ORIGINAL ARTICLE

CLINICAL EFFECTIVENESS OF AZITHROMYCIN VERSUS CIPROFLOXACIN IN THE TREATMENT OF UNCOMPLICATED ENTERIC FEVER IN CHILDREN; A COMPARATIVE STUDY CONDUCTED IN A TERTIARY CARE HOSPITAL OF PESHAWAR

Iqbal Hussain[1], Muhammad Saleh Faisal[2], Arshad Khan[3], Arif Jamal[1], Waqar Hayat[4]

[1]Health Dapartment, khyber Pakhtunkhwa - Pakistan

[2]Department of Pharmacology, Khyber Medical College, Peshawar - Pakistan

[3]Department of Pediatrics, Khyber Teaching Hospital, Peshawar - Pakistan

[4]Department of Rheumatology, Lady Reading Hospital, Peshawar - Pakistan

ABSTRACT

Objective: To compare the clinical effectiveness of oral azithromycin with oral ciprofloxacin in the treatment of uncomplicated enteric fever in children.

Material and Methods: A Quasi experimental study was carried out in the Pediatric department of Khyber Teaching Hospital for which a sample size of 282 patients was determined using WHO calculator with 5% level of significance and 80% power of test (Two sided). Children of both genders and age between 6 to 18 years were included in the study using simple random sampling. Eligible patients were randomly divided in two equal groups of 141 subjects where Group A was treated with oral azithromycin while Group B with oral ciprofloxacin for 7 days and difference in clinical cure between two groups were determined.

Results: A total of 282 patients were observed where majority were in age group of 13-18 years with male predominance. In azithromycin treated group, 128 (90.78%) while in ciprofloxacin treated group, 105 (74.46%) children were cured. Both groups responded to the study drugs having mean defervescence time of 4.5 ± 1.3 days and 3.8 ± 1.6 days with azithromycin and ciprofloxacin therapy, respectively.

Conclusion: Oral azithromycin is more effective than oral ciprofloxacin in the treatment of typhoid fever in children.

Keywords: Azithromycin, Ciprofloxacin, Enteric Fever

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INTRODUCTION

Enteric fever, caused by Salmonella typhi and para-typhi is a common and sometimes fatal infectious disease. It is mostly observed in the developing countries due to poor sanitation and its feco-oral route of transmission. An estimated 17 million cases of typhoid and paratyphoid fever occurred globally in 2015, mostly in South Asian countries. Left untreated, it may be fatal with estimated 178,000 deaths worldwide in 2015.[1]

Correspondence
Dr. Muhammad Saleh Faisal
Department of Pharmacology, Khyber Medical College, Peshawar - Pakistan
Email: drsalehfaisal@gmail.com
Cell: +92-347-5244271
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In addition to preventive strategies that target the risk factors, interventions focusing on timely diagnosis and appropriate clinical management can improve the outcomes of enteric fever. For decades, ampicillin, chloramphenicol and co-trimoxazole were the drugs of choice for enteric fever but the emergence of multi drug resistant strains of S. typhi and para typhi restricted their use. Later, fluoroquinolones turned out to be good alternative. However, 15-36% resistance to fluoroquinolones was reported from several parts of the world by 2011.[2] Currently, recommend therapy for enteric fever includes extended spectrum cephalosporins (ceftriaxone, cefixime) and azithromycin.[2-5] In cases of treatment failure to single therapy, combination of these drugs is needed to broaden the antimicrobial spectrum through potential drug synergism.[6] Several trials have demonstrated azithromycin efficacy better with reduction of relapse, duration of hospital

stay, clinical failure rate and well tolerated than many other competitive drugs.[7-9]

In our region, though azithromycin and ciprofloxacin are amongst most commonly prescribed oral antibiotics in uncomplicated enteric fever as an empirical therapy but concerns persist regarding variations in response to treatment which is evident from a huge study carried out in Bangladesh.[10] Recently, many cases have been reported in Pakistan regarding extensively drug resistant strains of Salmonella typhi, responsible for a large typhoid outbreak.[11] In addition to resistance, azithromycin and quinolones are reported to be associated with variable fever clearance time (FCT) averaging 4-5 days, resulting in sub-optimal treatment response, increased morbidity, treatment cost and healthcare burden.[12-15]

Due to this ever changing pattern of microbial resistance and variable drug responses, the choice of oral anti-microbial regimen for uncomplicated typhoid fever is unclear. To our knowledge, currently there is no data available regarding comparative efficacy between azithromycin and ciprofloxacin in terms of fever clearance time in our local population of children with uncomplicated enteric fever, so this study was an attempt to explore it.

MATERIAL AND METHODS

A Quasi experimental study was carried out at the Pediatric department of Khyber Teaching Hospital, Peshawar from February to October, 2016 after taking ethical approval from the committee. A sample size of 282 patients was calculated using WHO calculator, based on 77.78% efficacy of ciprofloxacin, 90% efficacy of azithromycin, 5% level of significance and 80% power of test (Two sided). Patients of both genders and age 6-18 years presented to OPD and/or admitted to pediatric unit were included in the study by simple random sampling. The diagnostic criteria for enteric fever was high grade continuous fever of ≥38°C for ≥5 days without a focus of infection plus physical examination to determine at least two of the following signs: abdominal tenderness, splenomegaly, hepatomegaly, rose spots and coated tongue plus laboratory tests like CBC and blood/stool culture for Salmonella typhi.[16,17]

Patients who were unable to swallow oral medication, allergic to study drugs, treated with study drugs or co-trimoxazole and ampicillin within last 48 hours, presented with major complications of enteric fever or other comorbidities like heart disease, asthma, or immune-deficiencies were excluded from the study.

After written informed consent from parents/guardians, patients fulfilling the inclusion criteria were randomly divided in two equal groups of 141 subjects. Group A was treated with oral azithromycin (10 mg/kg/day to maximum 500 mg/day) once daily while Group B was treated with oral Ciprofloxacin (15 mg/kg/day) twice daily for 7 days.

The patient's temperature was monitored three times a day from the day of admission till discharge and response to treatment was assessed strictly on clinical parameters i.e. fever defervescence (patient become afebrile and remain so for more than 48 hours without taking antipyretics) and resolution of associated signs and symptoms. A clinical treatment failure was defined as the persistence of fever and associated signs and symptoms for more than 5 days after the end of treatment or the development of severe complications during treatment, requiring an alternative therapy. Patients who became clinically cured were called for follow up visit one month after discharge (or earlier if signs and symptoms reappear) to identify the incidence of clinical relapses. Data was documented in a pre-designed proforma.

Data was analyzed in SPSS version 20. Percentages and Frequencies were calculated for qualitative variables like gender and patients showing clinical response. Mean ± SD was calculated for quantitative variables like age. Post stratification Chi Square test was applied among different groups and P value less than 0.05 was considered significant.

RESULTS

Two-eighty two patients ranging from 6 to 18 years were enrolled in the study and randomly assigned to one of the two treatment groups to compare the efficacy of ciprofloxacin and azithromycin in uncomplicated typhoid fever and results were analyzed. Distribution of age and gender is mentioned in Figure 1, displaying the male predominance in both the study groups (205 males versus 77 females). The mean age of subjects was 12.48 ± 3.48 years while 12.42 ± 3.48 years in azithromycin group and ciprofloxacin group, respectively.

Among clinical markers of Typhoid fever, a history of continuous fever ranging from 3-20 days with mean duration of 9.8 ± 4.1 days was found in all of the subjects. At the time of presentation, 102 (36%) patients had hepatomegaly, 35 (12.4%) had splenomegaly and 87 (31%) had abdominal pain or distension. Among associated symptoms, most common was diarrhea i.e. 118 (41.8%) followed by nausea and vomiting 94 (33.4%).

Figure 2 depicts the efficacy of study drugs where 128 (90.78%) patients in azithromycin group while 105 (74.46%) patients in ciprofloxacin group met the criteria of clinical cure within 7 days having a significant statistical difference between the results of two groups (p value=0.0003). Patients in both groups responded quickly to therapy with mean defervescence time of 4.5 ± 1.3 days and 3.8 ± 1.6 days with azithromycin and ciprofloxacin, respectively. For post treatment follow up, 101/128 subjects in azithromycin treated group and 56/105 subjects in ciprofloxacin treated group visited hospital. All the subjects were clinically well with no incidence of relapse in either

group. The response of study drugs was also analyzed at different age groups and genders where azithromycin was found significantly effective than ciprofloxacin in both age groups i.e. 6-12 years and 13-18 years with p value 0.020 and 0.005, respectively. Similarly, azithromycin was more effective than ciprofloxacin in males (p value=0.001) but no significant difference was observed between the response of study drugs in female gender with p value 0.401. (Table 1)

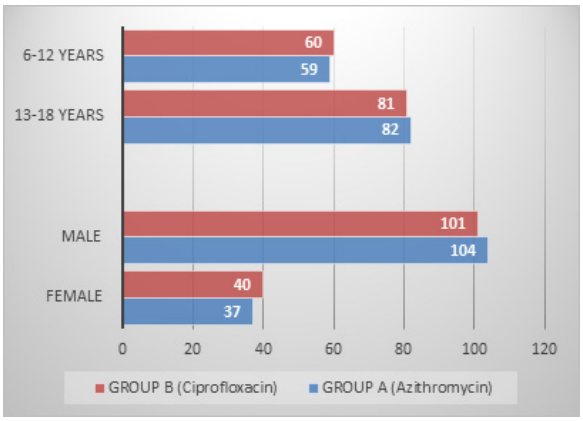

Fig 1: Distribution of Age and Gender

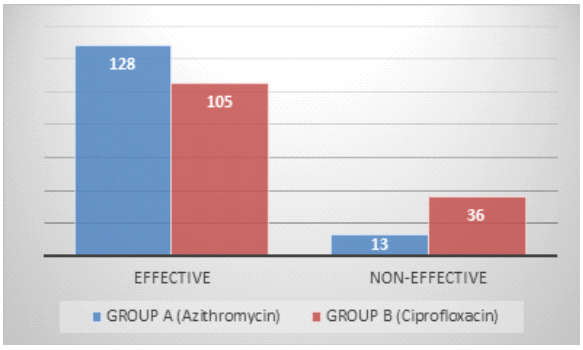

Fig 2: Comparative Efficacy of Azithromycin versus Ciprofloxacin

DISCUSSION

Enteric fever is a significant health problem in the developing countries like Pakistan and need treatment option which is not only efficacious but also cost effective to be used readily in our limited available resources. This comparative study between azithromycin and ciprofloxacin for uncomplicated enteric fever in children displayed high responsiveness of azithromycin with clinical efficacy more than 90%, resembling the results of many studies done previously.[8,18,19]

Few studies reported the efficacy of azithromycin therapy in adults but not significant enough in children, contrary to our results where majority responded well to azithromycin.[20,21]

The optimal dosing regimen of azithromycin for the treatment of enteric fever is yet to be determined. Like in this study, most studies used a regimen of 10-20 mg/kg/day for 5 to 7 days.[22] Some trials have used a loading dose of 1 gram azithromycin at day 1 followed by 6 days of treatment with 500 mg/day. But significant differences in fever clearance time was not observed when it was compared with quinolones treatment.[23]

In this study, clinical cure of 90.78% and 74.46% was achieved by day 7 in the azithromycin and ciprofloxacin group, respectively. This high responsiveness of azithromycin could be due to its remarkable intracellular penetration causing effective therapeutic activity against predominantly intracellular S. typhi. On the other hand, the non-responsiveness in the remaining patients of same group could be explained by the fact that approximately one-third of S. Typhi in the blood of patients are extracellular. As a consequence, the organisms may be exposed to inadequate drug concentrations resulting in prolonged fever clearance time due to slow clearance of bacteremia.[21] Moreover, emergence of resistant strains, genetic mutations in genes like msr A, msr D, ere A[24] or a recently

Table 1: Stratification of Efficacy with Age & Gender Distribution

Age		Group A	Group B	P value
6-12 year	Effective	53	44	0.020
	Not Effective	06	16	
Total		59	60	
13-18 years	Effective	75	61	0.005
	Not Effective	07	20	
Total		82	81	
Age		Group A	Group B	P value
Male	Effective	96	72	0.001
	Not Effective	08	29	
Total		104	101	
Female	Effective	33	33	0.401
	Not Effective	04	07	
Total		37	40	

discovered mutation in an efflux pump encoding gene acr B may also contribute to this non-responsiveness.[25]

Though, the clinical cure rate of azithromycin treated patients was higher than ciprofloxacin in our study but patients treated with ciprofloxacin showed a slightly shorter mean time to defervescence than did patients treated with azithromycin (difference was statistically insignificant with P value >0.05). The reason could be that while azithromycin appears to target only the intracellular bacteria when used at standard clinical doses, ciprofloxacin may simultaneously target both intracellular and extracellular populations.

We have also attempted to evaluate the clinical relapses of typhoid fever through scheduled follow-up visits. The absence of relapse in either study group is similar to the results reported previously.[21] This could be due to long half-lives of these drugs in addition to high intracellular concentrations.

Having said that, azithromycin seems to be a better alternative than ciprofloxacin due to its cost and clinical effectiveness and also better safety profile i.e. well established association of quinolones usage with damage to cartilage and growing bones in children.

One of the major limitations of the study was non-randomized experimental design. Randomized control trial involving large sample size is recommended to achieve evidence base results of higher level for a definite conclusion. Secondly, fever defervescence along with resolution of associated signs and symptoms was taken as criteria for clinical cure in this study. However, drug efficacy can be evaluated more accurately by determining the bacteriological cure in addition to clinical cure by performing sequential blood and stool cultures.

CONCLUSION

It is concluded that oral azithromycin in a dose of 10mg/kg/day to maximum 500mg/day, once daily for 7 days appears to have clinical efficacy more than oral ciprofloxacin in the treatment of uncomplicated enteric fever in children.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Hussain I:	Data collection
Khan A:	Data collection
Jamal A:	Statistical analysis, Critical review & Bibliography
Hayat W:	Statistical analysis, Critical review & Bibliography
Faisal MS:	Manuscript writing

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.