A comparative study of cefixime and ofloxacin for the treatment of uncomplicated Typhoid fever in Vietnamese children

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Abstract

Typhoid fever (TF) due to multi-drug resistant (MDR) Salmonella typhi has become a common problem in Vietnam since 1992. Recent studies have shown the oral fluoroquinolones (FQ) to be more effective than the parenteral third generation cephalosporins. However, concerns about the use of FQ in children and the emergence in Vietnam of S. typhi isolates resistant to nalidixic acid, with reduced sensitivity to the FQ, emphasises the need for effective alternative therapies. There is limited information concerning the effectiveness of the oral third generation cephalosporins for treating TF. 139 children with suspected TF were entered into an open randomised comparison of oral cefixime (20mg/kg/day in 2 divided doses) for 7 days and oral ofloxacin (10mg/kg/day in 2 divided doses) for 5 days. Ofloxacin showed a 5 day cure rate of 107 (95% CI) 1.7 to 36.7, *p = 0.002*. The clinical success rate was 75% with cefixime and 97% with ofloxacin, and the microbiological success rate was 94% and 100% respectively. There were no important side effects attributable to either drug. A 5 day course of ofloxacin proved to be a safe and effective treatment for children with uncomplicated typhoid fever. A 7 day course of cefixime was less effective, but may provide a useful alternative treatment in children, particularly if fluoroquinolone resistance becomes established.

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INTRODUCTION
Multidrug resistant strains of Salmonella typhi have emerged rapidly in Vietnam since 1990. These multidrug resistant strains are resistant to chloramphenicol, ampicillin and co-trimoxazole. The third generation cephalosporins and fluoroquinolones, however, both have good in-vitro activity. Recent studies from Vietnam have demonstrated that in adults, oral fluoroquinolones are more effective than parenteral third generation cephalosporins2,3. The fluoroquinolones have also been used effectively in children without short or long term adverse consequences despite earlier concerns about safety.4 Fluoroquinolones have thus become the treatment of choice for patients with uncomplicated enteric fever in Vietnam. However quinolone resistance has emerged in Vietnam since 1993. Patients infected with S. typhi resistant to the quinolone nalidixic acid are 13.5 times more likely to fail short course (3 day) fluoroquinolone treatment6 and there is therefore an urgent need to find effective alternative oral therapies. Cefixime, an oral third generation cephalosporin, has been found to be effective in 12 to 14 day courses in typhoid fever in open studies in Egypt and Pakistan7,9, but there have been no comparative studies between oral third generation cephalosporins and fluoroquinolones. We compared 7 days of cefixime and 5 days of ofloxacin treatment for uncomplicated typhoid fever in Vietnamese children.

METHOD
This study was conducted at the infectious diseases ward of the Dong Nai Paediatric Centre, Bien Hoa City, Vietnam. This is a paediatric referral hospital for the southern Vietnamese province of Dong Nai, where typhoid fever is endemic. Between July 1995 and April 1996, children (age <15 years) with suspected uncomplicated typhoid fever were studied. Patients were excluded if they had severe disease, were known to have received or be hypersensitive to quinolones or third generation cephalosporins. Patients who had received treatment with chloramphenicol, ampicillin, first or second generation cephalosporins, or co-trimoxazole were excluded if they had shown a clinical response to these drugs.

Patients were randomised to receive ofloxacin (Oflocet; Roussel, Paris), 10mg/Kg/day in 2 divided doses for 5 days or cefixime (Cefspan; Fujisawa, Japan), 20mg/Kg/day, in 2 divided doses for 7 days. A complete medical history was obtained and clinical examinations performed by a member of the study team on admission. Axillary temperature and other vital signs were recorded every 6 hours. Patients were examined daily until discharge and symptoms and clinical signs documented. On admission, blood was taken for haematocrit, platelet count, differential white cell count, examination for malaria parasites and Widal test. A blood culture and three stool cultures were taken before and after treatment.

Patients were considered clinically cured if they became afebrile, with resolution of symptoms and no evidence of relapse. Fever clearance time was defined as the time from the onset of treatment until the fever fell to 37.5°C or below for at least 24 hours. A clinical failure was defined as a deterioration in clinical condition or a failure of resolution of symptoms requiring further treatment. A microbiological failure was defined as a blood culture positive for S. typhi after completion of the treatment regime. Patients were requested to return if fever returned after discharge, and were asked to attend as an outpatient 4 weeks after completion of treatment. A relapse was defined as symptoms suggestive of typhoid fever with a blood culture positive for S. typhi during the 28 days after discharge.

RESULTS
Of the 139 patients with clinically suspected typhoid fever entered into the study, 82 (59%) had blood cultures positive for S. typhi. Twenty (24%) patients with positive blood cultures also had positive pretreatment stool cultures. There were no differences in presenting clinical features between the 2 treatment groups. All isolates of S. typhi were susceptible to both the study drugs. In the 82 blood culture isolates the percentage of antimicrobial resistance was: chloramphenicol (87%), ampicillin (87%), co-trimoxazole (83%), tetracycline (91%) and multiple resistance to all four antimicrobial agents (85%). There was no resistance to nalidixic acid. The proportion of multi-resistant isolates was the same in both treatment groups.

The mean (SD) fever clearance times were 109 hours (52) in the ofloxacin group compared with 197 hours (64) in the cefixime group (log rank test c2=39.2; p<0.001). There were 17 failures: 14 clinical failures, 2 microbiological failures, and 1 relapse. Fifteen of the treatment failures were in the cefixime group (relative risk=7.3, 95% CI 1.7-30.7; p=0.002). One six year old blood culture positive ofloxacin recipient died unexpectedly on the second day of treatment, 1
hour before the fourth dose of ofloxacin was due. An autopsy was not performed and a post-mortem clinical diagnosis of myocarditis was made. Sixty-nine patients (50%) were assessed at follow up. Ten patients had been febrile within one month of discharge (5 in each treatment group) but only one (in the cefixime group) was culture positive for S. typhi. He was readmitted and retreated successfully. No follow up stool cultures were positive.

**DISCUSSION**

Therapeutic options for multidrug resistant typhoid fever in children are limited. The fluoroquinolone drugs, which are the treatment of choice in adults, have traditionally been considered to be unsafe in children. In experimental animals, particularly beagle dogs, fluoroquinolones cause damage to cartilaginous end-plates of the long bones. However, there is no evidence that a similar process occurs in children, and their use is gaining increasing acceptance. Unfortunately quinolone resistance in S. typhi has already developed both in some parts of Vietnam and southern India. There is a need for safe, cheap and effective oral alternatives to fluoroquinolones.

Third generation cephalosporins have excellent in-vitro-activity against multidrug resistant S. typhi and these antibiotics have been assessed in recent clinical trials. Ceftriaxone, available only as the parenteral formulation, has been evaluated most thoroughly in comparative trials and proved inferior to the fluoroquinolones. Cefixime, a newer orally administered third generation cephalosporin has been evaluated in three previous trials in children. In open studies in Egypt, cefixime, given for a minimum of 12 days (20mg/Kg/day) was effective in 48/50 (96%) of patients. An 8 day course (20-30mg/Kg/day) was effective in 56/60 (93%). Cefixime (10mg/Kg/day for 14 days) was compared with ceftriaxone (65mg/Kg/day for 14 days) in 50 Pakistani children. The success rate for both drugs was 80%.

This study has demonstrated an overall failure rate of 21% in cefixime treated children. This was seven times higher than in the ofloxacin group (3%) although there were no nalidixic acid resistant strains in this series. There were no significant side effects in either group during the course of therapy. The unexplained death of a 6 year old patient receiving ofloxacin is of concern. Myocarditis is a recognised complication of typhoid fever occurring in 2-5% of cases in some series.

This study showed that cefixime (20mg/Kg/day) for 7 days was inferior treatment to ofloxacin (10mg/kg/day) in the treatment of multidrug resistant, but quinolone sensitive, typhoid fever in children. Although a longer course of cefixime may have been more effective, the cure rate still compared favourably with parenteral third generation cephalosporins in multidrug resistant strains and amoxycillin in sensitive strains.

**ACKNOWLEDGEMENTS**

We are grateful to the director and staff of the Dong Nai Paediatric Centre, in particular the doctors and nurses of the Infectious Diseases ward. We are also grateful to the Director and staff of the Centre for Tropical Diseases, Cho Quan Hospital, Ho Chi Minh City for support, in particular Drs Tran Tinh Hien, Delia Bethell and Tom Solomon. We thank Professor A. Bryskier, Roussel-Uclaf for donating the ofloxacin tablets used in the study. This study was funded by the Wellcome Trust of Great Britain.

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