

A Comparative Study of Efficacy and Safety of Azithromycin and Ofloxacin in Uncomplicated Typhoid Fever: A Randomised, Open Labelled Study

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ABSTRACT

Objective: To compare the efficacy and safety of azithromycin with ofloxacin in patients with uncomplicated typhoid fever.

Material and Methods: Forty adult patients with bacteriologically or serologically diagnosed, uncomplicated typhoid fever were included from Medicine out-patient department at Government medical college, Amritsar, India. They were randomized into 2 groups of 20 patients each. Group I: patients received ofloxacin 200mg orally twice daily for 7 days. Group II: Patients received Azithromycin orally 1 gm on day 1 and then 500 mg daily from day 2 to day 6. The following parameters were noted a) fever clearance time b) cure rate c) adverse drug reaction d) recurrence of symptoms, if any, during 4 weeks follow up.

Results: Nineteen out of 20 patients from group I were cured with mean fever clearance time of 3.68 days while all 20 patients from group II were cured with mean fever clearance time of 3.65 days. No significant side effects were noted in any of the patients. No relapse was recorded in the present study in a follow up period of 4 weeks in both study groups.

Conclusion: Both ofloxacin and Azithromycin are almost equally efficacious and safe in treatment of typhoid fever with no major adverse effect. Azithromycin is an effective alternative in conditions where ofloxacin is contraindicated i.e., children, pregnant women and quinolone resistant cases of typhoid fever.

Key Words: Typhoid fever, Azithromycin, Ofloxacin

INTRODUCTION

Enteric fever is a systemic infection caused by *Salmonella enterica* serovar Typhi (S. Typhi) and *Salmonella enterica* serovar Paratyphi A (S. Paratyphi A). Antimicrobial therapy is critical for the clinical management of enteric fever [1]. For many decades, antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole were used for treating enteric fever [2]. The emergence of Multiple-Drug-Resistant (MDR) *Salmonella* strains, which are resistant to chloramphenicol, ampicillin and cotrimoxazole, has changed treatment options. Second-line antibiotics like the fluoroquinolones (ciprofloxacin, ofloxacin), third-generation cephalosporins (ceftriaxone, cefixime), and azithromycin are often now used for treating MDR typhoid fever [3].

Fluoroquinolones are commonly used for treating enteric fever and have been recommended by the WHO for the treatment of uncomplicated enteric fever caused by fully sensitive and MDR organisms [1]. Ciprofloxacin and ofloxacin were chosen for treating typhoid because of potent bactericidal activity against *S. typhi* and *S. paratyphi A*. *In vivo*, both drugs have plasma levels considerably in excess of the prevailing MICs and excellent intracellular penetration [4]. Widespread use of fluoroquinolone therapy for enteric fever has been followed by the emergence of *S. typhi* and *S. paratyphi A* isolates with elevated Minimum Inhibitory Concentrations (MIC) to ciprofloxacin and ofloxacin across Asia and in parts of Africa. These strains are associated with point mutations in the *gyrA* gene and occasionally the *parC* gene [5]. Enteric fever caused by *S. Typhi* strains with an elevated MIC to ciprofloxacin and ofloxacin have been coupled with the failure

of treatment with these antimicrobials and increased disease severity [6]. There are also reports from the Indian subcontinent of isolates that are fully resistant to fluoroquinolones and the extended spectrum cephalosporins [7].

Azithromycin, a member of the macrolide group of antibiotics, has been used as an alternative drug for treating typhoid fever. It achieves low intra-vascular levels, has high intra-cellular tissue penetration, and a long elimination half life of 72 hours. These properties make for once-daily administration and reduction in the duration of therapy. The drug is rapidly absorbed from the gut and is well-tolerated when used orally [8]. *In vitro* studies have shown that it is more potent than traditional first-line drugs and other macrolides against *Salmonella* spp. with an average MIC of 8µg/mL (range 4 to 16µg/mL) [9]. There are no reports of resistance of *S. Typhi* to azithromycin, and recent studies have shown that it is effective both clinically and bacteriologically in treating enteric fever even in those caused by MDR strains [6]. So, the present study was conducted to compare the efficacy and safety of azithromycin with ofloxacin in patients with uncomplicated typhoid fever.

MATERIAL AND METHODS

It was a prospective, randomized, open labeled study. The study was approved by the Institutional Ethics Committee. Subjects were recruited in the Medicine outpatient department of a tertiary care teaching hospital after obtaining a written consent from each patient. Considering 80% power and $\alpha = 0.05$, the number of subjects required in each treatment group was 17.

Inclusion Criteria

Adults of either sex, aged between 18 and 60 were considered. The serological and bacteriological criteria for inclusion were a positive blood culture for salmonella typhi and/or agglutination titre (Widal test) 1/320 or more or agglutination titre 1/160 with a subsequent rise along with clinical picture suggestive of typhoid fever.

Exclusion Criteria

Patients were excluded if; they refused consent, had evidence of progressive or complicated disease, had inability to swallow oral medication, had a history of significant underlying disease, had hypersensitivity to either of the trial drugs or were pregnant or lactating. Additionally, patients who gave a history of treatment with a fluoroquinolone, a third generation cephalosporin or a macrolide within one week of hospital admission were also excluded.

Effectiveness Parameters

Patients were considered clinically cured when fever subsided within 7 days of antibiotic therapy and without any clinical relapse during four weeks follow up period. The following parameters were noted a) fever clearance time b) cure rate c) suspected adverse drug reaction d) recurrence of symptoms, if any, during 4 weeks follow up.

Study Visits

Each patient was evaluated for 5 weeks. The first week was active treatment period. The following weeks were treatment free follow up. Patients were evaluated clinically at baseline (day 0) and at subsequent follow up visits on week 1, 2, 3 and 4. Signs and symptoms were recorded at every visit.

Grouping

45 patients were screened. Out of them 40 patients were included in the study. Patients with uncomplicated typhoid fever were allocated to one of each of the treatment groups. A computer generated randomization list was produced by a member of staff. Patients in group I received ofloxacin tablet (200 mg) and group B received azithromycin tablet (500 mg). Since it was an open label study, patients in both treatment groups were aware of their study medications. Patients in group I received oral ofloxacin 200 mg twice daily for 7 days. Patients in group II received oral Azithromycin 1 gm on day 1 and then 500 mg daily from day 2 to day 6.

Supportive treatment included tablet paracetamol for remission of fever whenever indicated. Intravenous transfusions of dextrose saline, 5% dextrose and blood were also administered in some cases as supportive measures as and when indicated. High grade fever was brought down by the aid of hydrotherapy. The patients were given semi-solids to liquid bland diet.

The progress of the cases was recorded with special reference to period of defervescence of fever and general condition. All cases were followed up once weekly for a period of 4 weeks. All the cases came for follow up regularly and were examined for fever clearance time, cure rate and recurrence of symptoms of relapse. Patients were monitored continuously throughout the study for any Adverse Event (AE). Safety monitoring was done continuously throughout the study. All AEs spontaneously reported by the subjects or elicited by the investigators were recorded.

Statistical Analysis

Data in nominal scale were analyzed by Student's t test. Categorical data were analyzed by Chi-square test. P value < 0.05 was considered to be statistically significant.

RESULTS

In the present study, 40 patients of typhoid fever were included of which 24 were male and 16 were females in the range of 16-65 years. The maximum incidence was between the age group of 16-30 years (67.5%). The baseline demographic profile was similar in both study groups in the present study [Table /Fig-1].

Both groups were comparable in terms of age (mean age 29.3 ± 11.7 years for group I v/s 29.15 ± 11.2 years in group II) and sex distribution (male: female ratio being 1.5:1). Also the mean duration of fever before starting treatment was comparable in 2 groups [Table/Fig-2]. There was not much difference between 2 groups in terms of clinical symptoms and signs as well as severity of illness and laboratory findings.

Clinical cure

Patient was considered clinically cured when fever settles within seven days of antibiotic therapy and without any clinical relapse during four weeks follow up period. After Ofloxacin treatment, 18(90%) patients showed good or moderate response while a single patient showed poor response and 1(5%) patients did not responded even after 7 days treatment and was considered treatment failure [Table/Fig-3]. Cure rate was found to be 95%. After Azithromycin treatment, all 20 patients (100%) showed good or moderate response and no poor response case was observed. Treatment failure was not noted in any case in this group. Cure rate was found to be 100%. So, no significant difference in clinical cure rate was observed in two study groups.

Relapse

No relapse was recorded in the present study in a follow up period of 4 weeks in both study groups.

Fever clearance time

Fever clearance with Ofloxacin varied in this study from 2-6 days with mean fever clearance time 3.68 ± 0.92 days [Table/Fig-4]. Fever clearance time with Azithromycin varied in our study from 2-5 days with mean fever clearance time being 3.65±0.91 days. There was no statistically significant difference in the fever clearance time between 2 studies. So the two groups were found to be comparable in terms of mean fever clearance time.

Age groups	Group I				Group II			
	Male	%	Female	%	Male	%	Female	%
16-20	3	15	2	10	2	10	3	15
21-25	3	15	1	5	2	10	2	10
26-30	4	20	-	-	4	20	1	5
31-35	1	5	2	10	1	5	1	5
36-40	-	-	-	-	-	-	-	-
>40	1	5	3	15	3	15	1	5

[Table/Fig-1]: Showing Age and Sex Incidence in the Two Groups

Mean age for group I: 29.3±11.7 years.

Mean age for group II: 29.15±11.2 years

Duration of illness	Group I		Group II	
	No.	%age	No.	%age
<= 7 days	7	35	8	40
8-14 days	11	55	11	55
>14 days	2	10	1	5

[Table/Fig-2]: Showing Duration of Fever Before Starting Treatment

Mean duration of fever in group I - 8.95±3.58 days.
Mean duration of fever in group II - 8.6±3.35 days.

	Total cases	Good*	Moderate**	Poor***	No response	Relapse
GROUP I	20	9	9	1	1	-
GROUP II	20	9	11	-	-	-

[Table/Fig-3]: Showing Response to Therapy in Both Groups

*Temperature settling in 3 days; **Temperature settling in 3-5 days.
***Temperature settling in >5 days.

Groups	Mean fever clearance time ± SD
Group I	3.68±0.92 days
Group II	3.65±0.91 days

[Table/Fig-4]: Showing Mean Fever Clearance Time in Two Groups

Adverse Effects

Both drugs were well tolerated. Nausea and vomiting occurred in 10% patients in both groups, but it was unclear whether it was due to the drug or the disease process itself. A single patient developed skin rash with ofloxacin while abnormal liver function tests in the form of elevated serum alkaline phosphatase developed in one patient in Azithromycin treated group without any clinical signs of cholestasis. There was not much significant difference in side effects between two groups. Side effects were not serious enough to withhold the treatment. No serious complication related to typhoid fever appeared during the treatment in any of the patients in both groups.

DISCUSSION

Typhoid fever caused by *Salmonella* sp is one of the most common causes of systemic infections in India and is one of the common causes of travel associated illnesses [10]. Several developing countries recently reported the emergence and spread of drug resistant *Salmonella typhi* that resulted in significant increase in morbidity of typhoid fever and a frantic search for inexpensive but effective alternative drug. MDR strains of *S. Typhi* have been reported from all parts of the world. Second-line antibiotics like the fluoroquinolones (ciprofloxacin, ofloxacin, perfloracin), third-generation cephalosporins (ceftriaxone, cefixime), and azithromycin are often now used for treating MDR typhoid fever. Infections with isolates susceptible to nalidixic acid (prototype fluoroquinolone) respond extremely well to fluoroquinolones. Lately, there have been several reports of fluoroquinolone-resistant *S. Typhi* [3]. Quinolone-resistant strains are reportedly also MDR and infection with resistant *S. Typhi* is associated with increased morbidity and mortality. There are also reports from the Indian subcontinent of isolates that are fully resistant to fluoroquinolones and the extended spectrum cephalosporins. These reports further support the need for alternative antibiotics such as azithromycin for treating enteric fever [3].

In the present study both groups were compared in terms of mean fever duration, mean fever clearance time, cure rate and relapse rate. Both groups were comparable in terms of mean age and

fever duration prior to treatment. Similarly, no significant difference in mean fever clearance time and cure rate was observed between Azithromycin and ofloxacin treated group. Treatment was well tolerated with ofloxacin and azithromycin with only minor side effects. No major adverse effect was noted with these antibiotics.

Drug resistance in *Salmonella* has been on the rise in India with emergence of Nalidixic Acid-Resistant (NAR) *Salmonella* and an increasing clinical non-response to fluoroquinolones. Treatment options are getting limited with emergence of resistance to fluoroquinolones. The Western studies have favoured azithromycin as the potential drug that produces good clinical response. However, due to the lack of breakpoint concentrations in various international guidelines, its *in vitro* interpretation has often been difficult for *Salmonella*. In the Western literature, treatment has heavily banked upon the use of azithromycin due to its high intracellular concentration and good clinical response. Clinical trials suggest the use of 20 mg/kg per day with a maximum dose of 1000 mg/day for 5 to 7 days for complete cure [10]. Randomized trials have suggested similar efficacy of azithromycin and ciprofloxacin, both clinically and *in vitro* studies, against enteric fever caused by sensitive as well as MDR. A trial conducted by Girgis et al., in Egypt compared the effectiveness and safety of azithromycin and ciprofloxacin in uncomplicated typhoid fever. This trial suggested the effectiveness of azithromycin in uncomplicated typhoid fever [11]. However there was lack of substantial data in Indian population. This prompted us to compare the efficacy and safety of azithromycin with ofloxacin in patients with uncomplicated typhoid fever. Our study also suggests effectiveness of azithromycin in uncomplicated typhoid fever.

Some limitations of this study were as follows. A double-blind study could not be conducted due to financial constraints and logistic problems.

CONCLUSION

Both ofloxacin and azithromycin are equally efficacious and safe in treatment of typhoid fever. Hence, it is logical to conclude that both ofloxacin and azithromycin are useful for treatment of enteric fever. Azithromycin is an effective alternative in conditions where ofloxacin is contraindicated i.e., children, pregnant women and quinolone resistant cases of typhoid fever.

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FINANCIAL OR OTHER COMPETING INTERESTS:

None.

Date of Submission: **Jun 14, 2012**
Date of Peer Review: **Jul 15, 2012**
Date of Acceptance: **Aug 08, 2012**
Date of Online Ahead of Print: **Aug 25, 2012**
Date of Publishing: **Dec 15, 2012**