International Journal of Advances in Medicine
Chandey M et al. Int J Adv Med. 2016 Aug;3(3):764-767
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20162532

Research Article

Comparative efficacy and safety of azithromycin monotherapy and azithromycin+cefixime combination therapy in uncomplicated typhoid fever

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Received: 26 June 2016
Accepted: 12 July 2016

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ABSTRACT

Background: Typhoid fever continues to occur on a large scale in countries where sanitation is suboptimal. For the last few years quinolones resistant strains of salmonella typhi are being reported. Now the third generation cephalosporins are being used as first line agent for typhoid fever .Since last few years various oral drug combinations have been tried and are available in Indian market for the treatment of typhoid fever. The present study was designed to evaluate the clinical efficacy, side effects and relapse rate of azithromycin monotherapy in uncomplicated typhoid fever cases as compared to those who were treated with azithromycin and cefixime combination therapy in standard dosage.
Methods: 100 adult proven cases of typhoid fever of the age group of 16-65 years of either sex were included in the study. These patients were randomly divided into 2 groups of 50 patients each and then were followed up on and after treatment for 4 weeks. Group I: Patients were given oral azithromycin 500 mg twice daily for 7days. Group II: Patients were given oral Azithromycin 500 mg twice daily with oral cefixime 200 mg twice daily for 7 days.
Results: No statistically significant difference was found in fever clearance time in two study groups. So both study groups were found comparable in terms of mean fever clearance time and clinical cure.
Conclusions: Both mono and combination therapy could be equally effective oral therapy for typhoid fever. More studies have to be conducted in our scenario to reach a conclusion.

Keywords: Azithromycin combination therapy, Typhoid fever

INTRODUCTION

Typhoid fever is an acute systemic disease resulting from infection by a specific organism, salmonella typhi. Typhoid fever is characterised by malaise, fever, abdominal discomfort and tenderness, transient rose coloured eruptions, splenomegaly, sometimes hepatomegaly, pea - soup diarrhoea or sometimes constipation, toxaemia and leukopenia. Typhoid fever continues to occur on a large scale in countries where sanitation is suboptimal. Its incidence in India has been reported to be as higher 7.6 per 1000 per year with an estimated 6-8 million cases per year. Case fatality rate due to typhoid has varied between 1.1 and 2.5% in the last few years.[1]

Currently ciprofloxacin and ofloxacin are the most widely used quinolones for enteric fever. For the last few years quinolones resistant strains of salmonella typhi are being reported.[2-4]

Now the third generation cephalosporins are being used as first line agent for typhoid fever in many centres especially for paediatric age group. The azalides are another class of antibiotics which have shown promise in the treatment of typhoid fever. The initial results of azithromycin in enteric fever are reported to be encouraging.

Since last few years various oral drug combinations have been tried and are available in Indian market for the treatment of typhoid fever.

The present study was designed to evaluate the clinical efficacy, side effects and relapse rate of Azithromycin monotherapy in uncomplicated typhoid fever cases as compared to those who were treated with azithromycin and cefixime combination therapy in standard dosage.

Aims and objectives

The present study was for the following aims and objectives were

- To compare the therapeutic efficacy of Azithromycin monotherapy with that of combination therapy in treatment of uncomplicated typhoid fever.
- To find out side effects/toxicity of Azithromycin monotherapy and azithromycin and cefixime combination therapy.
- To find out the incidence of relapses in both the treatment groups during 4 weeks of post-treatment period.

METHODS

100 adult proven cases of typhoid fever of the age group of 16-65 years of either sex visiting OPD or admitted to Medical ward of Sri guru ram das institute of medical sciences and research, Amritsar, who did not took any antibiotic, were included in the study. The serological and bacteriological criteria taken to prove the typhoid fever are as indicated below,

- A positive blood culture for Salmonella Typhi
- When agglutination titre (Widal test) was 1/320 or more or
- When agglutination titre was 1/160 and showed a rise subsequently along with clinical picture suggestive of typhoid fever.

These patients were randomly divided into 2 groups of 50 patients each and then were followed up on and after treatment for 4 weeks.

Group I: Patients were given oral Azithromycin 500 mg twice daily for 7days.

Group II: Patients were given oral Azithromycin 500 mg twice daily with oral cefixime 200 mg twice daily for 7 days.

Prior written consent was taken from each patient in both study groups.

Exclusion criteria

- Patient having history of hypersensitivity to either drug (cefixime/azithromycin)
- Patients refusing consent
- Complicated typhoid fever (gastrointestinal bleeding/perforation or typhoid encephalopathy)
- Patients already on antibiotics
- Pregnant females

RESULTS

In the present study 100 patients of typhoid fever were included out of which 65 were male and 35 were females. Both the study groups were comparable in terms of age (Mean age of 31.2 years for group I versus 32.7 years for group II) and sex distribution(Male : Female ratio of 1.9 for group I versus 1.8 for group II) (Table 1). Both study groups were compared in terms of response rate, fever clearance time, relapse rate and clinical significant side effects/toxicity.

Table 1: Age and sex incidence in the two groups.

Age groups	Group I (n=50)				Group II (n=50)			
	Male	%	Female	%	Male	%	Female	%
16-25	15	30	8	16	8	16	5	10
26-35	11	22	4	8	12	24	4	8
36-45	3	6	3	6	8	16	6	12
46-55	3	6	2	4	3	6	2	4
56-65	1	2	-		1	2	1	2
Total	33	66	17	34	32	64	18	36

Mean age for group I: 31.2 years; Mean age for group II: 32.7 years.

Clinical cure

Patient was considered to be clinically cured if patients become afebrile and asymptomatic with 7 days of antibiotic therapy and shows no signs of relapse during 4 weeks follow up period

Group I – 49 out of 50 patients were clinically cured without any relapse.

Group II – 49 out of 50 patients were clinically cured without any relapse.

So, cure rate of 98% was found in both study groups. Both study groups have been found to be similar in terms of clinical cure (Table 2).

Table 2: Showing response to therapy in both groups.

	Total cases	Good response*	Moderate response**	Poor response***	No response	Relapse
Group I	50	24	23	2	1	-
Group II	50	26	21	2	1	-

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

Relapse

No relapse was found in both study group during four weeks follow up period (Table 2).

Fever clearance time

Fever clearance time varied from 2-7 days in group I with mean fever clearance time of 3.72±0.86 days. Fever clearance time in group II varied from 2-6 days with mean fever clearance time of 3.69±0.83 days. No statistically significant difference was found in fever clearance time in two study groups. So both study groups were found comparable in terms of mean fever clearance time (Table 3).

Table 3: Mean fever clearance time in two groups.

Groups	Mean fever clearance time±SD
Group I	3.72±0.86 days
Group II	3.69±0.83 days

Adverse effects

No serious side effect was noted in any patient in both study groups. A single patient showed mild nausea in group II, which was not serious enough to withhold the treatment and was managed well with conservative treatment. During treatment as well as follow up no serious complication related to typhoid fever developed in any patient of both groups.

DISCUSSION

Typhoid fever is a highly prevalent infection in Indian subcontinent. Due to multidrug resistant (MDR) strains in these geographical areas, the third generation cephaloporins are increasingly becomingly the drug of choice but these class of drugs suffer from poor cellular penetrance leading to poor overall clinical outcome indicators seen as long fever clearance time. Alternate drug regime such as monotherapy azithromycin are also suggested.

Indian academy of pediatrics (IAP) recommends cefixime and, as a second line agent azithromycin, for uncomplicated typhoid fever. For complicated thyroid fever, they recommend ceftriaxone. Aztreonam and imipenum are second line agents for complicated cases. However in recent years it has been noted that susceptibility of salmonella species to chloramphenicol, trimitropoin-sulphomethoxazole (TMP-SMZ) and ampicillin in South Asia is rebounding as more as more MDR strains remain predominant in environment. Azithromycin of the azalides class of drugs has found to be better than erythromycin against gram negative bacteria. Its effectiveness in a setting of MDR environment vis-a-vis fluroquinolones and cephalosporins is quite comparable.

Similar clinical cure rates of 98% by both regimes with no case of relpse is similar to work conducted by both Girgis et al and Butter et al.[5,6] The observed mean fever clearance time of 3.72±0.86 vers 3.69±0.83 in our study for monotherapy versus combination therapy is quite comparable with fever clearance time ranges between 3.8- 5.6 days.[7-9]

CONCLUSION

In one study similar clinical cure rates with no side effects were achieved by both mono and combination therapy. However; only point of difference was a shorter fever clearance time by combination therapy which was not statistically significant. This leads us to hypothesis that both mono and combination therapy could be equally effective oral therapy for typhoid fever. More studies have to be conducted in our scenario to reach a conclusion.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Chandey M, Kaur R, Mohan G, Mannan R, Mahajan K. Comparative efficacy and safety of azithromycin monotherapy and azithromycin+cefixime combination therapy in uncomplicated typhoid fever. Int J Adv Med 2016;3:764-7.