Brief Reports

Clinical Efficacy of *Cefuroxime axetil* in *S. typhi*

Y.C. Mathur
N.C. Mathur
H.M. Lal

The major challenge that pediatricians in the developing, world face today in treating enteric fever is the burgeoning problem of multi drug resistance(l). Whilst the traditional treatment of choice has hitherto been chloramphenicol, two major problems, one of toxicity and the other of bacterial resistance in recent years has necessitated the need for newer drugs(2). Although this need has partly been fulfilled in adults with the availability of quinolones, their limitation in children below 12 years, in view of the potential for cartilage toxicity, and initial reports of resistance even to this drug, has resulted in evaluation of the role of cephalosporins. In this context, we decided to conduct a pilot study to evaluate the efficacy and safety of an orally administered cephalosporin, namely, Cefuroxime axetil, which is a prodrug of Cefuroxime, shown to have good *in-vitro* activity against *S. typhi(3).*

From the Department of Pediatrics, CDR Hospitals for Children, Hyderabad and Medical Research Division, Glaxo India Limited.

Reprint requests: Prof. Y.C. Mathur, 5, Subhodaya Apartments Bogulkunta, Hyderabad 500 001.

Received for publication: July 21,1995;
Accepted: June 14,1996

Subjects and Methods

Eighty eight patients of either sex above the age of 6 years with a clinical suspicion of enteric fever later confirmed by a positive blood culture for *S. typhi* and sensitive to Cefuroxime were enrolled into the study after obtaining informed consent. Patients hypersensitive to cephalosporins, suffering from any chronic illness, or those needing any other antibacterial agent were excluded from the study. The patients were recruited at 3 centers—CDR Hospital for Children (n=37) which was the coordinating center, Aditya Children's Hospital (n=22) and Hari Prasad Memorial Hospital (n=15). All patients were hospitalized and a detailed clinical examination was performed recording baseline parameters such as temperature, pulse rate, respiratory rate and blood pressure, *etc.* Each of these patients were administered 250 mg of Cefuroxime axetil twice daily to be continued up to 7 days following normalizing of temperature(4). They were followed up as inpatients initially, with a daily record being kept of various symptoms and signs such as fever, abdominal pain, tenderness, distension, diarrhea, headache, nausea, toxemia, hepatomegaly, till normalization of temperature, when discharge was permitted, if requested. Such patients were however, followed up in the OPD on a regular basis.

Blood cultures for *S. typhi* were done at our hospital pre and post treatment on MacConkey's agar and Bactec methodology. Sensitivity to Cefuroxime was established using Oxoid discs. Post treatment blood culture was done three

days after discontinuation of Cefuroxime. Biochemical and hematological parameters were monitored pre and post treatment. Stool cultures were done post treatment in few patients where follow up was possible between two months to one year. All adverse reactions reported during the study, were recorded.

Evaluation of patients was made on both clinical and bacteriological parameters. Response was assessed clinically by measuring the time in days for temperature defervescence. Patients responding within 4 days were graded as 'excellent responders', those within 5-7 days as 'satisfactory responders' and those responding clinically between 7-14 days but were bacteriologically negative within 14 days were classified as 'late responders'. Patients not responding by the 14th day, both clinically and bacteriologically were graded as 'failures'. Bacteriological response was determined by performing post treatment blood culture, 3 days after stopping the treatment and only those having negative blood cultures were considered responders. Stool cultures were done between two months to one year following treatment, wherever follow up was possible and a positive stool culture was considered for ascertaining the carrier state.

Results

Eighty eight patients with a mean age of 7.7 years of either sex were enrolled into the study of which only 72 were considered evaluable at the end of the study. Four did not meet the inclusion criteria, 2 of these having negative culture for *S. typhi* and 2 others being resistant to Cefuroxime. Six patients deviated from the set protocol while 6 others were lost to follow up on discharge after defervescence of temperature. The general sensitivity patterns of cases that cultured positive for *S. typhi* are depicted in *Table I.*

TABLE I-*Antimicrobial Sensitivity Pattern in Culture Positive cases*

Drug	Tested	% Sensitive
Cefuroxime	82	97
Chloramphenicol	81	28
Ampicillin	76	20
Amoxycillin	65	20
Sulphamethoxazole	*77*	36
Trimethoprim	75	35
Ciprofloxacin	79	94

Blood culture for *S. typhi* was positive in all the 72 evaluable patients. Clinical evaluation was made by recording the time taken for the temperature to normalize. Eighty five per cent of the patients were graded as excellent to satisfactory responders and 14% as late responders. Of the early responders 46% were graded as excellent responders and 39% as satisfactory responders. Mean time for temperature defervescence in the responders was 3.4 days.

Of the patients retested on day 3 following stoppage of therapy, 71/72 had complete eradication of the causative pathogen. Only one case showed a positive culture post treatment. In 30 patients where follow up was possible, stool cultures were done at varying intervals during periods ranging from 2 months to 1 year. No positive yield was obtained. The side effects encountered during the study were mild and transient and occurred in 5 patients, with one reporting abdominal pain, two nausea and vomiting and three had diarrhea.

Discussion

The phenomenon of chloramphenicol resistance in enteric fever is not entirely new (l,2), but the emergence of *S. typhi* strains resistant to multiple drugs has posed serious problems in the management. With rampant, inappropriate antimicrobial usage and

availability of antimicrobials without prescription, it is not surprising that S. *typhi* strains have become resistant by a variety of mechanisms not necessarily restricted to R-plasmid transfer alone(5).

This pattern of emergence of resistance of the first line drugs for enteric fever, first as isolated reports and then as epidemics, is a grave concern to pediatricians in India(l,2,5) as well as other parts of the world(6-8). The initial reports of resistant *S. typhi* strains from Kerala and in Mexico were later followed by major outbreaks of multidrug resistant strains from Delhi, Calcutta, Bombay, Chandigarh and Srinagar in our country; the most notable one being labelled as the "Dombivali Fever" in Bombay(5). Similar increases in multidrug resistance have been reported from the Gulf(6), Spain(7) and UK(8).

While quinolones have been used mostly in adults with good efficacy, its toxicity profile especially in view of it not being recommended in children below 12 years, has been an area of concern for its wider use(2). The arthropathogenicity of the quinolones observed in juvenile animals mandates some caution with regards to their use in prepubertal patients. An ADR monitoring survey in India(9) has further shown that musculoskeletal side effects were reported in 8.6% patients on Ciprofloxacin, and arthropathy and CNS symptoms have been reported in pediatric patients given Pefloxacin.

This situation has led doctors to use the second and third generation of cephalosporins the latter having been widely used as parenteral preparations. Cefotaxime, Ceftriaxone, Cefoperazone and Cefuroxime have all been used with considerable success, with efficacy rates reported around 80-90%. The disadvantage of these drugs in young children is that they must be given intravenously for 10-14 days(10). For clinical success, it has been considered that antibiotic activity in the acidic environment of the phagolysomes that contain intracellular salmonella is very important, and so are high biliary excretion rates(ll). In this context it has been shown that the cephalosporins effectively penetrate into the intracellular environment of the reticuloendothelial System both experimentally as well as by autoradiography. In contrast, the aminoglycosides are ineffective due to suboptimal activity in the acidic pH of the phagolysomes. There is a dichotomy in the effectiveness of various cephalosporins because of their relative β-lactamase stability and certain members are therefore less useful than others. Cefuroxime was reported to be more stable to β-lactamases having a 100 fold greater ability to resist hydrolysis compared to Cephaloridine(ll). Cefuroxime, further has been shown to possess good 'in vitro' activity against salmonella species with the MIC for inhibiting most S. *typhi* strains ranging between 0.25 meg to 8.0 mcg(12). This coupled with its high biliary levels and clinically useful levels in other tissues, prompted our evaluation of this drug in enteric fever.

Cefuroxime axetil has a longer half life an can be administered in a twice daily dosage schedule. The results of our study with Cefuroxime axetil administered in doses of 250 mg b.d. have also been very encouraging in enteric fever, with the mean time for defervescence of temperature being 3.4 days. Various other studies have shown that cefotaxime may take on an average 10 days and Ceftriaxone and Ciproflaxacin about 4 days for defervescence of temperature.

The pattern of resistance to conventional drugs used to treat enteric fever, encountered in our study revealed that their sensitivity ranged from 40-50%, which is in consonance with those reported

by others in India (l,2). As opposed to this, overall sensitivity of Cefuroxime to *S. typhi was* of the order of 97%.

We observed that although 100% of our cases responded clinically, in 85% there was a very good clinical response, the rest taking somewhat longer to respond. There was only one case of failure to respond as the post treatment blood culture was positive in this case giving an overall success rate of 98.6%. Soe *et al*.(12) reviewing results with Cephalosporins in enteric fever have reported failure rates with Cefamandole-35%, Cefotaxime-12%, Ceftriaxone-4%, Cefaperazone-3% and Cefuroxime-0%. It has been postulated that their individual β-lactamase stability and biliary concentration may be contributory factors for these differences. There were no relapses reported by these authors except in 4% of cases given Ceftriaxone and 6% given Cefotaxime. Our results too do not show any case of relapse or complications.

Post discharge follow-up stool cultures were possible only in 30 of our cases, nevertheless, all cases that were investigated were negative. This fact is important in the final consideration of elimination of chronic carriage of *S. typhi,* especially from an epidemiological point of view, as even small numbers lurking may cause infection and this observation reflects the wide spectrum of organism virulence and patient susceptibility. The high biliary levels(ll) of Cefuroxime may also be a helpful factor in avoidance of the carrier state, but further work in a larger series may by required to confirm this.

This pilot study has, therefore, indicated that Cefuroxime axetil, a second generation oral cephalosporin in doses of 250 mg b.d. is effective and safe therapy for enteric fever in the pediatric age group and may be preferred over the quinolones due to the latter's toxicity potential. By virtue of its oral administration, Cefuroxime axetil has an advantage over the third generation parenteral cephalosporins that entail hospitalization and paramedical help, adding to the costs of treatment.

REFERENCES

1. Khubchandani RP, Sainani GS, Mahajan MN. Drug resistant enteric fever. J Appl Med 1990,16: 735-737.
2. Singh M. The challenge of multidrug resistant typhoid fever. Indian Pediatr. 1991, 28: 329-332.
3. Bryan JP, Rocha H, Scheld WM. Problems in salmonellosis. Rationale for clinical trials with newer beta lactam agents and quinolones. Rev Infect Dis 1986, 8: 189-207.
4. Antimicrobials and related therapy. *In:* Red Book: Report of Committee on Infectious Diseases, 23rd edn. Ed. Peter G. Elk Grove Village, IL, American Academy of Pediatrics, 1994, pp 541-599.
5. Sridhar H. Macaden R, Devi MC, Bhat P. Chloramphenicol resistant *Salmonella typhi* in Bangalore. Indian J Med Res 1983, 78: 314-318.
6. Anonymous. Spread of multi-resistant *Salmonella typhi.* Lancet 1990,336:1065-1066.
7. Munoz P, Diaz MD, Rodriquex-Criexems M, Cercenado E, Pelaez T, Bouza E. Anti microbial resistance of *Salmonella i*solates in a Spanish hospital. Antimicrob Agents Chemother 1993, 37:1200-1202.
8. Row B, Ward LR, Threlfall EJ. Treatment of multi-resistant typhoic fever. Lancet 1991,337: 1422.
9. Karande SC, Kshirsagar NA. Adverse drug reaction monitoring of Ciprofloxacin in pediatric practice. Indian Pediatr 1992, 29:181-188.
10. Mandal BK. Treatment of multi-drug resistant typhoid fever. Lancet 1990, 336:1383.
11. Norris SM. The cephalosporin antibiotic agents-II. First and second generation agents. Infection Control 1984,5: 577-582.
12. Soe GB, Overturf GD. Treatment of typhoid fever and other systemic salmonellosis with Cefotaxime, Ceftriaxone, Cefoperazone and other newer cephalosporins. Rev Infect Dis 1987, 9: 719-736.