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Comparison of Ofloxacin and Ceftriaxone for Short-Course Treatment of Enteric Fever

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An open, randomized comparison of ofloxacin (200 mg, every 12 h) given orally for 5 days and ceftriaxone (3 g, once daily) given intravenously for 3 days in the treatment of uncomplicated enteric fever was conducted in Ho Chi Minh City, Vietnam. *Salmonella paratyphi* type A was isolated from six patients. *Salmonella typhi* was isolated from 41 patients; 63% of these isolates were resistant to multiple antibiotics: ampicillin, chloramphenicol, sulfamethoxazole, trimethoprim, and tetracycline. Of the culture-confirmed cases, treatment with ofloxacin resulted in complete cure of all 22 patients, whereas 18 of 25 patients treated with ceftriaxone were completely cured ($P < 0.01$). In the ceftriaxone group, there were six acute treatment failures and one relapse. Mean ± standard deviation fever clearance times were 81 ± 25 h for ofloxacin and 196 ± 87 h for ceftriaxone ($P < 0.0001$). Short-course treatment with oral ofloxacin (5 days) is significantly better than that with ceftriaxone (3 days) and will be of particular benefit in areas where multiresistant strains of *S. typhi* are encountered.

Since the introduction of chloramphenicol in 1948, this antibiotic has been considered the treatment of choice for typhoid fever. Studies in the 1970s showed that ampicillin is slightly inferior, but amoxicillin and trimethoprim-sulfamethoxazole were considered to be as efficacious as chloramphenicol. These latter antimicrobial agents have been of particular value in recent years because of the rising incidence of chloramphenicol resistance in *Salmonella typhi*.

Recently, there have been an increasing number of reports of multiple antibiotic resistance in *S. typhi*. Outbreaks of multiresistant (chloramphenicol, ampicillin, sulfamethoxazole, trimethoprim) *S. typhi* have occurred in the Indian subcontinent (2, 4, 6), and multiresistant strains are now established in northeastern Africa (18). These strains have continued to spread. Because of increasing resistance and the problems of compliance and toxicity associated with 2-week courses of therapy with the established antibiotics, there is a real need for safe alternative agents that are effective in shorter treatment courses. Potential antimicrobial agents for this role include the broad-spectrum cephalosporins and the fluoroquinolone compounds. Both groups have excellent in vitro activities against *S. typhi*, and both have been used successfully for treatment. Indeed, it has been suggested recently that fluoroquinolones should be the treatment of choice for typhoid fever, particularly when multidrug resistance is likely, such as infections acquired in the Indian subcontinent (16, 21). However, there have been no comparative studies between broad-spectrum cephalosporins and the fluoroquinolones. In the present study, we performed an open, randomized comparison of ceftriaxone given for 3 days and ofloxacin given for 5 days.

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MATERIALS AND METHODS

The present study was conducted at the Centre for Tropical Diseases, Cho Quan Hospital, Ho Chi Minh City, Vietnam. This is the infectious disease referral center for southern Vietnam. The study was approved by the Scientific and Ethical Committee of the Centre for Tropical Diseases and was conducted between December 1992 and June 1993.

Patient selection. Adult patients (ages, ≥15 years) with clinically suspected or culture-confirmed enteric fever were recruited. Informed consent was obtained from all patients. Patients were excluded if they had known hypersensitivity to β-lactam antibiotics or quinolone compounds or if they had received previous treatment with a broad-spectrum cephalosporin or quinolone compound within 1 week of hospital admission. Patients who had received ampicillin, chloramphenicol, or trimethoprim-sulfamethoxazole were included, provided that they had not shown evidence of a clinical response.

Sample size calculation. In order to detect overall treatment failure rates of 10 and 1% for ceftriaxone and ofloxacin, respectively, the number of patients in each group was calculated to be 121 ($2\alpha = 0.05$; $1 - \beta = 0.8$).

Treatment regimens. Patients were randomized to receive either ceftriaxone, 3 g (approximately 60 mg/kg) intravenously once daily for 3 days, or ofloxacin, 200 mg orally every 12 h for 5 days. Treatment codes were contained in individual sealed envelopes which were opened at the time that a patient entered the study. Patients classified as treatment failures were retreated with the alternative regimen.

Assessment of treatment response. The response to treatment was assessed by improvement in symptoms and clinical parameters, fever clearance time (FCT), and evidence of relapse of infection. Axillary temperatures were recorded every 6 h. Defervescence was defined as a temperature of <37.5°C for at least 48 h. Acute treatment failure was defined as continuing symptoms and fever for at least 7 days after starting the treatment regimen. A patient was considered to be

cured if all symptoms improved, fever cleared, and there was no evidence of relapse.

Clinical and laboratory procedures. On admission, a full history was taken and a clinical examination was performed by a member of the study team. Blood was taken for hematocrit, differential leukocyte count, platelet count, and biochemical screen. Three blood samples for culture (5 ml placed into 50 ml brain heart infusion broth) were taken, together with urine and stool specimens for culture. Culture of bone marrow aspirate was not performed routinely.

Subsequently, a single blood culture was repeated on days 4, 6, and 8 (first 25 patients) or days 2, 3, and 8 (next 35 patients). On the eighth day, feces and urine were recultured, and a full blood count and biochemistry tests were repeated. After discharge from the hospital, patients were instructed to return if fever recurred and were asked to attend the hospital for an outpatient visit at least 4 to 6 weeks following the end of treatment.

Isolates of *S. typhi* or *Salmonella paratyphi* type A were identified by standard biochemical tests and agglutination with *Salmonella* antisera (Wellcome Diagnostics, Dartford, United Kingdom). Antimicrobial susceptibilities were tested by a standard agar dilution technique (19). In order to differentiate between relapse and reinfection, possible relapse strains were characterized by plasmid analysis (gel electrophoresis of whole plasmids and restriction endonuclease fragments) and ribotyping (3, 11). The restriction enzymes *Eco*RI, *Hin*dIII, and *Pst*I were used to digest chromosomal and plasmid DNAs. Vi phage typing was not performed.

Statistics. Normally distributed continuous data from the two treatment groups were compared by Student's *t* test or analysis of variance; data not conforming to a normal distribution were analyzed by the Mann-Whitney or Wilcoxon rank sum tests. Proportions were compared by the chi-square test with Yates' correction or Fisher's exact test (Epi Info; Public Domain Software, Centers for Disease Control, Atlanta, Ga.). Fever clearance in the two groups was also compared by using the Kaplan-Meier plot and log rank test.

RESULTS

Sixty patients with clinically suspected enteric fever were entered into the study; clinical specimens from 47 of these patients were culture positive on admission (for *S. typhi* in 41 patients; for *S. paratyphi* type A in 6 patients). These isolates were obtained from blood in 40 patients, blood and bone marrow in 2 patients, bone marrow only in 2 patients, and feces only in 3 patients. Culture of bone marrow was not performed for the three patients for whom the diagnosis was confirmed by fecal culture. Detailed analysis was limited to the 47 patients with culture-confirmed cases of infection. The demographic and clinical features of these patients are given in Table 1. There were no significant differences between the treatment groups in the parameters listed in Table 1. Likewise, there were no significant differences when considering all patients entered into the study, and there were no significant differences in clinical and laboratory parameters between culture-positive and culture-negative patients (data not shown).

All isolates of *S. typhi* and *S. paratyphi* type A were susceptible to both study drugs. No antimicrobial resistance occurred in isolates of *S. paratyphi* type A. In the 41 isolates of *S. typhi* resistance to the following antimicrobial agents occurred: ampicillin (63%), chloramphenicol (76%), sulfamethoxazole (76%), trimethoprim (68%), tetracycline (71%), and multiple resistance to all five antimicrobial agents (63%). The proportion of multiresistant isolates in the two treatment groups was similar.

TABLE 1. Demographic, clinical, and laboratory features of patients with culture-confirmed cases of infection by treatment group

Feature of patients	Ceftriaxone group (n = 25)	Ofloxacin group (n = 22)
No. of males, no. of females	15, 10	14, 8
Age (yr; mean [range])	26.4 (15–63)	22.9 (15–48)
Weight (kg; mean [range])	45.4 (36–54)	44.6 (32–66)
Fever duration before hospitalization (days; mean [range])	13.6 (6–27)	11.4 (3–21)
% Patients receiving previous antibiotics[a]	20	36
Admission temp (°C; mean [range])	39.5 (37.5–41)	39.4 (37.5–41)
Hepatomegaly (%)	40	41
Splenomegaly (%)	8	27
Leukocyte count (10^9/liter; mean [range])	6.9 (4–11)	6.3 (2.4–12)
SGOT[b] (IU/liter; mean [range])	164 (70–300)	178 (50–360)
SGOT >240 IU/liter (% of patients)	8	27
SGPT[c] (IU/liter; mean [range])	247 (56–593)	240 (70–477)
SGPT >220 IU/liter (% of patients)	40	50
Organism isolated (no.)		
S. paratyphi A	5	1
S. typhi		
All	20	21
Multiresistant[d]	12	14

[a] Only one patient in each group had received an antibiotic, prior to hospital admission, to which the organism isolated was susceptible in vitro.
[b] SGOT, serum glutamic oxalacetic transaminase.
[c] SGPT, serum glutamic pyruvic transaminase.
[d] Resistant to ampicillin, chloramphenicol, sulfamethoxazole, trimethoprim, and tetracycline.

Response to treatment. All patients completed their treatment regimen. Twenty-nine patients were allocated to receive ofloxacin, of whom 22 patients had culture-proven enteric fever. All patients in this group were cured, and there were no relapses. The mean ± standard deviation FCT was 83 ± 29 h overall and 81 ± 25 h in the culture-proven cases.

Thirty-one patients were allocated to receive ceftriaxone, of whom 25 had positive cultures on admission. Six of the patients with culture-confirmed cases of infection (five infected with *S. typhi*; one infected with *S. paratyphi* type A) did not respond to treatment and were classified as acute-treatment failures. Five of these patients were subsequently treated successfully with oral ofloxacin (200 mg every 12 h) given for 5 days, and the sixth patient received fleroxacin (400 mg once daily) for 7 days. In addition, two other patients who were initially culture negative failed to respond to ceftriaxone but responded to retreatment with ofloxacin. Of these, one remained culture negative, and *S. typhi* was cultured from the blood of the other patient 5 days after the patient completed the course of ceftriaxone. Although it is likely that this patient had typhoid fever at presentation, data for that patient are not included with those for the other patients with culture-proven cases of infection because the diagnosis was not confirmed on admission and hospital-acquired infection cannot be ruled out. The mean ± standard deviation FCT was significantly longer in the ceftriaxone group: 192 ± 85 h overall and 196 ± 87 h among the culture-proven cases ($P < 0.0001$). Thus, the mean (95% confidence interval) difference in time to fever clearance was

TABLE 2. Response to treatment of patients with culture-confirmed infection by treatment group

Treatment group	Mean ± SD (range) FCT (h)	Mean (range) days of hospitalization after starting treatment	No. of patients			
			Cured	Treatment failure		Reinfected
				Acute admission	Relapse	
Ceftriaxone (n = 25)	196 ± 87 (42–384)	12 (7–23)	18	6	1	1
Ofloxacin (n = 22)	81 ± 25 (42–156)	9 (6–13)	22	0	0	0
P value	<0.0001	<0.01		<0.01		

115 (77 to 153) h between the two antimicrobial regimens. A summary of the response to treatment of patients with culture-confirmed cases of infection is given in Table 2, and Kaplan-Meier plots of fever clearance times are shown in Fig. 1.

Overall, 50% of the patients returned for follow-up visits, with no difference in attendance rates between the two treatment groups. In the ceftriaxone group, culture-proven relapse and reinfection each occurred in one patient (35 and 31 days after completing treatment, respectively). Both patients were originally infected with multiresistant strains of *S. typhi* which had responded to treatment with ceftriaxone. The paired isolates from the patient designated to have a reinfection were of the same ribotype but had different plasmid profiles. These patients were successfully retreated with ofloxacin. The overall cure rate from ofloxacin treatment (22 of 22 patients) was significantly better than that from ceftriaxone treatment (18 of 25 patients) ($P < 0.01$).

All repeat cultures of blood taken between days 2 and 6 were sterile. In the ofloxacin group, blood cultures on day 8 were also sterile. In the ceftriaxone group, two patients who had failed to respond to treatment had positive blood cultures on day 8; one of these was the patient who was initially culture negative.

The adverse effects of the study drugs were mild. Two patients in the ceftriaxone group developed skin rashes, and one patient developed pruritus while taking ofloxacin.

DISCUSSION

Chloramphenicol resistance in *S. typhi* has been well documented in Vietnam. The proportion of resistant strains reached 75% by the late 1970s (8), but it later declined to approximately 50% after trimethoprim-sulfamethoxazole became the treatment of choice. Recently, there has been a sudden increase in the number of multiresistant strains isolated in southern Vietnam. From 1990 to early 1992, multiple resistance was found in only 2 of 102 *S. typhi* isolates (12), but during the latter half of 1992 the proportion rose abruptly. During the present study, 26 of 41 (63%) strains of *S. typhi* were multiresistant. Vietnam can now be added to the growing list of countries where multiresistant *S. typhi* has become established. Fortunately, *S. paratyphi* has remained susceptible to these antimicrobial agents.

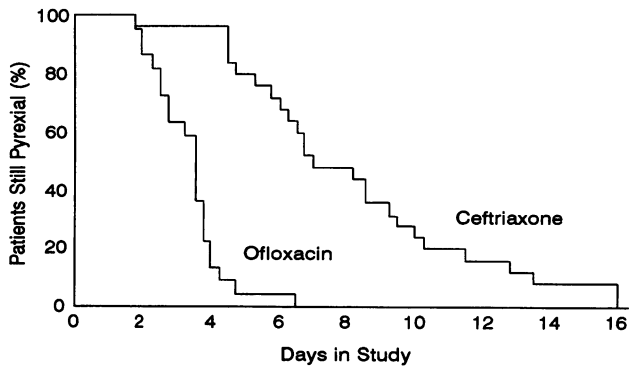

FIG. 1. Kaplan-Meier plots of fever clearance times for patients with culture-confirmed enteric fever treated with ofloxacin (n = 22) or ceftriaxone (n = 25) (log rank test X^2 = 39.4; $P < 0.0001$). In the ceftriaxone group, six of the nine patients defervescing after 9 days were "acute treatment failures" who were subsequently retreated with a fluoroquinolone.

In the search for improved treatments for enteric fever, and multiresistant *S. typhi* in particular, attention has focused on the flouroquinolone compounds and broad-spectrum cephalosporins because of their excellent activities in vitro. These highly active drugs also offer the prospect of reducing the duration of treatment from the traditional 14 days that is necessary with chloramphenicol. Short treatment regimens and reduced periods of hospitalization have obvious financial benefits, particularly in developing countries. They are also more likely to ensure compliance. Fortunately, resistance among *S. typhi* or *S. paratyphi* to fluoroquinolones or broad-spectrum cehalosporins is not a problem, although there has recently been one report of an *S. paratyphi* type A strain resistant to broad-spectrum cephalosporins (7) and one report of an *S. typhi* strain with reduced susceptibility to ciprofloxacin (22).

In 1987, Soe and Overturf (24) reported complete cures in 12 patients with enteric fever treated with cefotaxime for 6 to 14 days. Their review of the literature at the time suggested cure rates of approximately 82% with cefotaxime (50 of 61 patients) and 92% with ceftriaxone (23 of 25 patients), with relapse rates of 6 and 4%, respectively. In a randomized trial, Islam et al. (14) compared ceftriaxone (7 days) and chloramphenicol (14 days) in the treatment of 63 patients with typhoid fever. Cure rates were 91 and 94%, respectively. A subsequent study in which ceftriaxone was used for 5 days gave a cure rate of 79%, whereas the cure rate for chloramphenicol treatment was 90% (13). In those studies, continuation of fever for more than 7 days occurred in >40% of the patients, but most of these showed definite clinical improvement. Even shorter courses of ceftriaxone have been effective. In the Philippines, ceftriaxone treatment (3 or 4 g daily) for 3 days gave results similar to those after treatment with chloramphenicol for 14 days (15). In Nepal, ceftriaxone, 2 g daily for 3 days, cured 12 of 15 patients, with a mean FCT of 4 days (26).

There have also been many open, nonrandomized studies with fluoroquinolones in the treatment of enteric fever. In three studies, ciprofloxacin (500 mg every 12 h) or ofloxacin (300 mg every 12 h) given for 10 to 14 days resulted in complete cure of all evaluable patients (20, 25, 27). Meskin et al. (17) gave ciprofloxacin (750 mg every 12 h) for 7 days and reported that all 34 patients were cured. Chew et al. (10), using the same regimen, cured 24 of 25 patients. The remaining

patient in that study was febrile for 5 days after the end of treatment, but the fever resolved without further treatment. Two of the patients presented 6 weeks later with possible relapses, but typing was not reported for the "relapse" strains, and one of these patients may have been reinfected. Pefloxacin given for 7 days had efficacy similar to that of ciprofloxacin (1).

In a recent large multicenter comparative study, fleroxacin given for 7 days (28 patients) produced a clinical cure rate of 83% and was comparable to chloramphenicol given for 14 days (34 patients), whereas a 14-day course of fleroxacin resulted in the cure of all 35 patients (5). Four patients in the fleroxacin (given for 7 days) group presented with clinical relapses, but only one relapse was confirmed by positive blood culture. In a smaller study in India, norfloxacin (given for 7 days) and chloramphenicol (given for 14 days) both resulted in complete clinical and bacteriological cures of the 20 patients in each group (23). In those studies with fluoroquinolones, the mean FCTs were approximately 4 days.

In the present study, an even shorter course of oral ofloxacin (5 days) proved to be highly effective in all treated patients and significantly better than intravenous ceftriaxone given for 3 days. In contrast, fever continued for more than 7 days in 12 of 25 (48%) patients in the ceftriaxone group who were culture positive on admission. Six had continuing symptoms and were judged to be treatment failures. The other six (24%) improved clinically and were observed until the fever cleared (198 to 246 h). However, the persistence of fever for 1 week after starting antibiotic treatment should be considered unsatisfactory, even if eventual cure is effected. It has been postulated that continuing fever might be due to the residual intracellular *S. typhi* that are gradually being eliminated by the immune response (13). No patient in the ofloxacin group had fever for 7 days. This may reflect a greater intracellular activity of ofloxacin against *S. typhi*, although ceftriaxone and pefloxacin were shown to have comparable bactericidal activities in a human monocyte-derived macrophage model (9). Relapse rates may have been underestimated because of the relatively poor attendance for the follow-up examination. Only one patient, in the ceftriaxone group, suffered a relapse. The results of other studies with ceftriaxone suggest that, even when it is given for 5 days or longer, it would not have been as effective as ofloxacin given for 5 days.

In the present study ofloxacin was more rapidly and more completely effective than ceftriaxone in the treatment of enteric fever. This emphasizes the well-known discrepancies between in vitro susceptibility and clinical response commonly encountered in patients with enteric fever. The fluoroquinolones and the broad-spectrum cephalosporins have similar in vitro activities, but the former are considerably more effective in vivo. The fluoroquinolones have excellent tissue penetration and are concentrated in bile, orally active, relatively cheap, and very well tolerated.

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