UNCOMPLICATED TYPHOID FEVER;
COMPARISON OF AZITHROMYCIN AND CIPROFLOXACIN IN THE TREATMENT

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ABSTRACRT… Objectives: Objectives of this study were To compare the clinical and bacteriological cure rates of azithromycin and ciprofloxacin in the treatment of uncomplicated typhoid fever and To determine any difference in the clinical and bacteriological cure rates within the two groups of study. **Study Design:** Quasi experimental study. **Setting:** Department of Medicine, DHQ/ Teaching Hospital Dera Ghazi Khan. **Period:** April 2016 to September 2016. **Patients and Methods:** A total of 60 patients including both males and females over 18 years of age were included in the study by Simple random probability sampling. Patients fulfilling the inclusion criteria were divided in two equal groups of 30 by using the random numbers table. First group was treated with azithromycin one gram on day one and then 500 mg daily for next six days. Second group was treated with ciprofloxacin 500mg twice daily for ten days. All the data was analyzed by the computer programme SPSS. Frequency, percentages, mean values and standard deviations were calculated for age, sex, symptoms, signs, culture reports, clinical cure rates and bacteriological cure rates. **Results:** Most common clinical feature was fever noted in 100% patients followed by headache (86.6%) and nausea / vomiting (76.6%). Out of 60, 52 (86.6%) patients were culture positive. In Azithromycin group clinical and bacteriological responses were achieved in 93.3% and 92.3% respectively while in ciprofloxacin group they were 96.6% and 96.15% respectively. There was no significant statistical difference between the clinical and bacteriological cure rates among two groups. **Conclusion:** Both ciprofloxacin and azithromycin are equally effective in the treatment of uncomplicated typhoid fever.

Key words: Typhoid Fever, Azithromycin, Ciprofloxacin, Clinical Cure, Bacteriological Cure, Clinical Failure, Bacteriological Failure, Resistance.

INTRODUCTION

Typhoid fever can be defined as a systemic disease characterized by fever and gastrointestinal manifestations caused by dissemination of Salmonella typhi.[1] Typhoid fever is a global health problem. Sypmtoms of typhoid fever include fever ascending in stepwise fashion, malaise, headache abdominal pain, constipation, abdominal distension and other constitutional symptoms. Physical findings are raised temperature, relative bradycardia, spleenomegaly, hepatomegaly, abdominal tenderness, meningism and in some patients rose spots. Major complications include intestinal hemorrhage, intestinal perforation, urinary retention, pneumonia, thrombophlebitis, myocarditis, cholecystitis, nephritis, myocarditis, osteomyelitis and meningitis. Diagnosis of typhoid fever is mostly clinical however several laboratory tests like leucopenia, typhidot test, widal test, blood, stool or bone marrow culture do help in confirmation in suspected cases. Widespread emergence of multidrug resistant strains of Salmonella typhi has necessitated the search for other therapeutic options.[2] Flouroquinolones have proved to be effective, but quinolone resistant strains of Salmonella have been reported.[3] Azithromycin has better activity against gram negative bacteria including Salmonella typhi.[4] In an open randomized trial in Egypt, it was concluded that azithromycin and ciprofloxacin were equally effective, both clinically and bacterilogically, against typhoid fever caused by both sensitive and multi drug resistant strains of Salmonella typhi.[5] This prompted the current study of azithromycin versus typhoid fever in the treatment of uncomplicated typhoid fever at DHQ

/ Teaching Hospital Dera Ghazi Khan.

MATERIALS AND METHODS

It was a Quasi Experimental Study conducted at department of Medicine, DHQ/ Teaching Hospital Dera Ghazi Khan from April 2016 to September 2016. A total of 60 patients including both males and females over 18 years of age were included in the study by Simple random probability sampling. For patients presenting within first week of onset of fever the inclusion criteria were any two out of following three:
1. Documented continuous fever of > 38 °C
2. Positive typhoid test
3. Positive blood culture for Salmonella typhi.

For patients presenting in the second week of onset of fever the inclusion criteria were any two out of following three:
1. Strong clinical suspicion based on features like documented continuous fever of more than 38°C, abdominal pain, spleenomegaly and rose spots.
2. Positive Widal T:O titres of equal to or more than 1:160
3. Positive stool culture for Salmonella.

Exclusion criteria included pregnancy, lactation, allergy to ciprofloxacin or azithromycin, presence of any major complication of typhoid fever, inability to swallow oral medications, presence of focal signs likely to explain other causes of fever and treatment within last four days with an antibiotic potentially active against Salmonella typhi. Informed consent was obtained before including patients in the study. Patients fulfilling the inclusion criteria were divided in two equal groups of 30 by using the random numbers table. First group was labeled as Azithromycin group and was treated with azithromycin one gram on day one and then 500 mg daily for next six days. Second group was labeled as Ciprofloxacin group and was treated with ciprofloxacin 500mg twice daily for ten days. All the patients were assessed by detailed clinical history and physical examination. Specific investigations like widal test or typhidot test, blood or stool culture were also sent depending upon the duration of fever before the start of treatment. Temperature was recorded four times a day and a daily physical examination was performed to detect any improvement or development of a complication for ten days. Blood or stool cultures were repeated at day ten of therapy in culture positive cases. In our study clinical cure was defined as resolution of fever and other presenting symptoms by the end of seven days of therapy and clinical failures was defined as the lack of resolution of fever and other presenting symptoms by the end of seven days of therapy or development of a major complication of typhoid fever after the start of therapy. Bacteriological cure was defined as a negative blood or stool culture at day 10 of therapy and Bacteriological failure was defined as a positive blood or stool culture at day 10 of therapy. Findings about age, sex, clinical features, laboratory results, clinical cure or failure and bacteriological cure or failure were recorded in a predesigned Performa. Main variables which were measured included age and sex distribution, clinical cure (achieved or not), bacteriological cure (achieved or not) and any differences in the clinical and bacteriological cure rates among two groups. All the data was entered into and analyzed by the computer programme SPSS. Frequency, percentages, mean values and standard deviations were calculated for age, sex, symptoms, signs and culture reports. Chi-square test was applied to compare the results of two groups. A p value of less than 0.05 was considered significant.

RESULTS

Out of 60 patients 39 (65%) were males and 21(35%) were females. No patient expired or was excluded from the study. All the patients had good follow-up till the recommended period. Mean age was 22.10(+/- S.D 7.2) years (Table-I). All 60 patients were febrile at the time of presentation and both groups were comparable as for as the mean duration of fever is concerned. Headache was the second most frequent symptom, in 52 (86.6%) patients, followed by nausea or vomiting which were present in 46 (76.6%) patients. In the physical signs, fever of variable degrees was recorded in all 60 patients. Relative bradycardia was present in only 32 (53.3%) patients. Other frequent findings on physical examination were spleenomegaly in 28(46.6%) patients and

hepatomegaly in 16 (26.6%) patients. Table-II and III give the detailed statistics about the symptoms and signs of the patients included in study.

There were 35(58.3%) patients who presented in first week of onset of fever. Typhidot test was done in all of them it turned to be positive in 34 patients. 35(58.3%) patients presented within the first week of development of fever. Out of sixty, 25 (41.6%) patients presented in second week of fever, Widal test was done in all of them and it turned to be positive in 23 cases. Blood culture was sent 35 patients and it yielded Salmonella typhi in 30 patients. Stool culture was sent in 25 patients and it turned to be positive in 22 patients. So, in total 52 (86.6%) patents were culture positive.

Patients in both the ciprofloxacin and Azithromycin groups responded quickly to the therapy with the mean times to deffervescence of 3.3 and 3.8 days with ciprofloxacin and Azithromycin respectively. In azithromycin group, 28 (93.3%) out of 30 patients recovered fully within seven days and met the criteria of clinical cure in seven days. Only 02 (6.7%) patients did not respond in seven days but were afebrile on day 11 of therapy. None of these patients developed any major complication of typhoid fever. In ciprofloxacin group, 29 (96.6%) out of 30 patients recovered within seven days and fulfilled the criteria of clinical cure on day seven. Only 01 (3.4%) patient in this group was febrile at day 07 and was later treated successfully with ceftriaxone. Therefore, in total 57 (95%) patients achieved the desired clinical cure, while only 3 (5%) did not respond within the expected time period. P value was highly significant (<0.05) when results about clinical cure or failure within one group were analyzed. It suggested that both drugs are effective in treating typhoid fever. But the P value was statistically insignificant (>0.05) when the results about the clinical response of the two groups were compared by applying chi-square test suggesting that there is no significant statistical difference in the response of two drugs.

Out of 60, 52 (86.6%) patients were culture (either blood or stool) positive. Each group had 26 culture positive patients. In azithromycin group, bacteriological response was achieved in 24 (92.3%) patients and the organism disappeared from the blood or stool on day 10 of therapy. In ciprofloxacin group, bacteriological response was achieved in 25 (96.15%) patients and the organism disappeared on day. The results of the two groups were compared by applying chi-square test. There was no significant statistical difference (p value > 0.05) in the bacteriological response of the two drugs. However, in both groups, results about achievement or failure of bacteriological response were highly significant within the same group. This suggests that both drugs are equally effective in clearing Salmonella typhi from the body.

Group	Age (years)			Sex	
	Range	Mean	S.D	Male n (%)	Female n (%)
Azithro-mycin	15-50	21.12	6.6	18 (60%)	12 (40%)
Cipro-floxacin	15-50	23.12	7.7	21(70%)	09(30%)
Total	15-50	22.10	7.2	39(65%)	21(35%)

Table-I. Age and sex distribution (n=60)

Symptom	No of patients (n)	Percentage
Fever	60	100%
Headache	52	86.6%
Nausea/vomiting	46	76.6%
Insomnia	24	40%
Diarrhea	22	36.6%
Constipation	21	35%
Cough	20	33.3%
Dizziness	14	23.3%
Confusion	04	6.6 %

Table-II. Frequency of symptoms (n=60)

Signs	No of patients (n)	Percentage
Relative bradycardia	32	53.3 %
Spleenomegaly	28	46.6%
Hepatomegaly	16	26.6 %
Jaundice	05	8.3 %
Rose spots	03	5 %

Table-III. Frequency of signs (n=60)

Group	Responded n (%)	Not Responded n (%)	Re-marks
Azihromycin	28 (93.3%)	02 (6.6%)	P<0.05
Ciprofloxacin	29 (96.6%)	01 (3.4%)	P<0.05
Total	57 (95%)	03 (5%)	P<0.05
Table-IV. Clinical response (n=60) P>0.05			

Group	Responded n (%)	Not Responded n (%)	Remarks
Azihromycin (n = 26)	24 (92.3%)	02 (7.7%)	P<0.05
Ciprofloxacin (n = 26)	25 (96.15%)	01 (3.85%)	P<0.05
Total (n = 52)	49 (94.23%)	03 (5.77%)	P<0.05
Table-V. Bacteriological response: (n=60) P>0.05			

DISCUSSION

As the name implies typhoid fever is characterized by fever associated with constitutional symptoms most commonly the abdominal symptoms. Fever was noted in all 60 (100%) patients in our study and similar data was obtained in the study conducted at Abbottabad in 2002.[6] However the pattern of fever remains variable and the so called step ladder pattern is not common. Headache was noted in 52 (86.6%) patients, while it was found in 100% of patients in the study conducted in Abbotabad.[6] It suggests that headache is the commonest symptom of typhoid along with fever. Diarrhea and constipation were noted in 36.6% and 35% of patients respectively in our study and in above mentioned study they were present in 26 % and 20% patients only.

Relative bradycardia was detected in only 53.3% of patients, comparable to similar results in other studies. It suggests that relative bradycardia is expected to be present in only half of patients with typhoid fever and it is also not specific to this disease. Similarly spleenomegaly was noted in 46.6% of patients only. Rose spots were present in only 5% patients. Exactly same percentage was found in the study conducted at Abbotabad.[6] This may support the fact that rose sports are very uncommon and can be seen more easily on the skin of fair coloured people as compared to patients with relatively darker complexion. Widal test was performed in 25 patients who presented in the first week of onset of fever and it turned to be positive in 23 (92%) patients. In India O agglutination titre of 1: 160 had a specificity of 97% and sensitivity of 70%.[7] As the conditions in developing countries are comparable especially in India and Pakistan, a single Widal test with TO titre of equal to ore more than 1: 160 was used for the diagnosis of typhoid fever. Our results support the highly positive results of Widal test in the diagnosis of typhoid fever. Despite a number of limitations, this test may be useful, particularly in areas that can not afford the more expensive diagnostic methods. However, it should be remembered that significant results of Widal test can only be commented after the six days of onset of fever. Typhidot test was done in 35 patients who presented in the first week of the onset of fever and it turned to be positive in 34 (97%) patients. In an article published by World Health Organization in 2006.[8] 75% specificity and 95% sensitivity has been described for the Typhidot test. This test is becoming widely available in Pakistan and results of our and other international studies suggest that it can be used as simple, early, speedy and economical method for the diagnosis of typhoid fever.[9]

Blood culture was positive in 30 (85.7%) patients out of 35 presenting in the first week of fever. Stool culture was positive in 22 (88%) out of 25 patients presenting in the second week of onset of fever. The ratio of patients with positive cultures yielded in our study was quite high. These results are very different form other studies done in Pakistan. In a study done at Karachi in 1994, positive culture was obtained in only 26 (46.6%) out of 64 patients.[10] In Bangladesh, a trial showed only 60% yield. In the trial conducted in Egypt culture was positive in 100% cases. The prior use of antibiotics on self prescription basis is rampant in Pakistan and other third world countries. This may be the explanation of lower yield ratios. In our study, the exclusion criteria of prior use of antibiotics potentially effective against Salmonella typhi might have resulted in high yield. It should be remembered that a positive culture is still

recommended as a 'gold standard" for the diagnosis of typhoid fever.

In ciprofloxacin group, clinical response was achieved in 96.6% and bacteriological response was achieved in 95.15% of patients. This indicated that despite the strong suspicion that resistance has emerged to ciprofloxacin because of injudicious use of the drug in this part of world, it still remains an effective drug against Salmonella infection. In an experimental trial conducted in 1999 Egypt a clinical and bacteriological response rate of 100% were achieved with ciprofloxacin.[5] According to World Health Organization guidelines, ciprofloxacin and other quinolones are still recommended as a first line therapy for the treatment of uncomplicated typhoid fever.

In azithromycin group clinical response was achieved in 93.3% and bacteriological response was achieved in 92.3% of patients. This indicated that azithromycin is quite effective drug in the treatment of uncomplicated typhoid fever. Similar results have been achieved in other international studies. In the above mentioned trial at Egypt, clinical response was obtained with azithromycin in 100% of patients.[5] In this study antibiotic sensitivity was also determined and all 64 isolates were susceptible to treatment with azithromycin. These azithromycin results compare favorably with those of other antimicrobial agents tested recently for typhoid fever including ceftriaxone, cefixime and other fluoroquinlones[11] and confirm the earlier finding that azithromycin is effective against the infection caused by Salmonella typhi.

Our results of this comparative randomized trial of azithromycin and ciprofloxacin for typhoid fever indicated that the two treatments were effective and comparable in that they gave clinical cures of majority of the patients within seven days and also produced bacteriological eradication of Salmonella typhi in them. Few differences between the two treatment groups were noted because both were successful without occurrence of complications during or after the treatment. The patients treated with ciprofloxacin showed a slightly shorter mean time to defervesence (3.3 days) than did patients treated with azithromycin (3.8 days), but this difference was statistically not significant.

CONCLUSION

Based on the results and discussion we concluded that both azithromycin and ciprofloxacin are almost equally effective in achieving the clinical response (93.3% Vs 96.6%) and clearance of Salmonella typhi form the body (92.3% Vs 96.15%) in uncomplicated cases of typhoid fever. However the place of azithromycin in the treatment of typhoid fever needs to be defined by further clinical studies in adults and children.
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