Azithromycin Versus Ofloxacin in Treatment of Enteric Fever in Children

Ammara Manzoor, Tariq Mahmood, Rubina Zulfiqar
Department of Paediatrics, Holy Family Hospital and Rawalpindi Medical College, Rawalpindi

Abstract
Background: To compare the clinical efficacy of Azithromycin versus Ofloxacin in the treatment of typhoid fever in terms of the proportion of children becoming afebrile on 5th day of treatment.

Methods: In this randomized controlled trail 230 patients of Typhoid fever, age ranging from 2-12 years, were included. One hundred and fifteen patients were given Azithromycin and 115 patients were given Ofloxacin randomly. Patients were randomly divided into two groups. Group A was given Azithromycin 10 mg/kg/day once daily orally for 7 days. Group B was given Ofloxacin 15mg/kg/day in two divided doses orally for 7 days. Both the groups were observed for duration of becoming afebrile on 5th day of treatment. Investigation to be done during hospital stay was Typhidot (IgM antibodies). Chi-square test was used to compare efficacy (afebrile on day 5) of both drugs. P-value < 0.05 was considered significant.

Results: The age range was from 5 to 12 years with a mean age of 7.7 ±2.45. 125 (54.3 %) were males and 105 (45.7 %) were females. 59.1% patients became afebrile on 5th day of treatment while 40.9 % patients failed to become afebrile. In the Azithromycin group 69.6 % patients became afebrile on 5th day of treatment while 40.9 % patients failed to become afebrile. In the Ofloxacin group, 48.7% became afebrile on day 5th. Proportion of patients becoming afebrile on 5th day of treatment was significantly higher in the azithromycin group as compared to Ofloxacin group (p= 0.01)

Conclusion: Azithromycin is more effective in children with typhoid fever in terms of greater proportion of children becoming afebrile on day 5th of treatment

Key Words: Azithromycin, Ofloxacin, Enteric fever

Introduction
Typhoid fever is a major health problem. It is an important cause of mortality and morbidity worldwide but with high incidence in developing countries of Asia. It is endemic in Pakistan and India. A recent estimate of disease burden worldwide showed that in year 2000, about 22 million new cases of typhoid fever were reported with 210,000 deaths due to typhoid fever and 5.4 million cases of paratyphoid fever. A study conducted in May 2004 showed that South East Asia and Central Asia are the regions in which incidence of typhoid fever is high, 100/100,000 cases/year. Rest of Asia, Africa, Caribbean, Latin America, part of Europe and North America are the regions with medium incidence of typhoid fever, 10-100/100,000 cases/per year. The rest of the developed world have low incidence of typhoid fever, <10/100,000 cases/year. Pakistan has a high incidence of typhoid fever. It is the 4th commonest cause of death.

Risk factors for transmission of typhoid fever and paratyphoid fever include overcrowding, poor hand washing and poor personal hygiene, eating street food, using water without boiling, sharing food, consuming iced drinks, lower socioeconomic group, and poor sanitary conditions in houses. Typhoid fever is frequently transmitted in summer and during rainy season due to contamination of water used for drinking.

The incubation period of typhoid fever is one to two weeks. After ingestion of contaminated food or water, the bacteria enters into the lamina propia of intestine, from where it is taken up by macrophages which then spread the organism via lymphatics to various organs of host causing disease manifestations. The clinical picture of the disease may be mild or severe enough to cause fatal complications and death of the patient. Patients may present with high grade fever, anorexia, nausea, vomiting and diarrhea or sometimes abdominal pain, pallor, constipation, jaundice, myalgias, arthralgias and hepatosplenomegaly or encephalopathy, or ileus intestinal perforation. Factors that determine the severity of the disease include, the duration of illness before starting appropriate therapy, age of the patient, previous vaccination, immunity of the host, dose of inoculating organism and choice of antibiotic being used for treatment.
Gold standard for diagnosis of typhoid fever is blood culture and bone marrow culture. Other tests which are commonly used include Typhidot test and PCR. Case fatality rate of typhoid fever is 10 % without proper treatment however it can be reduced to 1 % with proper treatment with antibiotics. About 15 % of infected patients with salmonella died in past in pre-antibiotic era. The survivors used to have prolonged disability and illness lasting for weeks or even for many months. Antibiotic therapy is necessary for treatment of typhoid fever.

Multi Drug Resistance (MDR) is the term used to describe the resistance to all first line antimicrobials used for treatment of typhoid fever including ampicillin, Trimethoprim-Sulfamethoxazole and chloramphenicol. Due to these MDR strains, fluoroquinolones are the drugs of choice. A study was conducted in India in 2001 that showed 100% susceptibility of all isolated Salmonella strains to Ciprofloxacin. Increased use of fluoroquinolones again created problem in treatment of typhoid fever due to emergence of strains that were resistant to Fluoroquinolones.

This resistance again forced the physicians to search for newer antibiotics to which salmonella is sensitive. Among newer fluoroquinolones, Gatifloxacin is a better alternative. 3rd generation Cephalosporins like Ceftriaxone are now commonly being used for the treatment of typhoid fever. Treatment of ciprofloxacin resistant typhoid fever now narrows down to 3rd and 4th generation cephaplorins, Azithromycin, Penams and Tigecycline.

**Patients and Methods:**
This randomized controlled trail was conducted in Pediatric Department of Holy Family Hospital, Rawalpindi , from March 2012 to September 2012. Sample size was calculated by WHO calculator. Total 230 diagnosed patients of Typhoid fever, age range from 2-12 years, were included. Patients had fever >37°C in the presence of at least one or more of the signs and symptoms, i.e., persistent headache, abdominal pain or discomfort, splenomegaly / hepatomegaly, rose spots on skin and vomiting. One hundred and fifteen patients were given Azithromycin and 115 patients were given Ofloxacin randomly. Patients were randomly divided into two groups, A and B. Group A was given Azithromycin 10 mg/kg/day once daily orally for 7 days. Group B was given Ofloxacin 15mg/kg/day in two divided doses orally for 7 days. Both the groups were observed for duration of becoming afebrile on 5th day of treatment.

Investigation to be done during hospital stay was Typhidot (IgM antibodies) . Chi-square test was used to compare efficacy (afebrile on day 5) of both drugs. P-value < 0.05 was considered significant.

**Results**
The age range was from 5 to 12 years with a mean age of 7.7 ±2.45 (Figure 1). Majority (54.3 %) were males. The weight of the children ranged from 10 to 40 kg with a mean weight of 23±7.48 kg. In the Azithromycin group majority (69.6 %) became afebrile on day 5th. In the Ofloxacin group 48.7% patients became afebrile on day 5th. The proportion of patients becoming afebrile on day 5th was higher in the azithromycin group as compared to Ofloxacin group (p=0.01) (Table 1).

**Figure 1- Age distribution of study groups**

**Table 1: Frequencies of patients becoming afebrile on day 5th: Azithromycin versus Ofloxacin groups**

<table>
<thead>
<tr>
<th></th>
<th>antibiotic given</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>azithromycin</td>
<td>ofloxacin</td>
</tr>
<tr>
<td>AFEBRILE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>30.4%</td>
<td>51.3%</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

p=0.001

**Discussion**
The results of present study revealed children between age group 7-11 years, mostly infected with typhoid fever. This is in contrast to a study which showed that children less than 5 years of age are at risk.
high risk. Males were reported more than females in our study groups and it may be due to the reason that male children have easy access to street foods. Similar results were also obtained in Bangladesh in which male patients were more in number than the female patients infected with typhoid fever. In the Azithromycin group 69.6 % patients became afebrile on day 5. The proportion of patients becoming afebrile on day 5 was significantly higher in the Azithromycin group as compared to Ofloxacin group (p = 0.01). A case series reported from south India showed that fluoroquinolone use in fluoroquinolone reduced susceptibility strains should be done with great caution. Another study compared different antimicrobial regimens for the treatment of MDR (multidrug resistant) (nalidixic acid resistant) Na (r) typhoid fever. Vietnamese children and adults with uncomplicated typhoid fever were entered into an open randomized controlled trial. Ofloxacin (20mg/kg of body weight/day for 7 days), azithromycin (10mg/kg/day for the first 3 days) were compared. The clinical cure rate was 64% with ofloxacin, 76% with ofloxacin-azithromycin, and 82% (51/62) with azithromycin. The mean (95% confidence interval, fever, clearance time for patients treated with azithromycin (5.8 days [5.1 to 6.5 days]) was shorter than that for patients treated with ofloxacin-azithromycin (7.1 days [6.2 to 8.1 days]) and ofloxacin (8.2 days [7.2 to 9.2 days]) (p < 0.001). According to another study conducted in Amirtasir India, the safety of ofloxacin and azithromycin is equal in treatment of typhoid fever with no major side effects. However azithromycin is an effective alternative in conditions when ofloxacin is contraindicated.

In a study it was shown that about 20% of patients of typhoid fever treated with Ofloxacin had positive fecal cultures immediately in their post treatment period. This transient fecal carriage in post treatment period has the potential to allow further transmission of S. typhi among the family and close contacts. In a study the patients among this study group who were treated with Azithromycin in a dose of 10mg/kg/day once daily for 7 days had an average fever clearance time on day 5 of treatment and this was comparable to results of another study in which azithromycin was compared in terms of fever clearance time.

Studies have examined a regimen of azithromycin at a dose of 20 mg/kg/day (maximum, 1 g/day) in children or 1 g/day in adults given for 5 days. Of the Egyptian children, 94% (30/32) were cured of the disease, with a mean fever clearance time of 4.5 days. Of Vietnamese adults, 96% (42 out of 44) were cured, with a mean duration of fever of 5.4 days. The slightly lower cure rate in our study as compared to these studies may be due to higher doses of azithromycin used in these studies. Azithromycin can be used safely for the treatment of typhoid fever in children.

The persistence of fever in some patients of our study may be due to the continued production of pyrogenic cytokines. This shows that time taken to clear fever may not be an adequate measure of antibiotic efficacy, and consequently may not be an appropriate end point in typhoid therapy trials. Some investigators also did not specify whether clinical failures were excluded or included in calculations of mean fever clearance time.

In this study, a 7-day course of azithromycin was more effective as an initial oral treatment for uncomplicated typhoid fever. Appropriate treatment of typhoid fever is a clinical as well as a public health challenge due to rising levels of drug resistance and limited evidence for use of newer agents like Azithromycin, particularly for children.

**Conclusions**

1. Azithromycin is a better choice than Ofloxacin in terms of shorter time of fever clearance.
2. Clinical burden of typhoid fever, along with emergence of resistance to antibiotics which were considered appropriate for its treatment, needs exploration of more antibiotic therapies.

**References**