

# Study of the Efficacy and Tolerance of Pefloxacin (Peflacin) in Typhoid Fever

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## SUMMARY

*The efficacy and safety of Pefloxacin (Peflacin) 400 mg twice daily, for seven days, was evaluated in an open non-comparative study of 82 patients with enteric fever. Thirteen patients had serious illness, and were hospitalized. Blood cultures were positive for S. Typhi in 33 and for para typhi in 3 patients, all had positive widal test. Hospitalized patients were started on parenteral pefloxacin while others were given oral treatment. Clinical improvement was seen on third day in all the patients, and fever subsided in 4.11 (SD±1.1) days of treatment. Most of the patients (n=74), were cured with 7 day treatment of pefloxacin which was prolonged for 2 weeks in 8 patients with serious illness. At the end of one month treatment, follow-up assessment showed a clinical cure rate of 99%, with relapse in three patients. Pefloxacin was well tolerated with few major side effects, vomiting was seen in 20 patients (25%), thrombophlebitis in 2, in whom infusion was given in a peripheral small vein, and one patient had neurological symptoms of confusion, disorientation, delirium, warranting withdrawal of treatment. This study showed the efficacy and tolerance of a short 7 day course of Pefloxacin in typhoid fever.*

## INTRODUCTION

Typhoid fever continues to be a major health problem in Pakistan<sup>1</sup>. It may involve any organ in the body, can result in serious complications and death, if not diagnosed and treated at its earliest<sup>2,3</sup>. Treatment with chloramphenicol is known to shorten the course of the illness<sup>4</sup> but the emergence of chloramphenicol resistant strains and recent occurrence of multi-drug resistance has posed a major problem in the management of typhoid fever<sup>5,6</sup>. Second line drugs i.e; quinolones or third generation cephalosporins are the treatment of choice for the resistant strains of salmonella typhi<sup>7</sup>. Pefloxacin is a fluorinated quinolone that is structurally related to nalidixic acid, has high bioavailability after oral administration, a long half life and good penetration of tissues and body fluids<sup>8</sup>. It can be administered orally as well as intravenously and like other quinolones, possesses a high degree of in-vitro activity against salmonella

typhi<sup>9</sup>. It has been found to be effective in the treatment of enteric fever in several comparative trials<sup>10,11</sup>. An open non-comparative trial was conducted to assess the efficacy and safety of pefloxacin in our patients.

## PATIENTS AND METHODS

A total of 82 patients were enrolled in the study, thirty-four from Lahore, and 48 from Rawalpindi centre. All were febrile patients, clinically suspected to have typhoid fever, with positive blood culture and/or positive Widal test were included in this study. Others who had previously received antibiotics were also included. Patients less than 16 year age, pregnant and lactating females were excluded from the study. On high clinical suspicion, treatment was started after sending two blood cultures without waiting for the results. Either intravenous pefloxacin 400 mg diluted in 5% dextrose water was instituted over

one hour or oral therapy in form of tablet, 400 mg twice daily was started, according to the condition of the patient. Baseline CBC, widal test, liver function tests were obtained at the outset. Hospitalized patients were re-evaluated daily and those who were treated as outpatient, on the fourth day of treatment. In case of improvement, treatment with pefloxacin was continued for another three days in patients without complications and for further ten days in seriously ill patients. Blood cultures were repeated on day 7, to determine eradication of infection. Regular follow-up was done as outpatients for atleast one month after discontinuation of treatment and in case of clinical relapse within thirty days, a complete clinical and bacteriological evaluation was performed. Sensitivity of the pathogen was tested by the pefloxacin disk.

### RESULTS

Eighty-two patients were enrolled in the study, 13 had serious illness and were admitted in the hospital, 10 were started on intravenous pefloxacin, later switched over to oral therapy (Fig. 1). Forty eight patients were males and 34 females, mean age was  $25.5 \pm 9.1$  yrs, ranged between 18-75 yrs, one patient was 75 yrs old (Table 1).

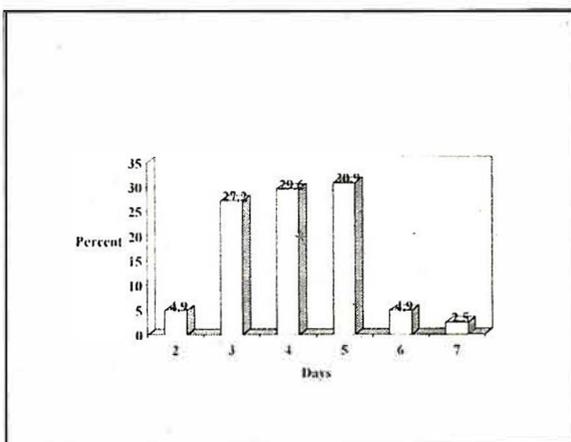


Fig. 1: Defervescence after initiation of pefloxacin therapy.

Table 1: Demographic features (n=82).

Total number of patients	82
Hospitalized	13
Male	48
Female	34
Age range yrs	18-75
Mean age in yrs	$25.5 \pm 9.1$

Table 2: Clinical features typhoid patients (n=82).

Clinical features	Number	Percent
Fever	82	100
Anorexia	80	97
Headache	75	91
Diarrhoea	41	50
Abdominal pain	39	48
Splenomegaly	28	34
Constipation	26	33
Coated tongue	26	33
Toxic facies	10	12
Relative bradycardia	10	12
Hepatomegaly	8	10
Jaundice	3	4
Hemolysis	1	1

Blood cultures were positive in 36 (45%) patients, 33 for salmonella typhi and 3 for S. paratyphi (Table 3). Bone-marrow culture was positive in one patient whose blood cultures were negative initially but became positive after ten days of sub-cultures. All patients had fever for more than one week duration prior to start of pefloxacin, 18 had fever for more than 3 weeks prior to presentation and had been exposed to other antibiotics. Anorexia and headache were present in more than 90% of the patients while diarrhoea, constipation, abdominal pain, and vomiting were not constant features (30-55%). Two patients had epistaxis and malena was seen in six. Clinical features were variable, temperature varied between (100-105°F), none presented with circulatory failure, although 36 were pale, while Relative bradycardia was seen in 10 patient, and splenomegaly was present in 28 patients (Table 2). Thirty patients had liver involvement, 1 went into encephalopathy, jaundice was seen in 3 patients and 8 had hepatomegaly which was tender in 4 patients. Alanine aminotransferase (ALT) levels were

increased significantly in 30 patients, alkaline phosphatase in 12 and hyperbilirubinemia was seen in 3 patients. One presented with typhoid hepatitis and renal failure, needed dialysis, and recovered completely with 14 day treatment of pefloxacin.

patients except minor problems, i.e. 20 had vomiting, 2 had thrombophlebitis in whom treatment was given through a peripheral vein. One patient became delirious and confused in whom pefloxacin was stopped, as it was implicated for this complication, was transferred to cefotaxime with satisfactory resolution.

Table 3: Bacteriological efficacy in typhoid fever (n=82).

Total number of patients	82
Isolated pathogens	36
<i>S. typhi</i>	33
<i>S. paratyphi</i>	03
Susceptibility to pefloxacin	36
Widal test positive	82
Cure	81
Failure	01
Relapse	03

## DISCUSSION

Pefloxacin has been found to be quite effective in our patients. Similar results have been seen in previous studies where different dosage schedules have shown complete eradication and few relapses. The drug was tolerated well and compliance was good<sup>12,16,18</sup>.

A trial conducted in Egypt with pefloxacin 400 mg B.I.D. for 7 days in 50 patients showed clinical and bacteriological cure without relapse in any of the patients. Tolerance was good, nausea and vomiting occurred in only 4 (8%) patients<sup>12</sup>. Ait Khalid et al reported similar results in 1990 with 7 day treatment of pefloxacin, 400 mg B.I.D. in 37 of their typhoid patients. A cure rate of 94.6% with relapse in 5% was seen. Temperature became normal in a mean of  $5.14 \pm 1.3$  days and clinical adverse reactions were reported in 5.9%<sup>13</sup>. Similar results were reported in a study from Pakistan, in which 25 patients with typhoid fever were given short (7 day) course of pefloxacin. Compliance was good and drug was well tolerated, and only 2 of 25 patients (8%) had nausea and vomiting. Clinical cure was achieved in all patients, none had relapse within 30 days after treatment<sup>14</sup>.

In a comparative trial of pefloxacin (400 mg B.I.D/day) with cotrimoxazole (160/800 mg daily) for 14 days, pefloxacin was found to be superior regarding its tolerance and clinical improvement, with defervescence over a shorter period<sup>15</sup>. Complete recovery was reported in another trial with a 15 day treatment with pefloxacin at daily divided dose of 1200 mg given intravenously for the first five days and orally for following ten days<sup>16</sup>.

Similar efficacy and tolerance was seen in a pilot study from Indonesia with pefloxacin (400 mg) daily dosage<sup>17</sup>. Another double blind randomized comparative trial done in the same population showed better results with once daily dose of pefloxacin 400 mg for 7 day treatment vs 14 day treatment with 50 mg/kg/day of chloramphenicol in

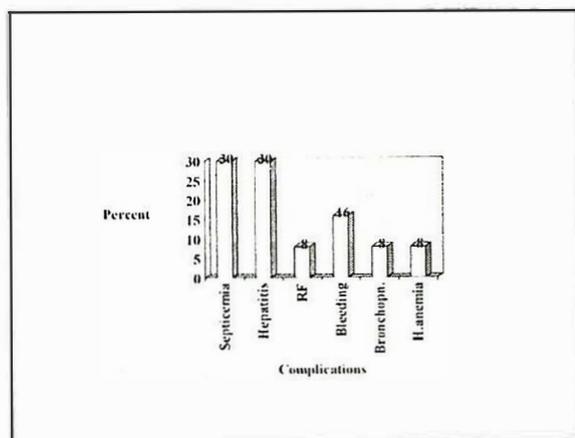


Fig. 2: Nature of complications in 13 hospitalized patients.

All patients showed improvement on third day with complete defervescence on  $4.11 (SD \pm 1.1)$  days (Fig. 2). Treatment was given for 7 days in most of the patients (n=74) but it was continued for 14 days in 8 patients who had developed complications. Eighty one patients were cured completely and three had relapse within one month. One patient who did not respond, was given another antibiotic (Table 3). Pefloxacin was tolerated well by most of the

four divided dosages. Defervescence was achieved in an average of  $3.8 \pm 1.6$  vs  $4.5 \pm 1.5$  days respectively. No complication occurred in pefloxacin group whereas 2 became carriers and 1 died in the chloramphenicol group<sup>18</sup>.

Pefloxacin has been found to be quite effective in our study, most of the patients (n=74) improved with 7 day treatment as was seen in previously conducted studies<sup>11,12,13</sup> Fever settled over 4.1 (SD±1.1) days, clinical and bacteriological cure was achieved in 80 of 81 (99%). One patient who failed to improve had to be treated with an alternative medicine. Seriously ill patients with hepatic encephalopathy due to liver involvement, severe septicemia, and one with acute renal failure improved remarkably well. Abnormal biochemical profile became normal over two weeks and on follow-up of 1 month remained normal.

Most of the patients tolerated the drug without any serious side effect - others have also reported only mild side effects with pefloxacin<sup>12,13,14</sup>.

## CONCLUSION

Rapid clinical response, complete cure and good tolerance was seen in our patients with typhoid fever. This study showed good efficacy and safety of a 7 day course of pefloxacin. We recommend this treatment in patients with typhoid fever.

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