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Treatment of Enteric Fever with Pefloxacin for 7 Days versus 5 Days: a Randomized Clinical Trial

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In this prospective study of enteric fever, 22 patients received 400 mg of pefloxacin twice daily for 5 days (group A) and 24 received 400 mg of pefloxacin twice daily for 7 days (group B). Causative microorganisms were *Salmonella typhi* (8 in group A, 11 in group B) and *Salmonella paratyphi* B (14 in group A, 13 in group B). The clinical cure and bacterial eradication rates were 96% (21 of 22) in group A and 100% in group B. In conclusion, 5-day oral administration of pefloxacin was as effective as 7-day treatment of enteric fever caused by *Salmonella* spp.

Enteric fever is a serious systemic infection and still common in most developing countries. It is caused by *Salmonella* spp., usually *Salmonella typhi*. At present, chloramphenicol, ampicillin, or trimethoprim-sulfamethoxazole (TMP-SMX) are the first-choice antibiotics for the treatment of enteric fever (7). However, increasing resistance to these drugs has necessitated the search for alternative drugs (4). In addition, the traditional antimicrobial agents must be given for 14 days to reduce the high relapse rates. This poses an important problem in patients' compliance to treatment as well as an economic burden, particularly in developing countries. Therefore, efforts should be directed to developing new antimicrobial agents and shortening the duration of treatment.

In vitro susceptibility tests have shown that fluorinated quinolones have excellent activity against *S. typhi* and *Salmonella paratyphi*, including the strains resistant to chloramphenicol, ampicillin, and TMP-SMX (6, 9). These agents also achieve good intracellular concentrations, particularly in phagocytes, and adequate levels in tissues, bile, and feces. The quinolone antibiotics, including ciprofloxacin, ofloxacin, pefloxacin, and fleroxacin, have been used in several clinical trials with a great success rate (3). Although a limited number of successful treatments as short as 2 or 3 days have been reported, the optimal duration of treatment remains to be determined (17, 19).

Here we report the comparative results of a 7-day versus a 5-day treatment of enteric fever with oral pefloxacin in an open, prospective, randomized study.

Forty-six patients (22 males, 24 females) hospitalized between June 1992 and October 1994 for enteric fever were randomized to receive pefloxacin for 5 days (group A) or 7 days (group B). All patients with febrile disease and at least one positive blood and/or bone marrow culture for *Salmonella* spp. were included. Patients under 16 years of age, pregnant and lactating women, those with jaundice and hepatic failure, and the patients who had received any antibiotic within the last 2 weeks were excluded. The daily dose of pefloxacin was 400 mg twice daily (BID) perorally in both groups, and the therapy was started as soon as the culture results were obtained.

Fever, gastrointestinal complaints (abdominal pain, nausea, vomiting, diarrhea, and constipation), anorexia, malaise, prostration, and headache were assessed as clinical symptoms. All patients underwent a complete physical examination. Urinalysis, complete blood count with differential, prothrombin times, and biochemistry profiles were determined, and radiographic tests were performed as needed. Hematological and biochemical parameters were repeated on the second or third day of therapy and 2 or 3 days after the completion of therapy. Three sets of blood, bone marrow, urine, and stool cultures were obtained on the first day of admission to the hospital. Blood, urine, and stool cultures were repeated 2 days after the treatment and 1 month after the completion of therapy. The isolated *Salmonella* strains were identified by standard biochemical tests and agglutination with salmonella antisera (Wellcome Diagnostics). Antibiotic susceptibilities were tested by a standard broth microdilution technique (14).

The physical examination was repeated, and fever, digestive, and neurologic symptoms were recorded daily. Fever was considered to be cleared if the patient's temperature was <37.5°C for at least 48 h. Clinical cure was defined as complete disappearance of clinical symptoms under treatment and lack of relapse within 30 days after the treatment, and failure was defined as continuing or worsening of symptoms 7 days after treatment with pefloxacin. Relapse was present if the patient had similar signs and symptoms after apparently being cured within a month. Tolerance was considered excellent if there were no side effects, intermediate if the side effects did not require interruption of the treatment, and poor if side effects required the cessation of the treatment.

Data were analyzed by Student's *t* test and chi-square test when applicable (Statistical Package for Social Sciences, SPSS version 5.01, 1992).

Twenty-two patients (9 males, 13 females) received 400 mg BID of pefloxacin for 5 days in group A and 24 patients (13 males, 11 females) received 400 mg BID of pefloxacin for 7 days in group B. The mean age was 24 years (range: 18 to 40 years) and 26 years (range: 18 to 68 years), respectively, for groups A and B. Demographic, clinical, and laboratory features of patients in both groups were similar (Table 1).

Bone marrow and/or blood cultures were positive for *Sal-*

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TABLE 1. Demographic, clinical, and laboratory features of patients

Parameter	Group A (n = 22)	Group B (n = 24)
No. of males/no. of females	9/13	13/11
Age (yr) (mean + SD)	24 + 7	26 + 11
Weight (kg) (mean + SD)	59.5 + 15.2	61.7 + 13.0
Admission temperature (°C) (mean + SD)	39.5 + 0.6	39.5 + 0.6
Fever duration before hospitalization (days) (mean + SD)	12.4 + 8.7	12.4 + 9.9
No. with hepatomegaly	4	3
No. with splenomegaly	12	13
No. with leukocytes <4,000/mm^3	7	14
ALT and/or AST elevation on admission[a]	12	13
Site of organism isolated		
Blood	14	15
Bone marrow	12	12
Both	4	3
Stool and one of the above	1	2
Causative organism		
S. typhi	8	11
S. paratyphi A		
S. paratyphi B	14	13
Multiresistant organisms[b] (no. of strains) resistant to:		
Pefloxacin	0	0
Chloramphenicol	5	5
Ampicillin	11	11
TMP-SMX	6	8
MIC_{90} (μg/ml)[c]		
Pefloxacin	0.05	0.05
Chloramphenicol	64	32
Ampicillin	128	256
TMP-SMX	64	64

[a] ALT, alanine amniotransferase; AST, aspartate aminotransferase.
[b] Resistant to chloramphenicol, ampicillin, and TMP-SMX.
[c] MIC_{90}, MIC at which 90% of the organisms are inhibited.

monella spp. The causative microorganisms were *S. typhi* (8 in group A, 11 in group B) and *S. paratyphi* B (14 in group A, 13 in group B). The MIC at which 90% of the isolated organisms were inhibited by pefloxacin was 0.05 μg/ml (MIC range; 0.06 to 1 μg/ml) in both groups. Six isolates (3 in group A and 3 in group B) were multiply resistant (resistant to chloramphenicol, ampicillin, and TMP-SMX).

All patients were clinically cured, and clinical response was obtained in 1 to 5 days after initiation of therapy in both groups. Bacteriological eradication rates were 96% (21 of 22) in group A and 100% in group B (Fisher's exact test; $P > 0.05$; 95% confidence interval, 0.1321 to 88.467). Control stool cultures remained negative 1 week and 1 month after the completion of therapy. Only one patient in group A relapsed symptomatically 26 days after the treatment. *S. typhi* with the same antibiotic resistance pattern was isolated from stool samples during the second episode for this patient.

Nausea and vomiting (3 patients in group A and 3 patients in group B) and increase in transaminases not exceeding twice the pretreatment levels (one patient in group B) were the only side effects noted. The outcome in both treatment groups are shown in Table 2.

The treatment of enteric fever is still challenging to most physicians because of increasing resistance rates to commonly used antibiotics including chloramphenicol, ampicillin, and TMP-SMX. Poor compliance, high relapse rates, and economical burden of long-term treatment are additional problems, especially in developing countries.

TABLE 2. Treatment results

Parameter	Group A (n = 22)	Group B (n = 24)
Mean day of disappearance of fever (mean + SD)	3.1 + 1	3.4 + 1
No. (%) of patients with:		
Clinical outcome		
Cure	21 (96)[a]	24 (100)
Failure and/or relapse	1 (4)	
Microbiologic eradication rate	21 (96)[a]	24 (100)
Tolerance		
Excellent	19 (86.4)	20 (83.3)
Intermediate	3 (13.6)	4 (17.7)
Poor		

[a] $P > 0.05$, Fisher's exact test; 95% confidence interval, 0.1321 to 88.467.

Fluoroquinolones have been used for the treatment of enteric fever since the 1980s, and 100% cure rates were obtained with 14- to 15-day regimens of ciprofloxacin (9, 11), ofloxacin (2, 16), and pefloxacin (1, 8), which have not been achieved with standard drugs. In addition, since quinolones are intracellularly active drugs, they may have lower relapse rates in the treatment of typhoid fever. In the majority of previous studies with quinolones, no relapses were reported.

The major problem with the quinolones is their cost. Clinical trials with shorter durations of therapy were carried out to improve the cost-benefit values. Several trials with short-course (7 to 10 days) ciprofloxacin (15), ofloxacin (12), and pefloxacin (13) in typhoid fever revealed high cure rates (82 to 100%) (10). Our previous experience in treating typhoid fever with a 10-day course of ofloxacin showed excellent results (100% cure in 32 patients) (18). The present study showed that patients with enteric fever had rapid defervescence and high cure rates with even shorter duration of treatment (5 or 7 days) with oral pefloxacin. In a multicenter noncomparative study, Bryskier et al. reported a 99% success rate in 106 patients with 5 days of ofloxacin treatment (5).

Although short-term treatment regimens have the advantage of reduced cost, improved patient compliance, and still high success rates, data on relapses are limited. In findings similar to those of our study, Waiz et al. reported no relapse in 30 patients with 7 days of pefloxacin treatment (20). These findings, however, should be interpreted with caution since the sample sizes of these studies are too small to draw a firm conclusion. There was only one relapse in 106 patients in the Bryskier group, but this study was an open, noncomparative trial (5). In a recent clinical study comparing 2 days of ofloxacin with 3 days of ofloxacin in 108 children with enteric fever, there was only one suspected relapse (19).

In conclusion, 5-day treatment of enteric fever with pefloxacin appears to be as effective as 7-day therapy. The efficacy of shorter courses (2 to 5 days) requires further evaluation in randomized clinical studies.

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