12. Von Hattingberg HM, Marget W, Belohradsky BH, Roos R. Pharmacokinetics of cefotaxime in *neonates and children: clinical aspects. J Antimicrob Chemother* 6 Suppl A:113, 1980.
13. Papadatos CJ, Kafetzis DA, Kanarios J. Cefotaxime in the treatment of severe paediatric infections. *J Antimicrob Chemother* 6 Suppl A:243, 1980.
14. McKendrick MW, Geddes AM, Wise R, Bax R. Cefotaxime in septicaemia including typhoid fever. *J Antimicrob Chemother* 6 Suppl A:227, 1980.