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ORIGINAL ARTICLE

EFFICACY OF AZITHROMYCIN IN UN-COMPLICATED ENTERIC FEVER. A STUDY FROM RURAL NORTH INDIA

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ABSTRACT: INTRODUCTION: Enteric fever is a systemic infection caused by the bacteria, Salmonella Typhi (S. typhi) and Salmonella Paratyphi (S. paratyphi A, B and C). Disease burden is more in the developing countries. There is day by day increase in the multidrug resistant strains. **OBJECTIVES:** This study was conducted to assess the efficacy of azithromycin as a first line antibiotic in the treatment of uncomplicated enteric fever. **METHODS:** This case series study was conducted in 90 children between 2- 15 years of age. Those patients who were Typhidot and/or blood culture positive included in this study and treated with azithromycin 20mg/kg/ single dose daily for 7 days. **RESULTS:** Out of the 90 children enrolled, 81 (90.00%) completed the study as the nine children lost to follow up. Male to female ratio was 1.5:1 with common age group between 6-10 years. S. typhi was isolated in 5 (6.17%) cases and all achieved bacteriological cure by day 7. Mean (SD) duration of fever at presentation was 6±2.07 days. Clinical cure was seen in 76 (93.82%) subjects. Mean day of response was 4 days. There was no death in the study. No serious adverse event was observed in the study. **CONCLUSION:** Azithromycin was found to be safe and efficacious for the management of uncomplicated typhoid fever in a dose of 20 mg/kg/day per oral once a day for seven days.
KEYWORDS: Azithromycin, Enteric fever, Salmonella typhi.

INTRODUCTION: Typhoid fever is a systemic infection caused by the bacterium Salmonella enteric serotype typhi, a member of the family Enterobacteriaceae. This organism is an important cause of febrile illness in crowded and impoverished populations with inadequate sanitation that are exposed to unsafe water and food[1, 2]. Salmonella is human restricted pathogen and transmission is faeco-oral.

S. typhi has no non-human vectors. An inoculum as small as 1, 00,000 organisms causes infection in more than 50% of healthy volunteers.[3]

Because of the ready availability of the over-the counter antibiotics and subsequent resistance to these drugs in areas of endemicity, enteric fever is harder to treat. Previously chloramphenicol was used to treat this infection but in 1980 emergence of resistance limited its use. This was followed by emergence of multidrug resistant (MDR) strains (combined resistance to chloramphenicol, ampicillin and cotrimoxazole) initially reported from India, Middle East and then from all over the world. There is emergence of resistance to first line drugs like chloramphenicol, ampicillin, cephalosporins[4] also.

On the other hand, widespread use of fluroquinolones led to the emergence of Salmonella Enterica serovar Typhi and Paratyphi strains with reduced susceptibility to fluoroquinolones[5]. Widespread emergence of multidrug resistant S. typhi has necessitated the search for other therapeutic options for typhoid fever.[6,7]

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Azolides are another class of antibiotics which have shown promise in the treatment of typhoid fever. Azithromycin is the first drug of this class and studies comparing the efficacy of azithromycin with cefixime in adults and children with typhoid fever have reported it to be safe and efficacious[8, 9].

Azithromycin has excellent penetration into most tissues and achievement in macrophages and neutrophils that are >100 fold higher than concentrations in serum. These together with azithromycin's long half-life of 72 hours, show potential in the therapeutic management of enteric intracellular pathogens[10]. Few studies are exclusively reported in children.[11]

We conducted this case series study to assess the safety and efficacy of single daily dose of azithromycin for uncomplicated typhoid fever in children.

MATERIAL AND METHODS: This is a case series study conducted in the department of Pediatrics, of our institute, from July 2011 to August 2012. All the children between 2-15 years of age who had typhidot IgM and/or blood culture positive and diagnosed as uncomplicated enteric fever were included in the study. All those children who fulfilled the following criteria were excluded from the study:

1. Any child who was already taking other antibiotics for more than 48 hours
2. Any child with poor oral intake.
3. Any child with life threatening complication of enteric fever (perforation, shock or seizures).
4. Any patient with congenital or acquired immunodeficiency.

Written consent was obtained from parents/guardians of all children. On day of admission a complete medical, treatment and vaccination history was recorded. Complete physical examination was carried out. All the children between 2-15 years of age who presented with the signs and symptoms of enteric fever and not taking antibiotics for more than 48 hours before presentation were started Azithromycin (20 mg/kg/day) dispersible tablet/suspension for seven days in a single daily dose after sending CBC, blood culture and sensitivity and typhidot IgM. After getting the reports of blood culture and sensitivity and typhidot IgM, only those patients having blood culture or/and typhidot IgM positive were included.

Study medication was dispensed and monitoring instruction provided to each patient. Children were treated at their home and reassessed in the out-patient department on day 4, day 7 and day 30 after the start of the treatment. On day 4 and day 7 temperature charts and symptom diary was evaluated with a complete physical examination. Drug compliance was assessed by history and collecting the empty wrappers/bottles.

Children who were blood culture positive were evaluated on day 7 also for repeat blood culture. If the temperature increased or the clinical condition of the patient worsened or there was a serious drug reaction, patient was taken off from the study and treated with intravenous Ceftriaxone (75 mg/kg/day). All follow ups were carried out in the out-patient department of the hospital.

TYPES OF OUTCOME MEASURES: Clinical Response: Resolution of symptoms and fever clearance (axillary temperature less than 38^0C for >72 hours) was considered sustained after 7 days of treatment. Microbiological Response: Was considered when the blood culture became negative for salmonella typhi or para typhi after 7 days of treatment.

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Clinical Failure: Lack of resolution of symptoms by day 7 or development of a major complication of typhoid fever (intestinal perforation, shock or seizures).

Microbiological Failure: Blood culture positive on day 7 for S.typhi or S. paratyphi.

Relapse: Recurrence of fever along with signs and symptoms of typhoid fever within 4 weeks of completion of therapy, along with isolation of the organism in blood culture.

RESULTS: We enrolled 90 children aged 2-15 years who fulfilled the inclusion criteria. Mean age at the time of presentation was 6.4±2.04 years.

60/90 (66.66%) patients were male while 30/90 (33.33%) were female. 63/90 (70.00%) belonged to middle class family while 27/90 (30.00%) were from the lower low socioeconomic background. Only 27/90 (30.00%) children had received antibiotics before presentation. None of the patients had received prior typhoid vaccination. There was no mortality amongst the patients included in this study. The clinical presentations of the patients at the time of inclusion in this study are shown in the table 1 while various clinical findings of the patients are shown in table 2.

Clinical findings	Visit 1 (Day 0)		Visit 2 (Day 4)		Visit 3 (Day 7)	
	No.	Percentage	No.	Percentage	No.	Percentage
Fever	81	100.00	11	13.58	05	06.17
Headache	24	29.62	04	04.93	00	00
Constipation	06	07.40	02	02.46	00	00
Diarrhoea	14	17.28	04	04.93	00	00
Anorexia	18	22.22	11	13.58	03	03.70
Pain abdomen	31	38.27	06	07.40	01	01.23
Hepatomegaly	58	71.60	34	41.97	10	12.34
Splenomegaly	17	20.98	11	13.58	04	04.93
Coated tongue	72	88.88	60	74.07	10	12.34

Table1: Clinical characteristics of study children at baseline and follow up

Clinical findings	No. of patients	Percentage
Coated tongue	76	93.82
Hepatomegaly	54	66.66
Abdominal tenderness	34	41.97
Splenomegaly	21	25.92
Rose spots	06	07.40

TABLE 2: Physical Examination

9/90 (10.00%) patients left the study. Out of these nine patients, 6 did not come at day 4 for visit and 3 did not come for visit on day 7. So the data from these 9 patients could not be collected completely. Only 81 patients completed the study. 27/81 (33.33%) patients had temperature between 101-102°F followed by 36/81 (44.44%) patients with 100-101°F while 18/81 (22.22%) had temperature between 103-104°F.

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Fever clearance time (FCT) was 96 hours (4 days) in 70/81 (86.41%) patients. Fever settled at day 5 in 4/81 (4.93%) patients while on day 6 in 2/81 (2.46%) but in 5/81 (6.17%) patients fever took more than 7 days to settle. In 4/81 (4.93%) patients relapse was documented. Blood culture was positive in five (6.17%) patients. All of these patients achieved bacteriological cure at 7th day. All the 81 patients had typhidot positive.

Treatment failure was observed in 5/81 (6.17%) children. These children were started on intravenous antibiotic (Ceftriaxone) and all improved by day 12-15.

DISCUSSION: Enteric fever is one of the very common cause of febrile illness and is the major reason for seeking health service by the common people.[12]

Due to the emergence of multidrug resistance to drugs (Chloramphenicol, Ampicilin, Cotrimoxa- zole), the need of newer drugs for the treatment of enteric fever is necessitated; the results with macrolides like Azithromycin is promising. In our study, a 7 day course of oral Azithromycin was found to be highly effective, showing efficacy of 93.82%. The efficacy of Azithromycin has also been established by other studies. Frenck et al 2004 showed a similar comparable high percentage of clinical response to azithromycin at an average rate which supports the present study.[11]

In this study, the most common age group affected was 6-10 years (45.33%), which is different from the study of Prajapati et al 2008 where result showed that common age group was 1-5 years.[13]

The fever clearance time was 96 hours (4days) in 70 (86.41%) patients which is also comparable with the study done by Frenck et al 2004[11], where fever clearance time was 4.5 days.

The bacteriological cure was seen in all the five patients in our study. Similar response was observed by the study done by Frenck et al 2004[11], where bacteriological cure with Azithromycin was also 100%. In the present study, Azithromycin was tolerated well. In only few patients, abdominal symptoms like diarrhoea and nausea was observed on 1st and 2nd day of treatment. But these symptoms did not require any therapy and settled by themselves although this cannot be proven; it is likely that many of the gastrointestinal tract symptoms were associated with the underlying disease and not with the treatment.

In our study, males had higher incidence of the disease (male to female ratio of 1.5:1). This is in accordance with the study done by Bhattarai et al 2003[14]. This study also showed that fever was present in all the patients followed by abdominal pain, headache and anorexia at the time of presentation which is similar to other studies.[15, 16]

The emergence of the resistant strains of S.typhi has become an area of concern for decades. Various trials have focused the mechanisms by which resistance to the first line drugs used in the therapeutic management of enteric fever develop. Hence the search for new drugs for which S.typhi shows evidence of clinical response.

Failure rate was found to be 5 out of 81 (6.17%) while the relapse rate was 4 out of 81 (4.93%). This has been observed in earlier studies on azithromycin.[5]

This study was a case series; however other studies where comparison of Azithromycin was done with intravenous ceftriaxone, the results were comparable. So, we suggest more studies of Azithromycin in comparison with other drugs in our country so that the efficacy and safety of Azithromycin can be established.

CONCLUSION: As there is rise in the emergence of multidrug resistant strains, Azithromycin may be considered in uncomplicated enteric fever in a dosage of 20 mg/kg/day per oral once a day for 7days (max 1000mg/day).

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