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RESEARCH ARTICLE

Novel considerations of antimicrobials

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ABSTRACT

Background: Various characteristics related to some microorganisms are important to deal with the therapeutics of many clinical illnesses. Antibiotics are important when used in infections caused by known a wide range of microorganisms. Their pharmacokinetic features are important to be noted by physicians. Regarding cephalosporins, the route of administration and combination of antibiotics are much more important to predict their effects. Age of patient is another consideration point regarding these drugs. We compared the clinical efficacy of ciprofloxacin versus ceftriaxone in terms of the proportion of children becoming afebrile in 96 h. It was a randomized, controlled design study. Place and Duration of Study: Department of Pediatrics, Holy Family Hospital, Rawalpindi, from March 2010 to September 2010. **Materials and Methods:** Eighty-eight children who fulfilled the clinical criteria of having typhoid fever were included in the study and were coming to the indoor and outdoor areas of the department. 44 patients were treated with injectable ciprofloxacin, and 44 were treated with injectable ceftriaxone. **Results:** The study included 88 patients with febrile illnesses suspected of having typhoid fever. The mean age was 8.3 ± 1.94 years, and 41 (46.6%) were males. The mean weight was 24.7 ± 6.3 kg. Only 15 (17%) used boiled water as a routine. 68 (77.3%) children in total became afebrile within 96 h, and 20 (22.7%) failed to become afebrile in 96 h. In the ciprofloxacin group, 25 (56.8%) patients became afebrile in 96 h, and 19 (43.1%) failed to become afebrile in 96 h. In the ceftriaxone group, 43 (97.7%) patients became afebrile in 96 h, and 1 (2.3%) failed to become afebrile in 96 h. The proportion of patients becoming afebrile within 96 h was significantly higher in the ceftriaxone group as compared to ciprofloxacin group (P = 0.00). **Conclusion:** It may be concluded that some antibiotics are important to study for alternative drugs related to their kinetic properties, like ceftriaxone.

Keywords: KW: cephalosporins, pharmacokinetics, typhoid fever, drug resistance

INTRODUCTION

The microbiology of some microorganisms is important to study because their resistance and sensitivity may challenge the therapeutic goal of treating a specific disease. Typhoid fever, a communicable disease caused by the bacteria *Salmonella* typhoid, has been a cause of significant morbidity and mortality since antiquity. Salmonellae are important gram-negative bacilli that cause a spectrum of characteristic clinical syndromes, including gastroenteritis, enteric fever, bacteremia, endovascular infections, and focal infections such as osteomyelitis or abscesses. Enteric fever, also called typhoid fever or paratyphoid fever, is a systemic febrile illness that is most commonly caused by *Salmonella* typhi; less frequent causes are Salmonella paratyphi A, *S.* Typhi B, and *S.* Paratyphi C. Even

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"nontyphoidal" Salmonellae may cause severe illness consistent with enteric fever. Complications are more common in untreated individuals and include intestinal hemorrhage and perforation or focal infections such as visceral abscesses.[1] In the pre-antibiotic era, approximately 15% of afflicted individuals died, with survivors experiencing a prolonged illness lasting weeks and debilitation often lasting months. Approximately 10% of untreated individuals relapse, and 1–4% become chronic carriers of the organism. Pakistan has the third highest incidence rate of typhoid occurring in the general population worldwide.[2] Typhoid fever is a common presentation in pediatric clinics. In the western world, the disease is close to eradication levels; however, globally, it affects at least 13–17 million cases, resulting in 600,000 deaths.[3] Typhoid fever represents the 4th most common cause of death in Pakistan.[4] It is transmitted by the fecal oral root and by contamination of food and water. The World Health Organization (WHO) identifies typhoid as a serious public health problem. Its incidence is highest in children and young adults between the ages of 5 and 19. WHO showed the incidence of typhoid fever in Pakistani children aged 2–5 years was 573.2/100,000 persons/year,[5] and a similar incidence was seen in school-going children and adolescents.[6] The highest burden of disease is in children aged 2–15 years. *S.* Typhi represents the commonest cause of bacteremia in this age group, and annual typhoid rates (confirmed by blood culture) in recent studies from India, Pakistan, and Indonesia range from 149 to as high as 573 cases/100,000 children. The definitive diagnosis of typhoid fever is made only on the isolation of *S.* Typhi from blood, stool, urine, bone marrow, etc., in the presence of characteristic clinical features. The case fatality ratio is 10% in the absence of treatment and <1% with antibiotics. Fluroquinolones, i.e., Ciprofloxacin, are recommended as first-line therapy for children and adults infected with sensitive as well as multidrug resistance. *S.* Typhi and Paratyphi[7] and third-generation cephalosporins, i.e., ceftriaxone, are also useful, but their use is reserved for complicated cases.[8] Multidrug resistance (resistance to chloramphenicol, ampicillin, and co-trimoxazole) sequentially increased from 34% in 1999 to 66% in 2005. In a prospective study in North India, there was a gradual development of resistance to fluoroquinolones over the course of 7 years. No resistance was observed to fluoroquinolones in 1999, while in 2005 4.4% resistance was observed to sparfloxacin, 8.8% resistance to ofloxacin and a high resistance, 13%, to ciprofloxacin.[9] Keeping in mind drug resistance in the community, it can be questioned that either of these drugs has a difference in efficacy in terms of sensitivity, resistance pattern, and relapse. We plan to conduct a study to find out the clinical response in children with typhoid fever treated with ciprofloxacin versus ceftriaxone. The results of the study will enable pediatricians to choose first-line therapy for the treatment of enteric fever in a similar setting.[9-13]

MATERIALS AND METHODS

Place of study

The study was conducted at the Pediatric Department, Holy Family Hospital, Rawalpindi. The study was conducted over 6 months, from March 25, 2010 to September 24, 2010.A total of 88 patients with a clinical diagnosis of typhoid fever were included in the study. Forty-four patients were treated with ciprofloxacin (Ciprofloxacin group), and 44 were treated with ceftriaxone (Ceftriaxone group).

Consecutive (non-probability) sampling technique. Children 5–12-years-old both sexes having typhoid fever, were included. All those with a current history of intake of oral or I/V antibiotics (third-generation cephalosporins and quinolones) and an absence of fever at the time of presentation were excluded. It was a randomized controlled trial study. Patients fulfilling the study criteria were admitted to the pediatric ward of Holy Family Hospital and were randomly divided into two groups, A and B, based on random numbers. Group A was given Inj. Ciprofloxacin 10 mg/kg I/V twice daily, and Group B was given Inj. Ceftriaxone 70 mg/kg I/V once daily for 7 days. Both groups were observed for the duration of becoming afebrile (96 h). The investigation to be done during the hospital stay

was typhidot (IgM antibodies) from the designated laboratory with the standard kit, and the results were verified by the consultant pathologist. Data were analyzed using the Statistical Package for the Social Sciences (V10). The mean and standard deviation were calculated for quantitative variables, i.e., age and duration of getting afebrile. Frequencies and percentages were calculated for qualitative variables i.e. gender, and getting afebrile in 96 h. The chi-square test was used to compare the efficacy (afebrile in 96 h) of both drugs. $P < 0.05$ was considered significant.

RESULTS

The study included 88 patients with febrile illnesses suspected of having typhoid fever on clinical grounds. Clinically, the patients had a fever >37°C in the presence of at least one or more of the following signs and symptoms: Persistent headache, abdominal pain or discomfort, presence of splenomegaly or hepatomegaly, rose spots on the skin, vomiting, and no evidence of chest bowel, urine, or meningeal infection. All subjects were <12 years of age. The age range was from 5 to 12 years, with a mean age of 8.3 ± 1.94 years [Figure 1]. 41 (46.6%) were males and 47 (53.4%) were females [Figure 2 and Table 1]. The weight of the children ranged from 14 to 41 kg, with a mean weight of 24.7 ± 6.3 kg [Figure 3]. 15 (17%) used boiled water as a routine, and 73 (83%) used unboiled water as a routine [Figure 4].

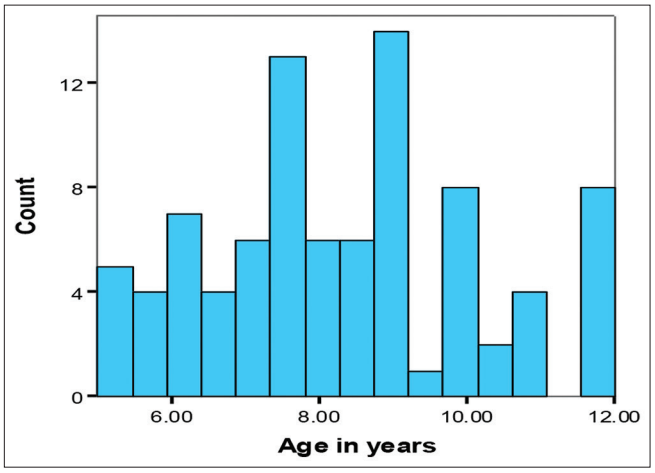

Figure 1: Histogram showing age distribution of study group

DISCUSSION

Enteric fever is a common illness in children and young adults. This magnifies the socio-economic impact of the disease on the community.[10] The industrialized and more prosperous countries

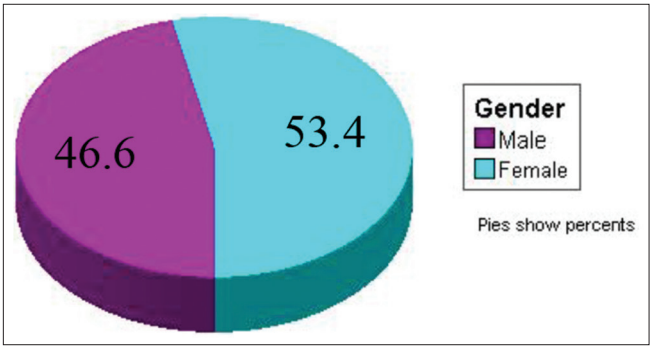

Figure 2: Pie graph showing gender distribution of study group

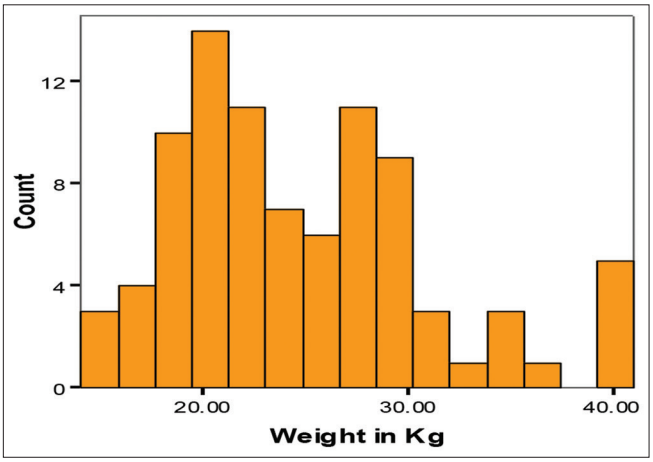

Figure 3: Histogram showing weight distribution of study group

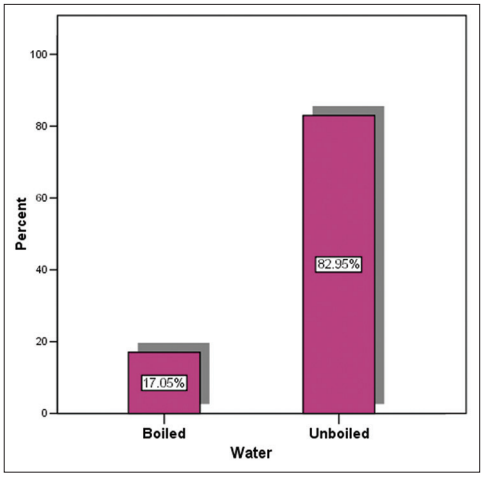

Figure 4: Water used boiled and non-boiled

have, to a great extent, controlled this illness by improving standards of public health, but the disease continues to be a major public health problem in less developed countries, including Pakistan.[11] The emergence of drug-resistant strains of *Salmonella* has made the treatment of enteric fever more difficult. The last two decades have also witnessed the appearance and spread of multidrug-resistant (MDR) strains of *S.* Typhi. Infection with these strains is associated with a longer duration of illness and higher morbidity and mortality.[12] It is occurring at a higher incidence throughout South Asia than previously thought, particularly in younger children.[13] Enteric fever is a significant problem in the preschool years.[14] Among children, 60% of cases are in the age group of 5 to 9 years, 27% in 2–5 years, and 13% in the age group 0–2 years. 208 after the emergence of chloramphenicol-resistant *S.* Typhi strains, ciprofloxacin has become the drug of choice for the treatment of typhoid fever, even in the pediatric age group [Table 2].

The present study was carried out to compare the clinical efficacy of ciprofloxacin versus ceftriaxone in terms of average time taken in the number of days for defervescence in the treatment of typhoid fever in children. The study included 88 patients with febrile illnesses suspected of having typhoid fever. The mean age was 8.3 ± 1.94 years, and 41 (46.6%) were males. The mean weight was 24.7 ± 6.3 kg. Only 15 (17%) used boiled water as a routine. 68 (77.3%) children in total became afebrile within 96 h, and 20 (22.7%) failed to become afebrile in 96 h. In the ciprofloxacin group, 25 (56.8%) patients became afebrile in 96 h, and 19 (43.1%) failed to become afebrile in 96 h. In the ceftriaxone group, 43 (97.7%) patients became afebrile in 96 h, and 1 (2.3%) failed to become afebrile in 96 h. The proportion of patients becoming afebrile within 96 h was significantly higher in the ceftriaxone group as compared to the ciprofloxacin group ($P = 0.00$).

Our results thus differ from those of a previous review, a summary of randomized controlled trials of enteric fever,[15] which found fluoroquinolones to be superior to ceftriaxone for clinical failure and fever clearance times. Although these data suggest that fluoroquinolones had significantly lower fever clearance times compared with chloramphenicol, cefixime, and ceftriaxone, the analyses of fever clearance times must be interpreted with caution. Mean fever clearance times often follow a skewed distribution—although most patients clear fever quickly, some take much longer times—so meta-analyses conducted using arithmetic means may not be accurate. The persistence of fever in some patients despite the apparent clearance of *S.* Typhi

Table 1: Gender distribution in study groups

Gender	Ciprofloxacin	Ceftriaxone
Male	24 (54.5%)	17 (38.6%)
Female	20 (45.5%)	27 (61.4%)

Table 2: Chi-square test comparing frequency of patients becoming afebrile in 96 h; ciprofloxacin versus ceftriaxone groups

Afebrile in 96 h	Antibiotic group		Total
	Ciprofloxacin	Ceftriaxone	
Yes 83%	25	43	68
No 17%	19	1	20
Total	44	44	88

Chi-square tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-square	20.965 (b)	1	0.000		
Continuity correction (a)	18.700	1	0.000		
Likelihood ratio	24.607	1	0.000		
Fisher's exact test				0.000	0.000
No. of valid cases	88				

a: Computed only for a 2×2 Table. b: 0 cells (0.0%) have expected count<5. The minimum expected count is 10.00

and *S.* Paratyphi from the bloodstream has been attributed to the continued production of pyrogenic cytokines.[16] This suggests that the time taken to clear a fever may not be an adequate measure of antibiotic efficacy and, consequently, may not be an appropriate end point in typhoid therapy trials. Some investigators also did not specify whether clinical failures were excluded or included in calculations of the mean fever clearance time. This may be due to the irrational use of quinolones even in minor infections most of which are infact viral fevers. This has resulted in an increasing resistance of *S.* Typhi to quinolones in our country.

Appropriate treatment for enteric fever is a clinical and public health challenge, with rising levels of drug resistance and limited evidence for the use of newer agents, particularly for children. Large, well-designed, and methodologically rigorous trials are needed to compare fluoroquinolones with first-line antibiotics in community or outpatient settings, reflecting practice in low-income countries, with accurate reporting of resistance data. Long-term follow-up and monitoring of adverse effects are also required. Investigators must standardize definitions and time points of measurements of outcomes, particularly those of a subjective nature, such as clinical failure. In addition to objective studies of treatment efficacy and cost effectiveness, we need evaluations of algorithmic approaches to the diagnosis and management of prolonged fever in children in regions where typhoid is endemic.[17] Such protocols will guide antibiotic use and may curb rising resistance. A study at the Divisions of Clinical Medicine and Microbiology, National Institute of Cholera and Enteric Diseases, Kolkata, India, evaluated the role of ceftriaxone therapy in bacteriologically confirmed MDR typhoid cases who did not respond to 12–14 days of ciprofloxacin therapy. Attempts have also been made to investigate the in vitro susceptibility of isolated *S.* Typhi strains to chloramphenicol, ciprofloxacin, and ceftriaxone. A total of 140 children, aged 3–10 years, clinically diagnosed as having typhoid fever, without any clinical response after 12–14 *day*s of ciprofloxacin therapy, were screened for *S.* Typhi by blood culture. In bacteriologically positive children, the treatment was changed to intravenous ceftriaxone for 14 days. The isolated strains of *S.* Typhi were tested for in vitro antimicrobial susceptibility. A clinical and bacteriological cure was observed with intravenous ceftriaxone therapy in all 32 bacteriologically positive patients. All isolated *S.* Typhi strains were uniformly (100%) susceptible to ciprofloxacin and ceftriaxone, but 50% of the strains were resistant to chloramphenicol. The MIC values of chloramphenicol, ciprofloxacin, and ceftriaxone ranged between 125 and 500, 0.0625–0.5, and < 0.0625 μg/mL, respectively. The study indicates that although the *S.* Typhi strains were susceptible to ciprofloxacin *in vitro*, the patients did not respond clinically or bacteriologically to ciprofloxacin therapy. Hence, ciprofloxacin may not represent a reliable and useful option for treating MDR typhoid fever; ceftriaxone may be an effective alternative for the treatment of such cases.[18]

Typhoid fever is widely prevalent in developing countries, with an annual burden of millions of cases globally. At Lady Reading Hospital, Peshawar, a study on drug resistance in enteric fever was carried out in the pediatric "A" unit. The inclusion criterion was positive blood and/or bone marrow culture. In total, 50 patients had a positive culture for Salmonella (blood in 26 patients and bone marrow in 49 patients). The organisms isolated were *S.* Typhi in 49 cases and *S.* Paratyphi A in one case. The single isolate of *S.* Paratyphi A was sensitive to all the antimicrobials tested except cotrimoxazole. Out of 49 isolates of *S.* Typhi, only 5 (10.2%) were sensitive to all the primary anti-typhoid antimicrobials, while 44 (89.8%) were resistant to multiple drugs. All of the isolates here are fully sensitive to ciprofloxacin and ofloxacin, while sensitivity to third-generation cephalosporins varied between 57% and 79%. In spite of *in vitro* resistance. 22 patients (44%) showed a good clinical response to amoxycillin and chloramphenicol. In the remaining 28 patients (56%), the response to the above drugs was poor, and they were started on ofloxacin (in children above 5 years of age) or third-generation cephalosporins. The response of the patients to these drugs was good, with defervescence within 8 days after the start of treatment. No significant untoward effects of quinolones were noted in these children. They concluded that quinolones can be

used in children above 5 years of age with MDR typhoid fever.[19] The rapid spread of MDR typhoid fever has posed a great challenge for the treatment of these cases the world over. After the emergence of chloramphenicol-resistant *S.* Typhi strains, ciprofloxacin has become the drug of choice for the treatment of typhoid fever, even in the pediatric age group. A study in Kolkata, India, evaluated the role of ceftriaxone therapy in bacteriologically confirmed MDR typhoid cases that did not respond to 12–14 days of ciprofloxacin therapy. They included 140 children aged 3–10 years. They found that ciprofloxacin might not represent a reliable and useful option for treating MDR typhoid fever; ceftriaxone may be an effective alternative for the treatment of such cases.[20]

CONCLUSION

It is concluded that pharmacokinetic features of ceftriaxone are predictable so this is much suitable in sensitive organisms.

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