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Original Article

Clinical Efficacy of Azithromycin in Typhoid and Paratyphoid Fever in Children

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Abstract

***Background**: Azithromycin sensitivity cannot precisely identify the strains of typhoid and paratyphoid fever for successful treatment. Most of the studies show that azithromycin is highly effective in uncomplicated typhoid fever. Very few studies have been carried out in Bangladesh to see the effectiveness and sensitivity of azithromycin in children with uncomplicated typhoid fever.* ***Objective**: To assess the clinical response of azithromycin in uncomplicated typhoid fever.* ***Materials and Methods**: This randomized clinical trial was conducted in Dhaka Shishu (children) Hospital from January to December 2009. Children between 2–12 years of age with characteristic clinical presentation of uncomplicated typhoid fever with positive blood culture for S. typhi or S. paratyphi were included in this study. Patients were treated with oral azithromycin 20 mg/kg/day for 7 days in one group and intravenous ceftriaxone 100 mg/kg/day in another group. Effectiveness and sensitivity pattern were documented and compared.* ***Results**: Fifty patients were allocated randomly with azithromycin and 48 with ceftriaxone. Twenty two percent of the subjects were below 5 years and 78% above 5 years. Average time of defervescence was 4.44 ± 1.25 days in azithromycin group and 4.38 ± 1.21 days in ceftriaxone group. Response to treatment in both groups was excellent: 94% in azithromycin and 97.9% in ceftriaxone groups. The occurrence of complication was very low in both groups. Eighteen percent showed resistance to azithromycin and 2.1% to ceftriaxone. In azithromycin sensitive group 97.6% showed improvement and in resistant group 77.8% showed improvement. A good percentage of patients who were resistant to azithromycin showed clinical improvement following treatment with this drug.* ***Conclusion**: Current study recommends that azithromycin is effective in the treatment of enteric fever in children. The study also shows that some patients resistant to azithromycin showed clinical improvement following treatment with azithromycin.*

***Key words**: Sensitivity; Azithromycin; Resistance; Enteric fever; In vivo; In vitro*

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Introduction

Typhoid and paratyphoid fever, also known as enteric fever[1], is a potentially fatal multi-system illness caused by Salmonella typhi or Salmonella paratyphi. It occurs throughout the world where water supply and sanitation are substandard. Typhoid fever is highly endemic in developing countries like Bangladesh[2] with documented high prevalence among children. Every year there are at least 13–17 million cases of typhoid fever worldwide resulting in 600,000 deaths; 80% of these cases occur in Asia alone. In South-East Asia >5% of the strains are multi-drug resistant.[3] In existing Clinical Laboratory Science Institute (CLSI) USA Guidelines it has been mentioned that azithromycin sensitivity cannot precisely identify the strains of

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Salmonella typhi and paratyphi.[4] But most of the studies found azithromycin highly effective in uncomplicated typhoid fever.[5-10] The recent availability of the azalide class of antibiotics has provided another potential option for the treatment of typhoid fever. Azithromycin, the first azalide evaluated, has in vitro activity against many enteric intracellular pathogens, including S. typhi.[5-7] Animal models have demonstrated that azithromycin is highly effective against both Salmonella enteritidis and Salmonella typhimurium, with drug efficacy related to the tissue concentration, rather than the serum concentration of the antibiotic.[8,9] A subsequent randomized trial demonstrated that azithromycin was as effective as ciprofloxacin for the treatment of uncomplicated typhoid fever in adults.[10]

Typhoid fever is a systemic infection found only in man. S. typhi has been a major human pathogen for thousands of years, thriving in condition of poor sanitation, crowding and social chaos. The name S. typhi is derived from the ancient Greek typos, an ethereal smoke or cloud that was believed to cause disease and madness.[11] In the advanced stages of typhoid fever, the patient's level of consciousness is truly clouded. Although antibiotics have markedly reduced the frequency of typhoid fever in the developed world, it remains endemic in developing countries. It is characterized by a continuous fever for 2–3 weeks, relative bradycardia, involvement of lymphoid tissue and constitutional symptoms. In western countries, it has been brought very close to eradication level. In UK, there is approximately one case per 100,000 population per year.[12] Definitive treatment of typhoid fever is based on susceptibility. Until susceptibilities are determined, antibiotic should be empirical. The 2003 World Health Organization (WHO) guideline recommended treatment with fluroquinolones for both complicated and uncomplicated typhoid fever. However, sensitivity profiles of S. typhi varies geographically.[13] Ciprofloxacin resistance is an emerging problem especially in the Indian subcontinent and South-East Asia. Nalidixic acid is a therapeutic drug that is used outside the United States. It is no longer used clinically.[14] In epidemics and less wealthy countries, therapeutic trial time with chloramphenicol is generally undertaken while awaiting the results of Widal test and cultures of blood and stool.[15] Where resistance is uncommon, the treatment of choice is fluoroquinolone such as ciprofloxacin[16]; otherwise a third generation cephalosporin such as ceftriaxone is the first choice.[17] Cefixime is a suitable oral alternative.[18] Antibiotics such as ampicillin, chloramphenicol, cotrimoxazole, amoxycillin and ciprofloxacin have been commonly used in typhoid fever in developed countries. Resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole and streptomycin is now common and these agents have not been used as first-line treatment for almost 20 years. Typhoid that is resistant to these agents is known as multidrug resistant typhoid. Ciprofloxacin resistance is an increasing problem globally, especially in the Indian subcontinent and South-East Asia.[19,20]

Now in many centers first-line treatment is ceftriaxone. It has also been suggested that azithromycin is better for treating typhoid in resistant cases than both fluoroquinolone and ceftriaxone.[21]Azithromycin significantly reduces relapse rate compared with ceftriaxone.[21]

Very few studies on azithromycin against S. typhi and paratyphi have been done in Bangladesh. So, this study was carried out to determine the efficacy of azithromycin and to observe both in vivo and in vitro sensitivity pattern in children with uncomplicated typhoid fever.

Materials and Methods

This randomized clinical trial was conducted in Dhaka Shishu Hospital from January to December 2009. Ninety eight children between 2–12 years of age with characteristic clinical presentations (e.g., fever, toxic appearance, abdominal tenderness, hepato- or splenomegaly, coated tongue, diarrhea or constipation etc.) of uncomplicated enteric fever with positive blood culture for salmonella were included in the study. Written informed consent was taken from the parents or legal guardians before enrollment in the study. Then detailed history was taken and a complete physical examination was done. Data were recorded in data collection sheet. Treatment of randomly selected 50 patients was started with oral azithromycin at dose of 20 mg/kg/day for 7 days. Effectiveness and sensitivity pattern were documented. If there was no response within 5 days the treatment protocol was changed. Adjuvant therapy as well as supportive treatment were provided in addition to antimicrobial therapy where needed. Another blood culture was done in all patients after 5 days of antibiotic therapy. Treatment with azithromycin was continued in patients who responded clinically in spite of showing

resistance to the drug in vitro. After completion of 7 days' treatment no further blood culture was sent to see the relapse. Forty-eight children were treated with intravenous ceftriaxone at the dose of 100 mg/kg/day. Treatment outcomes between azithromycin and ceftriaxone groups were compared. Permission of Ethical Review Committee of Dhaka Shishu Hospital was taken prior to the start of therapy. Data were analyzed with SPSS version 16.0.

Results

A total of 98 children of 2–12 years with uncomplicated enteric fever were enrolled. Fifty were allocated randomly with azithromycin and 48 with ceftriaxone. Among the patients, 22% were below 5 years and 78% above 5 years. In azithromycin group overall time of defervescence was 4.44 ± 1.25 days and in ceftriaxone group 4.38 ± 1.21 days (Table II). No difference in duration of defervescence was found between two groups (p>0.05). Only 16% children developed complications of which 4% had vomiting, 6% had abdominal pain, 2% had rash and 4% had difficulty in breathing.

Response to treatment in both groups was excellent. Overall improvement was 94% with azithromycin and 97.9% with ceftriaxone. In azithromycin group 82% were found sensitive and 18% resistant. In sensitive cases 97.6% showed improvement and in resistant cases 77.8% showed improvement. In ceftriaxone group 95.8% were found sensitive and 4.2% resistant. In sensitive cases 100% showed improvement and in resistant cases 50% showed improvement. Outcomes of treatment in azithromycin and ceftriaxone groups are shown in Table III and Table IV. Comparison of treatment outcomes between azithromycin and ceftriaxone groups is shown in Table V. No significant difference was found between two groups in terms of treatment outcomes (p=0.582).

Among the patients of azithromycin group, 42 (84%) were infected with S. typhi and 8 (16%) with S. paratyphi. In ceftriaxone group 41 (85.42%) were infected with S. typhi and 7 (14.58%) with S. paratyphi.

Table I: Age distribution of study subjects

Age groups	Treatment		Total
	Azithromycin	Ceftriaxone	
<5 years	11 (22%)	10 (20.8%)	21 (21.4%)
5–9 years	30 (60%)	30 (62.5%)	60 (61.2%)
>9 years	9 (18%)	8 (16.7%)	17 (17.3%)
Total	50 (100%)	48 (100%)	98 (100%)

Chi-square value=0.066, df=2, p=0.968

Table II: Time of defervescence in study subjects in days (n=98)

Treatment option	Mean ± SD (days)	t value	df	p value
Azithromycin (n=50)	4.44 ± 1.25	0.261	96	0.794
Ceftriaxone (n=48)	4.38 ± 1.21			

Table III: Outcomes of treatment in azithromycin group based on sensitivity (n=50)

Outcomes	Sensitive	Resistant	Total
Improved	40 (97.6%)	7 (77.8%)	47 (94%)
Not improved	1 (2.4%)	2 (22.2%)	3 (6%)

Chi-square value=5.12, df=1, p=0.023

Table IV: Outcomes of treatment in ceftriaxone group based on sensitivity (n=48)

Outcomes	Sensitive	Resistant	Total
Improved	46 (100%)	1 (50%)	47 (97.9%)
Not improved	0 (0%)	1(50%)	1 (2.1%)

Table V: Comparison of treatment outcomes between azithromycin and ceftriaxone groups

Outcomes	Azithromycin group (n= 50)	Ceftriaxone group (n= 48)	P value
Improved	47	47	0.582
Not improved	3	1	

p value was achieved by Chi-square test

Discussion

The present study shows that both azithromycin and ceftriaxone groups had similar time of defervescence. Both the drugs are highly effective in clearing the infection. This result shows azithromycin's effectiveness for the treatment of uncomplicated typhoid fever in Bangladeshi children. In this study we also found that most of the in vitro azithromycin resistant cases responded clinically. Outcomes of treatment were based on duration of defervescence, and development of complications. Regarding duration of defervescence, the average time of defervescence was 4.44 ± 1.25 days in azithromycin group. One previous study[22] showed the days of defervescence of azithromycin treatment 4.1 ± 1.1 days. Study by Giris et al[10] found that the days of defervescence with azithromycin treatment was 3.8 ± 1.1 days. Response to treatment with azithromycin was excellent. Overall improve-

ment rate was 94%. Franck et al[22] found the cure rate 91% with azithromycin. They concluded that oral azithromycin administered once daily appeared to be effective for the treatment of uncomplicated typhoid fever in children and recommended that the agent could be a convenient alternative for the treatment of typhoid fever, especially in developing countries where medical resources are scarce. Once-daily oral treatment for 7 days (20 mg/kg/day) is convenient and should be favorable for out-patient compliance. Although parenteral azithromycin is available, it has not yet been popular in typhoid fever treatment. The fluoroquinolones like ciprofloxacin and ofloxacin have been tested in adults in different geographical areas with multidrug resistance and gave good results.[23] However, the fluoroquinolones are generally not the best choice for use in children because these are potentially cartilage-damagers in growing bones of animals. The availability of a pediatric suspension of azithromycin provides an opportunity to examine the efficacy and safety of this drug in young children with typhoid fever. Among the study subjects treated with azithromycin 18% were found resistant in vitro (the treatment was started before the results of culture were available). Treatment was continued with the same drug until 7 days. Only two cases with no improvement with azithromycin in 5 days were shifted to ceftriaxone treatment. In azithromycin sensitive cases, 97.6% showed improvement and in azithromycin resistant cases 77.8% showed improvement. Clinical improvement of patients with azithromycin in azithromycin resistant cases raises question about the in vitro sensitivity of Salmonella to azithromycin.

In this study we found that in ceftriaxone group overall 97.9% subjects responded to treatment; in in vitro sensitive cases the response was 100%. In one study involving 5410 blood specimens, 715 were found positive for S. typhi and ceftriaxone showed 100% sensitivity.[24] In the studies of Soe et al[25] and Acharya et al[26] third generation cephalosporins such as cefotaxime, ceftriaxone and cefoperazone have been used successfully to treat typhoid fever, with courses as short as three days showing similar efficacy like the usual 10–14 days regimens. Chowta et al[27] also found in their study that sensitivity to ceftriaxone was 100% in enteric fever.

Findings of the present study show that azithromycin is effective in the treatment of enteric fever in children. A good percentage of subjects who were resistant to azithromycin showed clinical improvement although there was significant difference in treatment with azithromycin between in vitro-sensitive group and in vitro-resistant group. We recommend further studies with large sample size.

Limitation of the study

In this study duration of hospital stay was short. Once temperature settled down and found to have negative culture, patients were discharged. They were not followed-up for assessment of possible relapse.

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