Original Report

Therapeutic Efficacy of Perfloxacin in Treatment of Ampicillin-Resistant Typhoid Fever in 7 Days versus 10 Days

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ABSTRACT

Objective: Typhoid fever is endemic in Albania and is becoming increasingly resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. Perfloxacin has been shown to have significant activity in vitro against *Salmonella* species. The authors studied its therapeutic efficacy in patients with typhoid fever.

Methods: Thirty patients with ampicillin-resistant typhoid fever, who were admitted to the Infectious Disease Clinic at the University Hospital Center of Tirana, were enrolled in this prospective, nonblinded clinical trial. Patients were treated with oral perfloxacin at 400 mg twice daily. They were randomized to receive treatment for either 7 days (group I) or 10 days (group II).

Conclusions: Excellent therapeutic responses were observed in all patients in both groups. In every case, there was significant clinical improvement with defervescence and sterile blood cultures by day 4 and three consecutive negative urine and stool cultures at the end of treatment. Perfloxacin was highly effective in treatment of typhoid fever. Treatment for 7 days appeared to be as effective as treatment for 10 days. In both groups, bile cultures at the end of treatment and at 2 months follow-up were sterile, suggesting that both regimens were effective in preventing a chronic carrier state.

Key Words: *Albania, antimicrobial susceptibility, perfloxacin,* Salmonella typhi, *typhoid fever*

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Typhoid fever is endemic in Albania, at times reaching epidemic proportions. *Salmonella typhi* bacilli are becoming increasingly resistant to ampicillin, chloramphenicol, and sulfamethoxazole. The resistant strains cause more serious clinical complications and may lead to a chronic carrier state. Because of the high incidence of resistant strains, there is an urgent need for alternative therapies for typhoid fever. The newer quinolones have been shown to have significant in vitro activity against *Salmonella* species as well as other enteric pathogens. Perfloxacin has bacteriologic and pharmacokinetic properties that make it particularly promising for the treatment of these infections.[1-3] In cases of typhoid fever, 7 days of treatment with perfloxacin has been reported to be as effective as 10 days.[4]

To evaluate the effectiveness of oral perfloxacin in the treatment of typhoid fever due to multiresistant strains of *S. typhi,* a prospective study was done at the Department of Infectious Diseases at the University Hospital Center of Tirana. The purposes of the study were to evaluate the effectiveness of oral perfloxacin in the treatment of infections due to ampicillin-resistant strains of *S. typhi,* to study its efficacy in prevention of a chronic carrier state, and to compare outcomes after treatment for 7 or 10 days.

METHODS

Patients were eligible for this study if they had a positive blood culture due to an ampicillin-resistant strain of *S. typhi,* had signs and symptoms of typhoid fever, and had not received quinolones in the 2 weeks prior to hospitalization. Treatment was considered successful if all of the following cultures were negative for *S. typhi:* a blood culture during treatment, urine and stool cultures on 3 consecutive days following treatment, and bile cultures at the end of treatment and at 2-month follow-up.

Thirty patients, examined between May 1992 and February 1994, met the eligibility criteria listed above and were enrolled. There were 18 males (60%) and 12 females (40%); their ages ranged from 16 to 42 years (mean, 24 y). The patients were divided into two groups of 15. Group I received oral perfloxacin at 400 mg twice daily for 7 days, and group II received the same regimen for 10 days. Patients were evaluated by interview, physical examination, and laboratory testing of blood, urine, stool, and bile samples.

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Table 1. Clinical Findings, at Admission, of the 30 Patients with Typhoid Fever

Symptoms	*Group I n = 15 (100%)*	*Group II n = 15 (100%)*
Fever	15 (100)	15 (100)
Headache	12 (80)	14 (93)
Splenomegaly	11 (73)	12 (80)
Hepatomegaly	11 (73)	10 (67)
Anorexia	9 (60)	7 (47)
Chills	7 (47)	9 (60)
Diarrhea	7 (47)	9 (60)
Constipation	7 (47)	6 (40)
Abdominal pains	6 (40)	7 (47)
Rose spots	6 (40)	7 (47)
Nausea or vomiting	5 (33)	6 (40)
Cough	3 (20)	3 (20)
Rales	3 (20)	3 (20)
Cervical adenopathy	2 (13)	3 (20)
Neurologic manifestations	2 (13)	3 (20)
Dysuria	2 (13)	2 (13)

RESULTS

The clinical findings in the 30 patients are summarized in Table 1. On admission, all of the 30 patients had blood cultures that were positive for *S. typhi;* only 11 (36%) had positive urine cultures. Table 2 summarizes the antimicrobial susceptibilities of the blood culture isolates. All of the blood culture strains were sensitive to perfloxacin and resistant to ampicillin, 25 strains (83%) were resistant to ampicillin and chloramphenicol, 21 strains (70%) were resistant to ampicillin and trimethoprim-sulfamethoxazole, and 12 strains (40%) were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole.

Defervescence began on the second day in ten patients (67%) and on the third day in the remaining five cases in each group. All patients, in both groups, were afebrile by day 5. Blood cultures were sterile by day 3 in ten patients (67%) in each group, and in all patients by day 4. All stool cultures were negative by the third day of treatment.

Stool and urine cultures for *S. typhi* were done on days 7, 8, and 9 for group I and on days 10, 11, and 12 for group II; all of these cultures were negative. Bile cultures, performed at completion of treatment and at the 2-month follow-up, were negative for all patients in both groups. No relapses occurred during hospitalization or during the subsequent 2 months.

Treatment with perfloxacin resulted in nausea or abdominal discomfort in four patients (13%); however, it was not severe enough to warrant discontinuation of the drug. Other adverse reactions, such as rash, headache, fatigue, insomnia, or diarrhea were not observed. No alterations of hematologic or biochemical test results were seen that could be attributed to perfloxacin.

DISCUSSION

Because of the emergence of strains of *S. typhi* that are resistant to ampicillin, patients with typhoid fever are at risk of serious clinical complications if they do not receive appropriate therapies. The complications may include enteric hemorrhage, perforation, pneumonia, myocarditis, meningitis, cholecystitis, hepatic or splenic abscesses, phlebitis, spondylitis, spondylodiskitis, pyomyositis, and acute rhabdomyolysis.[5,6]

In this study, patients with typhoid fever due to ampicillin-resistant strains of *S. typhi* were treated with a 7- or 10-day course of oral perfloxacin at 400 mg twice daily. There was an excellent clinical and microbiologic response to both regimens. With treatment durations of either 7 or 10 days, there was significant clinical improvement with defervescence and sterile blood cultures by day 4, three consecutive negative urine and stool cultures at the end of treatment, and negative bile cultures at the end of treatment and 2 months later. The 7- and 10-day regimens were equally safe and effective both in treatment of the acute illness and in prevention of a chronic carrier state.

Fluoroquinolones are effective against enteric pathogens such as *Salmonella* species, *Shigella* species, and *Yersinia* species. They have several advantages over nalidixic acid, the parent compound of this class of antimicrobial agents; these include enhanced bioavailability with oral administration, reduced protein binding, and longer serum half-lives. Because of these characteristics, lower and more infrequent doses can be given.

The fluoroquinolones also have the advantage of being concentrated within phagocytes and other intracellular sites favored by pathogens such as *Salmonella* species; the intracellular concentration of perfloxacin may be 1.8 to 14 times the serum level.[4,7-10] This characteristic

Table 2. Results of Antimicrobial Susceptibility Testing of Isolates of *Salmonella typhi* from Blood Cultures of 30 Patients with Typhoid Fever

Antibiotic	*Number Resistant (%)*
Ampicillin	30 (100)
Ampicillin + chloramphenicol	25 (83)
Ampicillin + trimethoprim-sulfamethoxazole	21 (70)
Ampicillin + chloramphenicol + trimethoprim-sulfamethoxazole	12 (40)
Perfloxacin	0 (0)

may be critical for eradication of an enteric pathogen from intracellular sites within the intestinal or biliary tracts.[11]

CONCLUSION

Perfloxacin, because it is well tolerated, has significant pharmacokinetic advantages, and is highly effective in this indication, should be considered for use in cases of ampicillin-resistant typhoid fever. Treatment with 400 mg twice daily for 7 days appears to be safe and effective for typhoid fever. This regimen produced prompt relief from the acute symptoms of the infection and seemed to reduce the risk of its recurrence.

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REFERENCES

1. Keusch GT. Antimicrobial therapy for enteric infections and typhoid fever: state of the art. Rev Infect Dis 1988; 10(Suppl 1):199–205.
2. Bryan JP, Rocha H, Scheld W. Problems in salmonellosis: rationale for clinical trials with new β-lactam agents and quinolones. Rev Infect Dis 1986; 8:189–207.
3. DuPont HL, Ericsson CD, Robinson A, et al. Current problems in antimicrobial therapy for bacterial enteric infection. Am J Med 1987; 82(Suppl 4A):324–328.
4. Ait-Khaled A, Zidane L. A seven-day perfloxacin course for the treatment of typhoid fever in Algeria [Abstract 193]. Second International Symposium on New Quinolones, Geneva, Switzerland, August 1988.
5. Hook WE. *Salmonella* species (including typhoid fever). In: Mandell, Douglas, Bennett, eds. Principles and practice of infectious diseases. 2nd Ed. New York: John Wiley and Sons, 1985:1256–1268.
6. Kalo T, Feyzo E, Begari N. Rhabdomyolysis, a real complication of typhoid fever. Acta Cardiomyologia 1993; 5:85–91.
7. Hajji M, El Mdaghri N, Benbachir M. Prospective randomized comparative trial of perfloxacin versus cotrimoxazole in the treatment of typhoid fever in adults. Eur J Clin Microbiol Infect Dis 1988; 7:361–363.
8. Walker R, Wright AJ. The quinolones. Mayo Clin Proc 1987; 62:1007–1012.
9. Wolfson JS, Hopper DC. Fluoroquinolone antimicrobial agents. Clin Microbiol Rev 1989; 4:378–424.
10. Raymond J, Moulin F, Badoual J, Gengrel D. Eradication of convalescent phase *Salmonella* carriage with two oral doses of perfloxacin. Eur J Clin Microbiol Infect Dis 1994; 13: 304–307.
11. Asperilla MO, Smego RA, Kieth SL. Quinolone antibiotics in the treatment of *Salmonella* infections. Rev Infect Dis 1990; 12:873–889.