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Ciprofloxacin versus Ceftriaxone in the Treatment of Multiresistant Typhoid Fever

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A randomized trial comparing ceftriaxone (3 g given parenterally per day for 7 days) to ciprofloxacin (500 mg given orally twice a day for 7 days) in the treatment of blood culture positive typhoid fever was conducted. Twenty patients were openly randomized to receive ciprofloxacin and 22 to receive ceftriaxone. The outcome was classified as clinical failure in 6 patients (27 %) in the ceftriaxone group, but in none in the ciprofloxacin group ($p = 0.01$). The mean duration of fever was four days in the ciprofloxacin group and about five days in the ceftriaxone group ($p = 0.04$). In the six patients in the ceftriaxone group who experienced failure, therapy was switched to ciprofloxacin and the patients became afebrile and asymptomatic within 48 hours. Patients with resistant strains of *Salmonella typhi* and patients with sensitive strains responded equally well to ciprofloxacin therapy. Analysis of a subset of 12 of the multiresistant strains revealed that resistance was encoded for by a transferable 180 kilobase plasmid. Ciprofloxacin represents a useful treatment option in areas where multiresistant strains are likely to be encountered.

Typhoid fever is traditionally treated with a two-week course of either chloramphenicol, cotrimoxazole or ampicillin/amoxicillin. Despite minor differences in toxicity, duration of fever, carriage and relapse rate, these agents are roughly equal in clinical efficacy (1). Resistance to these agents has occurred sporadically over the past two decades in a variety of locations (1, 2), but beginning in 1989, *Salmonella typhi* strains resistant to all three standard antimicrobial agents have been reported with alarming frequency from locations as diverse as the Indian subcontinent, the Arabian (Persian) Gulf, the UK and China (1–4). These multiresistant strains are fully pathogenic, often causing illness more severe than that due to sensitive strains (5).

Treatment of typhoid caused by multiresistant *Salmonella typhi* strains is not standardized. Both third-generation cephalosporins (particularly ceftriaxone) and the new fluoroquinolones have been used with some success (1, 2), but no study has yet been published which makes a direct comparison of these two classes of antibiotics in the therapy of typhoid fever. In response to the rapid dissemination of multiresistant *Salmonella typhi* in Bahrain (4), we initiated a trial comparing oral ciprofloxacin with parenteral ceftriaxone for the treatment of typhoid fever. We also investigated the nature of antibiotic resistance in selected multiresistant *Salmonella typhi* recently introduced into the Arabian Gulf area.

Patients and Methods

Patients. Adult patients were eligible for enrollment in the study if they had blood culture positive, acute *Salmonella typhi* infection. Patients with only a positive Widal test and/or a positive stool culture were not eligible. Other exclusion criteria were age less than 16 years, inability to take oral medication, possible or proven pregnancy and lack of fever at the time of admission.

Treatment and Assessment. Informed consent was obtained from all subjects. Once enrolled, patients were

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randomized to receive ciprofloxacin 500 mg orally twice a day or ceftriaxone 3 g intravenously once a day for seven days. A complete history was documented and physical examination performed in all patients at study entry; all subjects were hospitalized for the duration of their illness. Two blood cultures were obtained on the day of study entry and again three days later. If patients were still febrile or symptomatic after the initial seven-day course of therapy repeat blood cultures were performed at that time. Stool samples were obtained for culture on days 1, 7, and 28. Admission laboratory investigations included a complete blood count, a Widal test, determination of serum sodium and creatinine levels, and a chest radiograph. Patients were evaluated three times daily, and the temperature, pulse and blood pressure recorded. The daily clinical evaluation and examination were directed toward detecting complications, defined as gastrointestinal bleeding, peritonitis, shock or deteriorating mental status.

Outcome Definitions. In patients who remained febrile (> 38 °C) after seven days of therapy or who deteriorated clinically after five full days of therapy the outcome was classified as failure. Such cases were allocated to receive the other study antibiotic, blood cultures being repeated prior to administration of the alternative antibiotic. The outcome was classified as success if a patient was afebrile and asymptomatic on or before day 7 and did not require additional therapy during two months of follow-up. A relapse was defined as readmission for typhoid within two months of discharge with a stool or blood culture positive for *Salmonella typhi* possessing the same antibiogram as the initial isolate.

Antimicrobial Susceptibility Testing. All *Salmonella typhi* isolates were tested for resistance to ampicillin, chloramphenicol, cotrimoxazole, ciprofloxacin and ceftriaxone using the Kirby-Bauer technique. A subset of 12 multiresistant strains was further studied at the Central Public Health Laboratory, London, UK. These isolates were phage typed by the methods of Craigie and Felix (6) and again tested for resistance to antibacterial drugs by the methods of Anderson and Threlfall (7) and Ward et al. (8). Drugs tested included chloramphenicol, ampicillin, trimethoprim, nalidixic acid and ciprofloxacin. Sensitive strains were included as controls in these tests.

Resistance Transfer Studies and Plasmid Analysis. The 12 drug-resistant strains evaluated in the UK were tested for their ability to transfer resistance at 28 °C and 37 °C to a standard nalidixic acid-resistant strain of *Escherichia coli* K12 $F'lac^+$ (= 14R525). Counter-selection was exercised with nalidixic acid (40 mg/l) and resistance plasmids were tested for incompatibility with standard plasmids of defined incompatibility groups. Plasmid DNA was extracted by the method of Kado and Liu (9) and molecular weights (MWs) determined in relation to standard plasmids of 180, 147, 63, 36, and 6.9 kilobases (kb) carried in laboratory strains of *Escherichia coli* K12.

Statistical Analysis. Comparisons of proportions were done using the χ^2 test with Yate's correction or the Fisher's exact test. Mean values (reported with ± 1 SD) were compared using the Mann-Whitney test. Significance was set at the 0.05 level.

Results

Patients and Bacterial Strains. A total of 43 patients met the study entry criteria. One patient was subsequently excluded when he proved to have active tuberculosis in addition to *Salmonella typhi* bacteremia and failed to become afebrile after more than two weeks of therapy with both ciprofloxacin and ceftriaxone. Of 42 evaluable patients, 20 were randomized to receive ciprofloxacin and 22 to receive ceftriaxone. There were no significant differences when the treatment groups were compared by age, duration of fever prior to admission, prevalence of multiresistant strains, white blood cell count, serum sodium level, hematocrit, or proportion of patients with diarrhea, constipation, splenomegaly or occult blood in the stool (Table 1). All *Salmonella typhi* isolates were sensitive to both ceftriaxone and ciprofloxacin when tested by the Kirby-Bauer technique. Triresistant strains were defined as those resistant to cotrimoxazole, ampicillin and chloramphenicol, whereas sensitive strains were sensitive to all three antibiotics. No isolate had an intermediate pattern of sensitivity.

Outcome of Therapy. There were no cases of clinical failure in the ciprofloxacin group, whereas there were six cases of failure in the ceftriaxone group ($p = 0.01$). All ciprofloxacin patients were asymptomatic and afebrile by day 6 (mean: 4 days of fever). The ceftriaxone group required a significantly longer time for resolution of fever (mean: about 5 days, $p = 0.04$). Five of the six cases of failure in the ceftriaxone group were thus classified because of persistent fever after a full seven days of therapy; the sixth patient had fever and

Table 1: Comparison of the two treatment groups at study entry.

	Ciprofloxacin (n = 20)	Ceftriaxone (n = 22)
Mean age (years)	26.8	28.2
Mean duration of fever prior to admission (days)	9.7	10.2
Triresistant strain (%)	55	50
Mean leukocyte count (x 10^9/l)	6.715	7.818
Mean hematocrit (%)	38.6	39.1
Mean serum sodium level (mmol/l)	131	131
Stool with occult blood (%)	32	30
Diarrhea (%)	60	59
Constipation (%)	10	14
Splenomegaly (%)	10	18

persistent severe neuropsychiatric symptoms on day 6 of ceftriaxone therapy and was deemed a case of clinical failure by the investigators (Table 2).

All six cases of failure in the ceftriaxone group were subsequently allocated to receive ciprofloxacin therapy. These six patients were afebrile and asymptomatic within 48 hours, and all patients had an uneventful recovery while completing a one-week course of ciprofloxacin.

Blood cultures were done on day 3 of initial therapy in all 42 study patients and on day 8 in the six patients receiving ciprofloxacin after failure of ceftriaxone; all cultures were negative.

One patient in the ceftriaxone group experienced relapse four weeks after therapy, both blood and stool cultures being positive for a *Salmonella typhi* strain with the same antibiogram as the initial isolate. One patient in the ciprofloxacin group was readmitted with fever eight weeks after discharge. This patient's stool grew a sensitive *Salmonella typhi*; however, her prior isolate was triresistant and infection was attributed to reinfection rather than relapse. All other patients had negative stool cultures four weeks after therapy and did not relapse within a two-month follow-up period.

The study was terminated when the clinicians involved in the study felt that it was no longer ethical to randomize patients to receive ceftriaxone, given the higher cost, need for intravenous access and lower efficacy of this regimen.

Phage Types and Drug Resistance. Seven of the 12 randomly selected strains belonged to Vi-phage type E1, three to type M1, one to type A, and one to type 51. All these strains were resistant to chloramphenicol, ampicillin and trimethoprim, but were sensitive to ceftriaxone, nalidixic acid and ciprofloxacin. The complete spectrum of resistance was transferable at 28 °C but not at 37 °C. In all cases, the spectrum of resistance was encoded for by plasmids of approximately 180 kb, belonging to incompatibility (Inc) group H1. All 12 of the strains were isolated from patients who had recently arrived in Bahrain from the Indian subcontinent.

Table 2: Outcome of therapy in the two treatment groups.

	Ciprofloxacin (n = 20)	Ceftriaxone (n = 22)	P value
Clinical failure	0/20	6/22	0.01
Relapse	0	1	NS
Days to resolution of fever (mean)	4.0	5.2	0.04

NS: not significant.

Discussion

In this study, ciprofloxacin given orally produced more rapid and reliable resolution of fever than parenteral ceftriaxone. Prolonged fever in ceftriaxone treated typhoid patients has been observed in other studies (10, 11) and may reflect the relatively poor intracellular penetration of cephalosporins. Ciprofloxacin, with its excellent intracellular penetration, has been almost uniformly successful in the treatment of typhoid caused by both sensitive and resistant *Salmonella typhi* isolates (1, 12, 13). The short course (7 days) of ciprofloxacin used in our study was efficacious and not associated with a high rate of stool carriage or relapse, thus having significant advantages compared to the longer two-week course of traditional agents. Because of these advantages, ciprofloxacin has recently been advocated in the UK as the drug of choice for treatment of typhoid in patients with a high pretreatment likelihood of infection with strains resistant to traditional agents (14). Despite its advantages, ciprofloxacin does have appreciable drawbacks. Its use in children and pregnancy is controversial due to concern about possible cartilage injury. While much less expensive than ceftriaxone, ciprofloxacin is still more expensive than oral drugs of choice used in the past. Although touted as a drug for treatment of typhoid carriers (15), its failure to reliably eliminate stool carriage in a recent outbreak of *Salmonella java* is also disquieting (16). Most disconcerting of all is a report from India of decreasing susceptibility of *Salmonella typhi* to ciprofloxacin and the need for higher doses (1.5 g/day) to achieve a cure (17). In spite of these potential problems, on the basis of the findings of this study, oral ciprofloxacin (500 mg orally b.i.d.) can be recommended for the initial therapy of typhoid in areas where resistant strains are responsible for a sizeable proportion of cases of typhoid fever. It is an effective oral drug which can cure typhoid in a one-week course of therapy. The rapid spread of multiresistant typhoid fever over large geographic areas presents multiple challenges, especially in less developed countries where access to newer and more expensive antimicrobial agents

may be limited. Further research efforts must continue to focus on oral agents with good intracellular penetration which can be used for short courses of therapy with the chances of a high cure rate.

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