Two or Three Days of Ofloxacin Treatment for Uncomplicated Multidrug-Resistant Typhoid Fever in Children

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An open randomized comparison of 2 days (Ofx2) versus 3 days (Ofx3) of oral ofloxacin treatment (15 mg/kg/day) was conducted with Vietnamese children between 1 and 15 years of age with suspected typhoid fever. Of 108 children enrolled, 100 were blood culture positive for Salmonella typhi, and 86% of the isolates were multidrug resistant. There were no significant adverse effects. The therapeutic responses were similar in both groups, with mean (± standard deviation) fever clearances of 107 ± 60 h in the Ofx3 group and 100 ± 64 h in the Ofx2 group (P > 0.2). There were six “clinical” failures in the Ofx2 group and two clinical failures in the Ofx3 group (P > 0.2), in which fever and symptoms persisted for more than 1 week after the start of treatment, but only one of these was culture positive (Ofx3). There was one suspected relapse, and one carrier was identified. Short courses of ofloxacin are simple, inexpensive, safe, and effective for the treatment of uncomplicated multidrug-resistant typhoid fever.

Typhoid is a major cause of morbidity in tropical countries. Over the past decade, strains of Salmonella typhi resistant to the three frontline antibiotic treatments chloramphenicol, ampicillin, and co-trimoxazole have been reported from South America, the Indian subcontinent, Africa, and, more recently, Southeast Asia (2, 4, 8, 9). In the southern part of Vietnam, there has been a significant increase in the incidence of typhoid associated with the rapid emergence of multidrug-resistant strains of S. typhi over the past 2 years. These strains now constitute the majority of those isolated (6, 7a, 11). Therapeutic options are limited to the broad-spectrum cephalosporins or the fluoroquinolone antibiotics (12, 15). Recent studies demonstrate clearly the superiority of oral fluoroquinolones over parenteral broad-spectrum cephalosporins in the treatment of uncomplicated typhoid (7, 11, 14). The fluoroquinolones have excellent bioavailability in typhoid fever (1), and they are effective in short courses—of particular importance in the containment of epidemics. Unfortunately, this group of drugs is generally contraindicated in children because of cartilage toxicity reported in young beagles. However, there is now considerable clinical experience with fluoroquinolone use in children (3, 5, 6, 10) both in typhoid fever and in cystic fibrosis, and no evidence of toxicity has been reported (1a). There is increasing acceptance among pediatricians that these drugs can be used to treat conditions such as multidrug-resistant typhoid fever where there is no alternative. We recently showed that courses of ofloxacin as short as 3 days (Ofx3) were almost completely effective in an epidemic of multidrug-resistant typhoid in the Mekong Delta region of Vietnam (6). To confirm these surprisingly good results in a broader spectrum of strains, to identify the optimum length of treatment, and to investigate whether courses even shorter than 3 days would still be effective, we subsequently evaluated the efficacy of Ofx2 in children with uncomplicated multidrug-resistant typhoid fever.

MATERIALS AND METHODS

Study site. This study was conducted in the Centre for Tropical Diseases, Cho Quan Hospital, Ho Chi Minh City, Vietnam, between September 1993 and October 1994. This is an infectious disease referral hospital and receives patients from Ho Chi Minh City and surrounding provinces.

Patients. Children between 1 and 15 years of age were eligible for inclusion in the study if they were suspected clinically of having typhoid fever or had cultures positive for S. typhi, and they or their accompanying parents or guardians gave fully informed consent to participation in the study. Children with unexplained fevers but no signs of severity were usually admitted for investigations, and treatment was given on the basis of microbiological investigations. Children were excluded and treated immediately with parenteral antibiotics if they had evidence of severe disease or complications of typhoid fever: i.e., reduced level of consciousness, jaundice, shock, gastrointestinal bleeding, clinical signs of intestinal perforation, were prostrate (unable to sit unaided), or were vomiting and unable to take oral treatment. Children with known allergies to fluoroquinolones or those who had received antibiotics with known efficacy against this organism were also excluded. On enrollment into the study, a detailed history was taken, a clinical examination was performed, and the details were recorded on a standard proforma form. Venous blood was taken for blood culture (3 to 5 ml), a full blood count, and routine biochemistry. A stool sample was taken for culture. A detailed questionnaire on symptoms and adverse effects was then completed. Thereafter, axillary temperature, pulse, blood pressure, and respiratory rate were recorded every 6 h together with other symptoms and signs. The patients were assessed for possible adverse effects (in particular joint symptoms) twice daily during the inpatient stay. Patients were discharged when afebrile and well. This study was approved by the Ethical and Scientific Committee of the Centre for Tropical Diseases.

Treatment regimens. After enrollment in the study, a sealed envelope containing the treatment regimen to be given was opened. Patients were randomized to receive either ofloxacin (Olocet; Roussel, Paris, France) at 15 mg/kg of body weight divided into two daily doses given for 2 days (Ofx2) or for 3 days (Ofx3): i.e., total doses of 30 or 45 mg/kg respectively. In 17 patients (9 in the Ofx3 treatment arm and 8 in the Ofx2 treatment arm), either the first or the second dose of ofloxacin was given by intravenous infusion over 30 min as part of a pharmacokinetic study to be reported elsewhere. Any child who was unable to take the oral medication or whose clinical situation deteriorated was to be taken out of the study and treated with intravenous ofloxacin at 10 mg/kg/day for 7 days.

Sample size. On the basis of our previous community-based study (6), the failure rate with Ofx3 was anticipated to be low. The study was therefore designed to detect a difference in failure rates of 4 and 25% or greater with 95% confidence and 80% power.
TABLE 1. Symptoms and signs in 108 children with uncomplicated typhoid fever

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Total no. (%) of patients</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>108 (100)</td>
</tr>
<tr>
<td>Chills</td>
<td>72 (67)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>91 (84)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54 (50)</td>
</tr>
<tr>
<td>Cough</td>
<td>49 (45)</td>
</tr>
<tr>
<td>Headache</td>
<td>48 (44)</td>
</tr>
<tr>
<td>Constipation</td>
<td>32 (30)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>25 (23)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Confusion</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>98 (91)</td>
</tr>
<tr>
<td>Coated tongue</td>
<td>83 (77)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>43 (40)</td>
</tr>
<tr>
<td>Rose spots</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Fecal blood</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Microbiological procedures. On admission, 3 to 5 ml of venous blood was cultured at a dilution of 1:10 in brain heart infusion broth (Unipath, Basingstoke, United Kingdom) containing 0.05% sodium polyanethesulphonate (Sigma, Moos, United Kingdom). Additional cultures were taken 48 h after the last dose of ofloxacin (either day 4 for Ofx2 or day 5 for Ofx3) and on day 7 if patients were still febrile on that day. Bone marrow aspiration was performed only if all cultures were negative and diagnostic uncertainty was influencing management. Stool samples were collected on admission; on days 7, 8, and 9; and thereafter at 1 and 3 months to assess carrier status. Fecal samples were cultured within 4 h of collection on xylose lysine desoxycholate agar and MacConkey agar, and 1 g was enriched in selenite broth (all from Unipath) before the final culture. Urine cultures were taken on day 0 and day 7. All isolates of S. typhi were identified with specific antisera (Wellcome Diagnostics, Crewe, United Kingdom), standard biochemical tests, motility at 37°C, indole production, reaction on Kliegler iron agar (Unipath), and urease production. Antibiotic susceptibility was tested by the Kirby-Bauer method initially, and then MICs were assessed by standard agar dilution methods.

Assessment of the treatment response. Fever clearance was defined as the time from the start of ofloxacin treatment until the axillary temperature fell below 37.5°C and remained below this level for more than 48 h. A clinical treatment failure was defined as continuation of symptoms and fever for more than 7 days after treatment. A microbiological failure was defined as a positive blood or bone marrow culture for S. typhi taken more than 48 h after the last dose of treatment. A relapse was defined as the return of clinical symptoms and signs of typhoid fever and/or positive blood or bone marrow cultures for S. typhi within 1 month after discharge. The carrier state was defined as the presence of S. typhi in stools 1 month or more after treatment. At follow-up appointments 1 and 3 months later, children were also asked for symptoms of bone or joint adverse effects and a stool sample was taken for culture.

Statistical analysis. Analysis of variance was used for normally distributed data, and the Mann-Whitney U test was used to compare data that were not normally distributed. The chi-square test with Yates' correction or the Fisher's exact test was used to compare proportions. Fever clearance was assessed by survival analysis by the log rank test.

RESULTS

Of the 108 children recruited into this study, 100 had blood cultures positive for S. typhi. The majority of patients were entered into the study when the culture results became available. There were 53 children in the 2-day treatment group and 47 children in the 3-day group. The clinical signs and symptoms and the laboratory features are shown in Tables 1 and 2. There were no significant differences between the two treatment groups in any of the clinical or laboratory parameters on admission to the study.

Therapeutic response. There were no significant differences in any of the measures of therapeutic response between the two treatment groups. Six children in the Ofx2 group were clinical failures compared with two children in the Ofx3 group (relative risk [95% confidence interval], 2.9 [0.5 to 21.8]; P = 0.28). There were no relapses, and there were only one microbiological failure and one fecal carrier (in a single child in the Ofx3 group). Overall, 66 children came back for a 1-month follow-up (71%), and 26 attended for the 3-month follow-up. The mean (± standard deviation) fever clearance times were 107 ± 60 h in the Ofx3 group and 100 ± 64 h in the Ofx2 group (P > 0.2) (Fig. 1). Fever clearance times were significantly shorter in the 8 culture-negative patients than in the 100 culture-positive patients (P < 0.05). Overall, 32 of the 47 patients in the 3-day treatment group and 46 of the 53 patients in the 2-day treatment group were still febrile on the day after antibiotics were stopped. The only patient in the study who had a microbiologically confirmed treatment failure was a 5-year-old girl in the Ofx3 group whose fever continued for 7 days after treatment and who developed gastrointestinal bleed-

FIG. 1. Kaplan-Meier plots of fever clearance in children receiving ofloxacin for 2 days or 3 days for typhoid fever.
ing requiring blood transfusion. The blood cultures 48 h after completion of the ofloxacin treatment course were still positive for *S. typhi*. The admission and recrudescence isolates were both fully sensitive to ofloxacin in vitro. The patient was treated with intravenous ceftriaxone at 70 mg/kg/day for 7 days. She recovered completely but became a febrile carrier with *S. typhi* persisting in stool cultures 50 days after discharge. Thirteen patients had stool cultures which were positive for *S. typhi* on admission, and 3 patients had positive stool cultures 3 to 4 days after treatment, although stool cultures on admission were negative. All of these patients except for the girl with the treatment failure described above were negative at the 1-month follow-up.

**Antimicrobial susceptibility.** Of the 100 isolates tested, 86 were multidrug resistant: i.e., resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, and tetracycline. Fourteen isolates were either fully sensitive or resistant to one or two of the antibiotics listed above. All isolates were fully sensitive to ceftriaxone and ofloxacin. There was no significant difference in any of the clinical or laboratory features on admission for patients with multidrug-resistant isolates compared with patients with isolates that were either fully sensitive or resistant to one or two of the conventional treatment antibiotics. The mean (± standard deviation) fever clearance in the patients with multidrug-resistant isolates was 111 ± 66 h, which was significantly longer than that in patients with isolates which were fully sensitive or of intermediate sensitivity (72 ± 29 h; *P* = 0.035).

**Relapse.** Only one child in the Ofx3 group had fever and clinical signs of typhoid fever after being discharged from the hospital. This child was blood culture negative (a bone marrow culture was not done) but was retreated as a presumed relapse with ofloxacin at 10 mg/kg/day for 7 days and recovered uneventfully.

**Adverse effects.** Ofloxacin treatment was generally well tolerated. One child in the Ofx3 group became delirious on the day after treatment. Her temperature was 37°C. The delirium lasted for 4 h and resolved completely. Whether this was related to typhoid or its treatment cannot be ascertained. Another child in the Ofx3 group had spontaneous urticaria 1 day after antibiotic treatment was stopped, which resolved gradually over the subsequent 4 days. Only one patient vomited after swallowing ofloxacin, and for this child the drug was readministered 10 min later and retained successfully. There were no bone or joint symptoms after treatment with ofloxacin during the hospital stay or at any time during the follow-up period.

**DISCUSSION**

Fluoroquinolone antibiotics are already established as the antimicrobial treatment of choice in adults with multidrug-resistant typhoid fever (13, 14). They have excellent oral bioavailability, and they are effective in short courses (6). Previously, the duration of treatment usually recommended has been for between 7 and 14 days, and cure rates of between 94 and 100% have been reported. Recent studies from Vietnam involving over 500 patients have shown conclusively that shorter courses of fluoroquinolones are equally effective in uncomplicated enteric fever (6, 11). In a large community-based study involving adults and children, a 3-day course of ofloxacin (45 mg/kg) was compared with a 5-day course (50 mg/kg). Both regimens were well tolerated, and the 3-day course was 100% effective (6).

The use of fluoroquinolone antibiotics in children is still contraindicated because of dose-dependent drug-induced damage to the articular cartilage of weight-bearing joints of growing experimental animals (particularly beagles). The fluoroquinolones have been associated with Achilles tendon rupture in humans, but there is no evidence that articular cartilage damage also occurs, and no adverse effects on joints or on growth have been seen with long-term follow-up of children receiving fluoroquinolone treatment of typhoid fever (1, 5, 6, 10). Furthermore, the older quinolone compounds, notably nalidixic acid, which also produce arthropathogenicity in growing experimental animals, are still recommended in children for the treatment of shigellosis (16). This study with children had limited sensitivity to detect long-term adverse effects, but no short-term effects were noted.

There are no orally active alternative antibiotics to the fluoroquinolones for the treatment of multidrug-resistant typhoid fever. The parenteral broad-spectrum cephalosporins have already been shown to be inferior to the fluoroquinolones, and it is unlikely that the oral drugs of the same class would be any better (7, 11, 14). This study proves that courses of fluoroquinolone treatment as short as 2 days are very effective, both in terms of the acute treatment response and in terms of carrier rates. These excellent results and those of the previous study with 3 days of treatment (6) are a far cry from traditional courses of treatment with chloramphenicol, trimethoprim-sulfamethoxazole, or ampicillin for 2 or more weeks. Whether typhoid fever in countries other than Vietnam would be as sensitive to fluoroquinolone treatment remains to be seen. These multidrug-resistant strains have similar in vitro susceptibility to those reported elsewhere, but the role of background immunity in determining the therapeutic response has not been assessed. It is possible that cross-reacting immunity to other *Salmonella* spp. or related members of the family *Enterobacteriaceae* may complement antibiotic treatment, allowing a shorter course of antibiotics than that for a nonimmune patient to be effective.

Physicians are often reluctant to stop antibiotic treatment before defervescence because they assume this indicates continuation of active infection. In most of the children treated in this study (78 of 100 culture-confirmed cases), fever persisted for longer than the duration of antibiotic therapy. Pyrexia was not associated with continued bacteremia, which suggests that the pathogenesis of fever was not related to continued active bacterial multiplication in vivo. Fever may be caused by pyrogenic mediators of inflammation induced by phagocytosis of killed organisms.

Short-course treatment is affordable in many parts of the rural tropics, provides a minimum of drug pressure to the evolution of fluoroquinolone resistance, would limit any potential toxicity, and provides a reliable treatment for a potentially lethal disease. Short courses of treatment are also ideal for epidemic containment. The efficacy of 2 days of treatment emphasizes that there is a considerable margin of safety for the use of a 3-day course of fluoroquinolone antibiotics for the treatment of uncomplicated multidrug-resistant typhoid in this area. The low carrier rates documented in this and other studies (circa 1% compared with up to 20% after treatment with chloramphenicol) also indicate that these drugs will have improved efficacy in the prevention of transmission. The lack of adverse effects in children, ease of administration, and rapidity of the therapeutic response make a 3-day course of fluoroquinolones an appropriate treatment for patients of all ages with multidrug-resistant typhoid fever in this area in which *S. typhi* is endemic. Short-course treatment should now be evaluated in other geographic areas where multidrug-resistant strains of *S. typhi* are prevalent.
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