

Randomised trial of azithromycin versus ofloxacin for the treatment of Typhoid fever in adult T-7

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Abstrak

Selama beberapa tahun terakhir telah timbul galur kuman *Salmonella typhi* yang resisten terhadap berbagai jenis antibiotika (MDR) di berbagai negara termasuk Vietnam. Di Vietnam dan anak benua India juga ditemukan adanya isolat *S. typhi* yang resisten terhadap asam nalidiksik yang disertai berkurangnya sensitifitas terhadap obat fluorokuinolon. Sefalosporin generasi ketiga dan fluorokuinolon merupakan obat-obat yang sering dipergunakan untuk pengobatan demam tifoid (DT) pada masa kini. Azitromisin (AZM) mempunyai aktifitas sedang terhadap *S. typhi*, tetapi dapat mencapai konsentrasi intraseluler yang tinggi dan terbukti efektif untuk pengobatan DT bila diberikan selama 7 hari atau lebih lama. Tidak didapatkan adanya suatu hasil penggunaan jangka pengobatan AZM yang lebih pendek yang dilakukan secara acak. Lima penderita dewasa dari Vietnam dengan hasil biakan yang positif diikutsertakan dalam suatu penelitian percobaan dan mendapat pengobatan dengan AZM dengan dosis 1 gram secara oral sekali sehari selama 5 hari. Biakan darah diulang pada hari ke 6 dan dilakukan biakan dari tinja pada hari ke 6, 7, 8 dan 30 sejak dimulainya pengobatan. Semua pasien mengalami penyembuhan dengan median penurunan panas (sebaran) terjadi setelah 138 (78-228) jam. Tidak dijumpai adanya kekambuhan. Penelitian ini selanjutnya diikuti dengan suatu penelitian perbandingan acak secara terbuka dengan membandingkan AZM dengan dosis oral 1 gram/ hari selama 5 hari dibandingkan dengan pemberian ofloksasin 200 mg oral dua kali sehari selama 5 hari. Analisis awal dari 26 penderita dengan biakan darah positif, yang 12 di antaranya mendapat AZM dan 14 mendapat OFL, ternyata 17/24 (71%) hasil isolat merupakan MDR, dan 1/24 (4%) resisten terhadap asam nalidiksik, tetapi tidak dijumpai isolat yang resisten terhadap kedua jenis obat dalam penelitian ini. Semua pasien dalam kedua kelompok pengobatan mengalami penyembuhan. Median (sebaran) jangka waktu penurunan panas masing-masing adalah 126 (60-252) jam untuk AZM dan 99 (42-228) jam untuk OFL ($p=0,08$). Semua hasil biakan darah dan tinja yang dilakukan setelah selesai pemberian pengobatan ternyata negatif. Didapatkan gejala gastroenteritis ringan yang tidak memerlukan pengobatan pada kelompok AZM, tetapi tidak terdapat gejala samping yang lain secara bermakna pada kedua kelompok pengobatan. Hasil analisis awal dari penelitian ini menunjukkan bahwa pengobatan selama 5 hari dengan AZM atau OFL keduanya efektif untuk pengobatan DT pada penderita dewasa yang disebabkan oleh *S. typhi* yang resisten terhadap berbagai jenis obat.

Abstract

In recent years multi-resistant (MDR) strains of *Salmonella typhi* have emerged in many countries including Vietnam. In Vietnam and the Indian sub-continent isolates of *S. typhi* resistant to nalidixic acid with a reduced sensitivity to fluoroquinolones have also appeared. Third generation cephalosporins and fluoroquinolones are currently used widely for treating typhoid fever (TF). Azithromycin (AZM) has moderate in-vitro activity against *S. typhi* but achieves high intracellular concentrations and has been shown to be effective for treating TF when given for 7 or more days. There have been no randomised comparisons using shorter courses of AZM. Five blood culture positive Vietnamese adults were enrolled in a pilot study and received AZM 1gm orally once a day for 5 days. Blood cultures were repeated on day 6 and stool cultures on days 6, 7, 8 and 30 days after the start of therapy. All five patients were cured with a median (range) fever clearance time of 138 (78-228) hours. No relapses were detected. An open randomised comparison was therefore commenced comparing AZM 1gm orally once a day for 5 days versus Ofloxacin 200 mg orally twice a day for 5 days. An interim analysis of the first 26 blood culture positive adults included 12 treated with AZM and 14 with OFL. 17/24 (71%) of the isolates were MDR, 1/24 (4%) were nalidixic acid resistant but none were resistant to either of the study drugs. All patients in both groups were cured. The median (range) fever clearance time was 126 (60-252) hours for Azithromycin and 99 (42-228) hours for Ofloxacin ($p=0.08$). Cultures of blood and faeces after the end of therapy were negative in all cases. There were mild self limiting gastrointestinal side effects in the AZM treated patients but no other significant side effects attributable to either antibiotic. These interim results suggest that a five day course of AZM or OFL are both effective for the treatment of the TF in adults due to multi-resistant *S. typhi*.

INTRODUCTION

With more than 12.5 million cases occurring each year throughout the world, typhoid fever continues to present a considerable health problem, particularly in developing countries. In recent years, multi-drug resistant strains of *Salmonella typhi* have emerged in

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many countries including Vietnam¹. Although fluoroquinolones are used widely for treating these resistant strains their use is relatively contraindicated in children and in pregnancy because of possible adverse effects on cartilage. Furthermore, isolates of *S. typhi* resistant to nalidixid acid with a reduced sensitivity or resistance to fluoroquinolones have appeared in Vietnam and the Indian sub-continent^{2,3}. Azithromycin, the first of a new class of azalides, has moderate *in-vitro* activity against *S. typhi*⁴ but achieves high intracellular concentrations and has been shown to be effective in a murine typhoid caused by *Salmonella typhimurium*⁵ and for treating typhoid fever when given for 7 or more days⁶⁻⁹. There have been no randomised comparisons using courses of azithromycin shorter than 7 days in typhoid. In a pilot study, five Vietnamese adults with blood culture positive TF received azithromycin 1 gm orally once a days for 5 days. All five patients were cured with a median (range) fever clearance time of 138 (78-228) hours. No relapses were detected. A study was therefore commenced to compare the clinical and bacteriological efficacy of a five day course of azithromycin or ofloxacin for the treatment of typhoid fever in adults.

METHODS

The study was performed on the adult typhoid ward at the Centre for Tropical Diseases, Ho Chi Minh City. The hospital is a 500 bed referral centre for Ho Chi Minh City and the surrounding provinces. The study had received ethical approval from the Scientific and Ethical Committee of the Centre for Tropical Diseases and all patients gave informed verbal consent. Adults (15 years old) with the clinical features of enteric fever and who were blood culture positive with *S. typhi* or *S. paratyphi* A were enrolled in the study. Patients were excluded if they had evidence of severe or complicated disease (coma, shock, visibly jaundiced, gastrointestinal bleeding, intestinal perforation, pneumonia), a history of significant underlying disease, had a previous history of hypersensitivity to either of the trial drugs and had previous treatment with a quinolone or 3rd generation cephalosporin or macrolides within one week of hospital admission and were pregnant. Patients were allocated to one of two treatment groups in an open randomised comparison. The treatment allocation were kept in a sealed envelope which were only opened when the patient had been entered into the study. Patients received either azithromycin 1gm orally once a day for 5 days or ofloxacin 200mg orally twice a day for 5 days.

Blood cultures were obtained before therapy and 24 hours after the end of therapy (day 6). Faecal cultures (three specimens) and a urine culture were performed before therapy and faecal cultures were repeated on days 6, 7, 8 and 30 after the start of therapy. Isolates of *Salmonella* were identified by standard biochemical test and agglutination with *Salmonella* antisera. Antimicrobial sensitivities were performed by the modified Bauer-Kirby method with zone size interpretation based on NCCLS guidelines. Patients in whom *S. typhi* with an intermediate sensitivity to azithromycin were still treated with azithromycin if randomised to that drug. A full blood count, SGOT, SGPT, creatinine and urinalysis were performed before therapy and on day 6. If the SGOT, SGPT or creatinine were abnormal they were repeated until they had become normal. Chest X-ray and other radiological investigations, including abdominal ultrasound, were performed as clinically indicated. Patients were examined daily with particular reference to clinical symptoms, fever clearance time, any side effects of the drug and any complication of the disease. The response to treatment was assessed by clinical parameters (resolution of clinical symptoms and signs), fever defervescence (time to first fall below 37.5° C, axillary, and to remain below 37.5° C for 24 hours), time to eradication of bacteraemia, development of complications and evidence of relapse of infection.

Treatment failure was defined as the persistence of fever and symptoms for more than five days after the end of treatment or the development of any severe complications. Patients who failed were retreated with ofloxacin 10mg/kg per day for 7 to 10 days or ceftriaxone 2g/day for 7 to 10 days. Patients were followed up 4 - 6 weeks post treatment. At this time any clinical evidence of relapse was sought, three stool cultures were performed and any abnormal laboratory investigation was repeated. A full set of microbiological cultures were performed if the symptoms and signs suggested further infection.

To detect failure rates of 1% and 20% for ofloxacin and azithromycin respectively (80% power, 5% significance level), 50 patients will need to be recruited in each group. Proportion were compared with the Chi squared test with Yates' correction or the Fisher's exact test. Non-normally distributed data were compared using the Mann Whitney U test. Statistical analysis was performed using the Staview software package.

Table 1 Clinical and laboratory features and response to treatment of patients with culture-confirmed of Typhoid fever

| Features of patients | OFL group (n=14) | AZM group (n=12) | P |
|---|------------------|-----------------------------|--------|
| No. of males / females | 9 / 5 | 4 / 8 | > 0.05 |
| Age (year, median [range]) | 25 (16-40) | 24 (17-37) | > 0.05 |
| Duration of fever before admission (days) | 11.5 (7-30) | 11.0 (5-18) | > 0.05 |
| Admission temp (°C, median [range]) | 39.9 (38.0-40.5) | 39.4 (39.0-40.5) | > 0.05 |
| Hepatomegaly (%) | 40 | 16.6 | > 0.05 |
| Splenomegaly (%) | 6.6 | 8.3 | > 0.05 |
| White cell count (x10 ⁹ /L) | 7.0 (4.2-10.0) | 5.5 (3.1-11.2) | 0.05 |
| Hematocrit % | 38 (28-47) | 39 (30-43) | > 0.05 |
| SGOT (IU/L, mean [range]) | 75 (25-294) | 105 (31-169) | > 0.05 |
| SGPT (IU/L, mean [range]) | 71 (22-237) | 64 (21-136) | > 0.05 |
| Organism isolated | | | |
| <i>S. typhi</i> | 14 | 12 | |
| Multi-resistant (%) | 10 (71) | 7 (58) | |
| Nalidixic acid resistant | 0 (0) | 1 (8) | |
| Treatment failures | 0 | 0 | |
| Acute complications | 0 | 0 | |
| Microbiological relapse | 0 | 0 | |
| Fever clearance time (hours, median [range]) | 99 (42-228) | 126 (60-252) | 0.08 |
| Duration of admission after starting treatment (days, median [range]) | 11 (7-16) | 12 (10-17) | 0.06 |
| Side effects | none | Nausea : 2 Diarrhoea : 3 | |

RESULTS

An interim analysis of the first 26 blood culture positive adults included 12 treated with azithromycin and 14 with ofloxacin. *S. typhi* was isolated from all of the blood cultures and 8/26 (31%) of the patients had at least one positive pre-treatment faecal culture. All isolates were sensitive to ofloxacin although 1/26 was resistant to nalidixic acid. None of the isolates were resistant to azithromycin although 8/26 (31%) (3 randomised to azithromycin) were of intermediate sensitivity on the basis of the zone size. The demographic, clinical and laboratory findings for the culture confirmed cases of typhoid fever are shown in the Table 1. There were no important differences between the admission characteristics of the two groups. There were no treatment failure in either group. Cultures of blood and faeces after the end of therapy were negative in all cases. Mild self limiting gastrointestinal side effects were seen in five of azithromycin treated patients but there were no other significant side effects attributable to either antibiotic. No relapses were detected.

DISCUSSION

Since 1991 *S. typhi* resistant to all the conventional first-line antibiotics, ampicillin, cotrimoxazole and chloramphenicol, has been reported from Central and South America, the Middle East, the Indian Sub-continent and South East Asia. In Vietnam by 1996 the proportion of multi-resistant strains isolated from blood cultures at this centre increased to over 80%. Furthermore, strains with resistance to nalidixic acid and reduced sensitivity to the fluoroquinolones, have emerged². Third generation cephalosporins and fluoroquinolones are currently used widely for treating multi-resistant typhoid fever in many countries. In Vietnam randomised comparative studies of fluoroquinolones (floxacin and ofloxacin) and ceftriaxone in adults have shown the fluoroquinolones to be superior. Ceftriaxone given for three or five days gave clinical and microbiological cure rates of 72-87% and 92-93% respectively^{9,10}. With fluoroquinolones (ofloxacin or floxacin used for 2, 3 or 5 days) the cure rates were 97-100% and 99-100%¹⁰⁻¹⁴. The results of treatment with fluoroquinolones were

significantly worse, however, in patients infected with isolates of *S. typhi* resistant to nalidixic acid and reduced sensitivity to fluoroquinolones. When treated with ofloxacin for 2 to 3 days patients infected with nalidixic acid resistant *S. typhi* had a significantly longer fever clearance time compared with patients infected with a nalidixic acid sensitive isolate and had 44 fold increased risk of needing a further course of antibiotic². The study of new drugs for treating multi-resistant *S. typhi* is therefore important.

Azithromycin, the first of a new class of azalides, has moderate activity against *S. typhi*. The reported *S. typhi* activity of azithromycin against *S. typhi* (MIC₉₀ 8mg/L, Range 2-16 mg/L)⁴ is above the reported peak serum level of azithromycin following a 500 mg dose of 0.4 mg/L¹⁵. Azithromycin, however, is concentrated in the tissues 50 to 100 fold compared with the serum levels and achieves high intracellular concentrations. In a murine model of salmonellosis it was found to be highly active⁴. This discordance between *in-vitro* susceptibility and *in-vivo* effectiveness is probably explained by the fact that *S. typhi* is predominantly an intracellular pathogen.

Azithromycin 500 mg once daily for between 7 and 14 days was found to be effective in adults with typhoid fever in Chile. The fever clearance time was 5.4 days for 5 patients treated for 14 days and 4.8 days for 5 patients treated for 7 days. In an open study in Cairo, 14 patients received azithromycin as a single dose 1 g on the first day, followed by 500mg for 6 additional days were cured with a fever clearance of 4.3 days⁶. In these two studies 3/24 (13%) of patients were still blood culture positive at day 4. In a study in Bahrain three of four adults failed azithromycin given as 1 gm on day one and then 500 mg a day for the next six days¹⁶. The three failures had clinically deteriorated by day four or five of therapy and one was blood culture positive on day four. Comparative studies in Cairo of azithromycin (1 gm on day 1, 500 mg a day for the next 6 days) in 16 adults and ciprofloxacin (500 mg twice daily for 7 days) in 17 adults cured all patients and gave a fever clearance of 4.1 and 3.6 days respectively⁷. In a similar study in India comparing azithromycin 500 mg a day for 7 days with chloramphenicol 2-3 g per day for 14 days was 88% clinically and 100% microbiologically successful in 42 adults treated with azithromycin and 86% and 94 % successful in 35 adults treated with chloramphenicol⁸.

We wished to use a five day course of azithromycin both to be comparable to the five day course of ofloxacin which is widely used for nalidixic acid sensitive isolates in Vietnam and to ensure compliance. However we were concerned about the reports of the blood cultures remaining positive after 4 days of treatment with the standard regimen. Furthermore our studies of the localisation of bacteria in the blood of patients with typhoid have shown that many of the bacteria are in fact extracellular [Wain J, unpublished observations]. Doses of azithromycin higher than the recommended 5-10mg/kg have been tolerated^{17,18}. We therefore investigated the efficacy and tolerability of a short course high dose regimen. This interim analysis has shown that the clinical and microbiological and cure rate with azithromycin was 100% and the fever clearance time of 5.2 days was comparable to the other studies. Apart from some mild side effect with nausea, vomiting and diarrhoea, the azithromycin was well tolerated. In this study three patients randomised to azithromycin had strains with intermediate sensitivity to azithromycin on the basis of disc zone size. All of them had a good response to azithromycin with fever clearances of 60, 138 and 162 hours. Ofloxacin in a course of five days was also 100% effective with a fever clearance time comparable to a previous study. All of the patients randomised to receive ofloxacin had nalidixic acid sensitive isolate.

Our interim results therefore suggest that a five day course of azithromycin or ofloxacin are both effective for treating typhoid fever in adults in an area with a high incidence of multi drug resistant typhoid fever.

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