

Azithromycin versus Ciprofloxacin for Treatment of Uncomplicated Typhoid Fever in a Randomized Trial in Egypt That Included Patients with Multidrug Resistance

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To compare clinical and bacteriological efficacies of azithromycin and ciprofloxacin for typhoid fever, 123 adults with fever and signs of uncomplicated typhoid fever were entered into a randomized trial. Cultures of blood were positive for *Salmonella typhi* in 59 patients and for *S. paratyphi* A in 3 cases; stool cultures were positive for *S. typhi* in 11 cases and for *S. paratyphi* A in 1 case. Multiple-drug resistance (MDR; resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) was present in isolates of 21 of 64 patients with positive cultures. Of these 64 patients, 36 received 1 g of azithromycin orally once on the first day, followed by 500 mg given orally once daily on the next 6 days; 28 patients received 500 mg of ciprofloxacin orally twice daily for 7 days. Blood cultures were repeated on days 4 and 10 after the start of therapy, and stool cultures were done on days 4, 10, and 28 after the start of therapy. All patients in both groups improved during therapy and were cured. Defervescence (maximum daily temperatures of $\leq 38^{\circ}\text{C}$) occurred at the following times [mean \pm standard deviation (range)] after the start of therapy: 3.8 ± 1.1 (2 to 7) days with azithromycin and 3.3 ± 1.0 (1 to 5) days with ciprofloxacin. No relapses were detected. Cultures of blood and stool during and after therapy were negative in all cases, except for one patient treated with azithromycin who had a positive blood culture on day 4. These results indicated that azithromycin and ciprofloxacin were similarly effective, both clinically and bacteriologically, against typhoid fever caused by both sensitive organisms and MDR *S. typhi*.

Typhoid fever, a common and sometimes fatal infection of adults and children that causes bacteremia and inflammatory destruction of the intestine and other organs, is endemic in most countries, especially throughout Asia and Africa (2). Chloramphenicol has been the treatment of choice for typhoid fever for 40 years, but the widespread emergence of multidrug-resistant (MDR) *Salmonella typhi* (resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) has necessitated the search for other therapeutic options (12, 15). Fluoroquinolones have proven effective, but to date they are restricted from use in children, and quinolone-resistant strains of *S. typhi* have been reported (17, 19). The azalides, are another class of antibiotics which have shown promise in the treatment of typhoid fever. Azithromycin, the first drug of this class, is a derivative of the basic macrolide nucleus with better activity than erythromycin against gram-negative bacteria. In vitro, azithromycin has an MIC range of 4 to 16 $\mu\text{g/ml}$ against *S. typhi*, suggesting that the drug has limited utility for the treatment of typhoid fever (11). However, in the murine typhoid model, azithromycin given once daily was highly effective in clearing the infection and this activity was attributable to the remarkable property of intracellular concentration of azithromycin in macrophages (>100 times the concentrations in serum) (4). These promising results led to a small, open-label, nonrandomized trial of azithromycin in which adults with uncomplicated typhoid fever were treated (18). All 14 adults had a clinical and bacteriological cure without adverse effects (18).

This prompted the current study of azithromycin versus ciprofloxacin for the treatment of uncomplicated typhoid fever in adults.

MATERIALS AND METHODS

Study population. Both males and females over 18 years of age admitted to the Abbassia Fever Hospital in Cairo, Egypt, with a clinical diagnosis of typhoid fever were evaluated regarding enrollment in the study. To be eligible for study entry, subjects were required to have a documented fever (temperature, $\geq 38.5^{\circ}\text{C}$) plus a history of fever for at least 4 days in addition to two or more of the following: abdominal tenderness, hepatomegaly (>2 cm below the right costal margin), splenomegaly (>2 cm below the left costal margin), and rose spots. Exclusion criteria included pregnancy or lactation, allergy to ciprofloxacin or erythromycin (or other macrolides), complication of typhoid fever (pneumonia, intestinal hemorrhage or perforation, shock, or coma), inability to swallow oral medication, significant underlying illness, and treatment within the past 4 days with an antibiotic potentially effective against *S. typhi*. Only patients with blood and/or stool cultures positive for *S. typhi* or *S. paratyphi* were evaluable.

Sample size. The study was designed to detect a 50% difference in clinical success rates between the two groups and assuming that 60% of the subjects treated with ciprofloxacin would respond to therapy as defined by becoming afebrile within 5 days of starting treatment. Accepting a type 1 error of 0.05 and a type 2 error of 0.2, it was projected that 30 evaluable subjects (positive blood or stool culture) would be needed for each treatment arm (22). Assuming that 50% of the patients with clinical typhoid fever would have blood cultures positive for *S. typhi* or *S. paratyphi*, 60 subjects were initially enrolled for each treatment arm.

Randomization and treatment. Subjects were screened for eligibility, and informed consent was obtained before each subject was randomly assigned to a treatment arm. Neither subjects nor investigators knew before randomization which medication each subject would receive. Treatment assignments, determined by block randomization based on a random number list, were sealed in envelopes by a statistician uninvolved in the treatment trial. At the time of enrollment, the investigator unsealed the envelope to determine which treatment the subject would receive. After randomization, subjects were treated in an open-label format with either azithromycin (1 g given orally on the first day, followed by 500 mg given orally once daily for the next 6 days) or ciprofloxacin (500 mg given orally twice daily for 7 days).

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Procedures. Cultures of blood (10 ml), stool, and urine were performed prior to initiation of antibiotic therapy. Blood was obtained for hematologic measurements and serum chemistry determination, and urine was obtained for urinalysis before subjects received a study drug. During treatment, rectal temperatures were recorded three times a day and daily physical examinations were performed. Subjects were also administered a structured questionnaire regarding changes in symptomatology and possible adverse events. On days 4 and 10 after treatment was started, blood was obtained for culture, hematologic measurements, and serum chemistry determination. Stool for culture was collected 4 and 10 days after the start of treatment, as well as 1 month after completion of therapy. Subjects were asked to return 2 and 4 weeks after completion of treatment for physical examination and administration of a questionnaire to determine if the subjects had remained well.

In vitro susceptibilities and phage typing. Antimicrobial susceptibilities were determined by disk diffusion. Strains were considered susceptible when zone diameters for azithromycin disks containing 15 µg were ≥13 mm and those for ciprofloxacin disks containing 5 µg were ≥21 mm. Isolates were sent to a reference laboratory at Texas Tech University Health Sciences Center for determination of MICs and to a reference laboratory in Ottawa, Ontario, Canada, for Vi phage typing (10). MICs of azithromycin were measured by the tube dilution method in cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) containing calcium at 25 mg/liter and magnesium at 12.5 mg/liter.

Analysis of data. Responses of patients to treatment were classified by the following definitions. Clinical cure was resolution of symptoms by the end of 7 days of therapy. Microbiological cure was sterile blood cultures at days 4 and 10. Clinical failure was lack of resolution of symptoms by day 7 or development of a major complication of typhoid fever (such as intestinal hemorrhage or perforation or seizures) after 5 days of therapy. Microbiological failure was a blood culture positive for *S. typhi* or *S. paratyphi* on day 4 or 10. Relapse was recurrence of fever with signs and symptoms of typhoid fever within 4 weeks of therapy completion along with isolation of the organism in culture. Defervescence was defined as the first day on which the maximum temperature was ≤38.0°C with maintenance of the temperature at this level for at least 48 h.

RESULTS

One hundred twenty-three patients (77 males, 36 females) ranging in age from 18 to 32 years (mean, 20.3 years) were enrolled in the study and randomly assigned to one of the two treatment groups. A total of 64 subjects (36 receiving azithromycin, 28 receiving ciprofloxacin) had blood cultures or stool cultures from which *S. typhi* or *S. paratyphi* was isolated, and these subjects comprised the basis for analysis. Ten subjects grew *S. typhi* or *S. paratyphi* from both stool and blood samples, 52 subjects had the bacteria isolated only from the blood, and 2 subjects had the bacteria isolated only from the stool.

Demographic and pretreatment laboratory evaluations of the subjects with positive blood cultures are shown in Table 1. Overall, there were no significant differences between the treatment groups. However, there were individual variations. Five subjects in the azithromycin group had initial platelet counts below 100,000/mm³, compared to two subjects in the ciprofloxacin group. Four subjects in the azithromycin group had pretreatment aspartate aminotransferase (AST) values of over 100 IU, compared to seven subjects in the ciprofloxacin group. One subject in each group had renal failure on study entry with blood urea nitrogen values of 70 and 30 mg/dl (azithromycin versus ciprofloxacin) and creatinine values of 3.5 and 1.7 mg/dl (azithromycin versus ciprofloxacin).

Antimicrobial susceptibility testing showed that all 64 culture isolates of *S. typhi* and *S. paratyphi* were susceptible to both azithromycin and ciprofloxacin. However, 21 of 64 isolates were resistant to at least two drugs (chloramphenicol, ampicillin, and/or trimethoprim-sulfamethoxazole) commonly used in the treatment of typhoid fever. A subset of 23 of the strains of *S. typhi* was tested for MICs of azithromycin in Texas. MICs were 8 µg/ml for 19 strains, 4 µg/ml for 3 strains, and 16 µg/ml for 1 strain. Seven of the 23 strains showed MDR. For five of these seven MDR strains, the MIC of azithromycin was 8 µg/ml and for two it was 4 µg/ml. Phage typing was performed on a subset of 30 of the isolates randomly selected from the initial 64 isolates. The most common Vi phage type was E2,

TABLE 1. Characteristics of 64 patients with culture-positive typhoid fever before treatment

Parameter	Azithromycin	Ciprofloxacin
No. of patients treated	36	28
Age (yrs)		
Range	18–30	18–32
Mean	19.6	20.3
No. of male	24	19
No. of female	12	9
No. of days of fever before admission		
Range	3–30	3–15
Mean	9.7	9.2
No. of patients with:		
Blood cultures with <i>S. typhi</i>	34	25
Blood or stool cultures with <i>S. typhi</i> showing resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole	6	15
Blood cultures with <i>S. paratyphi</i> A	1	2
Stool cultures with:		
<i>S. typhi</i>	4	7
<i>S. paratyphi</i> A	1	0
Mean laboratory value ± SD (normal range)		
Hemoglobin (11–18 g/100 ml)	11.6 ± 2.4	12.4 ± 1.9
Hematocrit (35–60%)	35.1 ± 4.7	36.6 ± 5.0
Leukocyte count ([4.5–10.5] × 10 ³ /mm ³)	5.44 ± 2.10	5.12 ± 1.65
Platelet count ([150–450] × 10 ³ /mm ³)	171 ± 78	179 ± 72
Bilirubin (0.2–1.0 mg/100 ml)	0.67 ± 0.32	0.58 ± 0.26
AST (5–49 IU)	69.2 ± 43.4	87.1 ± 106.8 ^a
Blood urea nitrogen (7–18 mg/100 ml)	16.4 ± 16.4 ^b	12.4 ± 5.9
Creatinine (0.7–1.5 mg/100 ml)	0.97 ± 0.54	0.91 ± 0.31

^a One patient had a value of 527 IU, and one had 310 IU, causing the mean and standard deviation to be high.

^b One patient had a value of 87 mg/100 ml, and one had 70 mg/100 ml, causing the standard deviation to be high.

which was present in 13 subjects, followed by C1 in 6 subjects, E1 in 3 subjects, B group in 2 subjects, and 27 in 2 subjects. The D1-N-CR'T' and 28 phage types were each present in one subject.

Responses to treatment were excellent in both groups (Table 2). All patients in both groups had a clinical cure. Microbiological cure was also achieved in all subjects except one individual in the azithromycin group whose blood culture on day 4 of therapy grew *S. typhi*. The subject was clinically well, and the day 10 blood culture was sterile. Patients in both the ciprofloxacin and azithromycin treatment groups responded quickly to therapy with mean times to defervescence of 3.3 and 3.8 days with ciprofloxacin and azithromycin, respectively (no statistically significant difference).

No subject, including the 12 with *S. typhi* or *S. paratyphi* isolated from the pretreatment stool culture, had positive stool cultures after treatment was initiated or on the 1-month post-treatment follow-up visit. Additionally, neither microbiological nor clinical relapses occurred in either treatment group.

Mild-to-moderate adverse events, all of which were short-term and self-limited were reported equally in both treatment groups (Table 3). All subjects with pretreatment laboratory abnormalities (thrombocytopenia, elevated liver function tests, or renal abnormalities) had normal values at the end of therapy. Four patients in the azithromycin group and one in the

TABLE 2. Responses to treatment

Parameter	No. of patients or mean \pm SD	
	Azithromycin	Ciprofloxacin
No. of patients treated	36	28
Blood culture positive for <i>Salmonella</i>		
Day 4	1	0
Day 10	0	0
Stool culture positive for <i>Salmonella</i>		
Day 4	0	0
Day 10	0	0
Week 4	0	0
Clinical cure on or before day 10	36	28
No. of days to defervescence (temp, $\leq 38^\circ$) after start of treatment	3.8 \pm 1.1	3.3 \pm 1.0 ^a
Relapse after completion of treatment	0	0
Laboratory values on day 10 (normal ranges)		
Hemoglobin (11–18 g/ml)	11.9 \pm 1.6	11.9 \pm 1.6
Hematocrit (35–60%)	35.6 \pm 4.7	36.2 \pm 4.5
Leukocyte count ([4.5–10.5] $\times 10^3/\text{mm}^3$)	6.93 \pm 2.00	6.15 \pm 1.55
Platelet count ([150–450] $\times 10^3/\text{mm}^3$)	356 \pm 160	313 \pm 91
Bilirubin (0.2–1.0 mg/100 ml)	0.54 \pm 0.16	0.52 \pm 0.18
AST (5–49 IU)	48.8 \pm 41.7	63.0 \pm 43.6 ^a
Blood urea nitrogen (7–18 mg/100 ml)	11.3 \pm 3.4	10.9 \pm 3.1
Creatinine (0.7–1.5 mg/100 ml)	0.66 \pm 0.18	0.66 \pm 0.19

^a Student's *t* test showed the difference between the means not to be significant ($P > 0.05$).

ciprofloxacin group had thrombocytosis (platelet count of $>500,000/\text{mm}^3$) on the day 10 blood evaluation, but all subjects were asymptomatic. Additionally, three subjects treated with ciprofloxacin and two treated with azithromycin developed mild, asymptomatic AST elevations (range, 111 to 208 IU) during the course of therapy.

DISCUSSION

Our results of this comparative randomized trial of azithromycin and ciprofloxacin for typhoid fever indicated that the two treatments were effective and comparable in that they gave clinical cures of all patients within 10 days and produced bacteriological eradication of *Salmonella* from the blood cultures of all of the patients. Few differences between the two treatment groups were noted because both were successful without occurrence of complications during or after treatment. The patients treated with ciprofloxacin showed a slightly shorter mean time to defervescence (3.3 days) than did patients treated with azithromycin (3.8 days), but this difference was not statistically significant ($P > 0.05$). Stool cultures of all patients were negative during and after therapy, and no relapses were detected after therapy. Adverse events of nausea or vomiting, lightheadedness, dry throat or mouth, and loose stools were reported occasionally in both groups. These events were mild or moderate and did not result in interruption of therapy and could be attributed in part to the enteric infections. Laboratory results showed that rises in AST values occurred in some patients after therapy, with the mean AST being higher in the group treated with ciprofloxacin than in the group treated with azithromycin; however, the difference between the mean values was not statistically significant ($P > 0.05$), and these

results could have been caused, in part, by typhoid fever. These azithromycin results compare favorably with those of other antimicrobial agents tested recently for typhoid fever, including ceftriaxone, cefixime, and fluoroquinolones (16, 20), and confirm the earlier finding that azithromycin is effective against infections caused by *S. typhi* and *S. paratyphi* A (18).

Our results confirm that azithromycin is active in vitro against strains of *S. typhi*, regardless of whether they are MDR or susceptible to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. Six of our patients treated with azithromycin were infected with MDR strains. The MICs of azithromycin reported in the literature are in the range of 4 to 32 $\mu\text{g}/\text{ml}$, and for most strains the MICs are 4 to 8 $\mu\text{g}/\text{ml}$ (11). In an earlier study, two patients' strains of *S. typhi* in Egypt and seven patients' strains of *S. typhi* in India were MDR but also were susceptible to azithromycin and the patients were cured by azithromycin treatment (6, 18).

The two study drugs were very different in regard to their administration, pharmacokinetics, and therapeutic principles. Azithromycin was given once daily in a dose of 1,000 mg on the first day and 500 mg a day for 6 more days, whereas ciprofloxacin was given twice a day at 1,000 mg/day for 7 days. Both drugs penetrate cells effectively, and this intracellular penetration explains the effective therapeutic activity against the predominantly intracellular pathogen *S. typhi*. On the other hand, the reported concentrations of azithromycin in serum of 0.04 to 0.4 mg/liter during treatment (14) are less than the MIC for *S. typhi*. The ability of azithromycin to achieve intracellular concentrations in monocytes and polymorphonuclear leukocytes 231 and 83 times greater than the concentrations in serum, respectively (13, 21), appears to be essential for its therapeutic activity against typhoid fever.

The place of azithromycin in the treatment of typhoid fever needs to be defined by further clinical studies with adults and children. Once-daily oral treatment for 7 days is convenient and should be favorable for outpatient compliance. Some patients with typhoid fever are unable to swallow oral preparations or have vomiting and could not be included in this study. A parenteral preparation of azithromycin has become avail-

TABLE 3. Adverse events reported by patients

Symptom and severity	No. of subjects reporting event	
	Azithromycin	Ciprofloxacin
Nausea or vomiting		
Mild ^a	4	4
Moderate ^b	2	0
Lightheadedness		
Mild	2	2
Moderate	0	0
Dry throat or mouth		
Mild	2	4
Moderate	1	0
Loose stools		
Mild	0	3
Moderate	3	0
Constipation		
Mild	2	1
Moderate	0	1

^a Mild indicates no change in lifestyle.

^b Moderate indicates a change in lifestyle that did not require treatment.

able but has not been used for typhoid fever. The sample size in this study showed no difference between the clinical responses of the two groups, but larger numbers of patients are required to exclude the possibility that smaller differences between treatment groups occurred. The fluoroquinolones ciprofloxacin and ofloxacin have been tested in adults in geographic areas with MDR and gave good results (16, 20). However, the fluoroquinolones are generally not approved for use in children because of the potential for these drugs to damage cartilage in growing bones in animals. Children are affected by typhoid fever more frequently than are adults (5). Children and adults with MDR typhoid fever have been treated successfully with ceftriaxone, cefixime, aztreonam, and furazolidone (1, 3, 7–9). The availability of a pediatric suspension of azithromycin provides an opportunity to examine the efficacy and safety of this drug for young children with MDR typhoid fever.

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