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Original Article

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Clinical Effectiveness and Safety of Cefixime in Managing Typhoid Fever in Indian Population: A Real-world Evidence Study

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Abstract

Objective: To evaluate the effectiveness and safety of cefixime for managing typhoid fever among Indian patients. ***Design:*** Multicenter, single-arm retrospective study. ***Patients:*** Patients with typhoid fever who received cefixime as part of routine clinical practice. ***Methods:*** The study retrospectively assessed the data from January 2023 to April 2024. Patient demographics data and clinical evaluation was collected at baseline. At end-of-therapy (7±2 days) and follow-up period (14±2 days), assessment included clinical outcome, persisting symptoms, laboratory tests, and adverse event incidences. ***Results:*** Interim data of 6274 patients were retrospectively assessed. Most patients 4,446 (70.9%) presented with a single symptom, while 1761 (28.1%) patients presented with a combination of the symptoms. The WIDAL test at the initiation of the therapy reported 134 (2.14%) positive cases, reducing to 76 (1.21%) at 7±2 days and 28 (0.45%) at 14±2 days follow-up. The average duration of cefixime therapy was 8.21 (3.68) days, with a mean duration of hospital stay of 7.60 (3.84) days. A majority of patients demonstrated clinical cure (96.68%) at 7±2 days, which increased to 99.35% at 14±2 days. Incidence of adverse events was rare, with 6 (0.09%) and 4 (0.06%) documented cases at 7±2 days and 14±2 days, respectively. ***Conclusion:*** Cefixime demonstrated high effectiveness and a favourable safety profile among Indian patients with typhoid fever.

Keywords: ***Cefixime, Retrospective, Typhoid fever, Third generation cephalosporins***

Introduction

Typhoid fever, also known as enteric fever, is a bacterial infection caused by Salmonella typhi [1,2]. It is a significant public health concern, affecting approximately 7 million people in South Asia [3]. The contamination of water and food with excretions from individuals carrying Salmonella Typhi is a major source of transmitting typhoid fever. Typhoid fever is characterized by a prolonged fever lasting three to four weeks, often presenting with relative bradycardia, gastrointestinal symptoms, involvement of lymphoid tissues, and constitutional symptoms [4,5]. Certain severe complications may arise including intestinal perforation, hepatitis, gastrointestinal hemorrhage, encephalopathy, myocarditis, acute renal damage, cholecystitis, pneumonia, disseminated intravascular coagulation, and anemia [6,7].

Typhoid fever is more prevalent in resource-limited countries compared to their high-income counterparts. Within high-income countries, typhoid is largely eradicated due to advancements in sanitation and water treatment [8-10]. India has a disproportionate burden of typhoid fever, with approximately ten million typhoid fever patients reported in 2021, making India the country with the highest global incidence [11]. Compared to similar developing neighboring, India exhibits higher rates of disease, underscoring the urgent need for robust prevention and treatment strategies [12]. To manage typhoid fever, fluoroquinolones have been widely administered to South Asian patients over the past 20 years [13]. However, there has been an increase in the occurrence of resistance to these drugs on a global scale [14]. In India, multidrug-resistant (MDR) strains of Salmonella Typhi have been increasingly reported, with a recent study documenting an MDR prevalence of 7% among typhoid patients [15]. To overcome the challenge of bacterial strains showing antibiotic resistance, it is important to evaluate available and new drugs continuously.

Cefixime, an orally administered third-generation cephalosporin, is commonly used to treat typhoid fever in both pediatric and adult populations to inhibit Salmonella typhi growth [13,16]. Cefixime acts by attaching to certain penicillin-binding proteins, disrupting peptidoglycan synthesis and inhibiting cell wall formation, which ultimately results in bacterial cell death [17]. Cefixime has demonstrated clinical efficacy, with fever resolution occurring within 6 to 8 days [13]. The clinical success rate ranged between 73% to 94%, and microbial success was achieved in 94.5 to 100% of the typhoid patients receiving cefixime [13]. Therefore, cefixime offers a valuable and effective therapeutic option for managing typhoid fever.

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Despite the established efficacy of cefixime in patients with typhoid fever, there is limited real-world evidence of its clinical effectiveness and safety, particularly in India, where the burden of the disease is the highest. Most existing research is performed under controlled, international settings, which may not fully reflect the patient populations and demographics found in the diverse regions of India. Moreover, the increasing threat of antibiotic resistance and the reduced availability of effective treatments for typhoid fever underscore the urgent need for evaluating the real-world performance of antibiotics such as cefixime. The present retrospective, observational study investigates the clinical effectiveness and safety of cefixime for managing typhoid fever in real-world healthcare institutes in India.

Methods

Study design

A multicenter, single-arm, retrospective observational study was conducted based on real-world evidence obtained from medical records. The study included a mixed population diagnosed with typhoid fever who either visited outpatient departments (OPDs) or were admitted to inpatient departments (IPDs) at participating healthcare institutions. The study retrospectively assessed the data from patients receiving cefixime treatment from the period of January 2023 to April 2024.

Inclusion and exclusion criteria

Clinically confirmed typhoid cases, supported by laboratory confirmation such as positive culture for Salmonella Typhi and/or with clinical features, receiving treatment with cefixime either as monotherapy or in combination with other antibiotics, and for whom medical records are available for the start of therapy, end of therapy (7 ± 2 days) and follow-up (14 ± 2 days) (optional) were included. Patients were excluded if 1) there was no definitive diagnosis of typhoid fever, 2) cefixime was not administered for typhoid treatment, or 3) medical records were incomplete or missing essential data points.

Data collection

Study investigators, along with site personnel, identified eligible patients from existing medical records as per the study's selection criteria. Relevant medical records were screened, and available data were extracted and documented under standardized reporting systems. Each patient record was provided with a unique ID. The date of cefixime therapy initiation was regarded as the baseline visit. Data collection was completed for three key time points: the baseline, the end of therapy, and the post-therapy follow-up.

At the baseline visit, demographic details, including age, gender, height, weight, and medical history, were recorded. Radiographic assessments of the patients were recorded when available. At the end of cefixime therapy, the duration of treatment, clinical outcomes (cure, improvement, worsening, or mortality), symptom resolution, treatment regimen, and adverse events were noted. At the post-treatment follow-up (14±2 days), data were collected for clinical outcomes such as cure, improvement, or recurrence of symptoms, total duration of hospital stay, and symptom improvement. The occurrence of any secondary infections, relapse of typhoid fever, or adverse events was documented.

Statistical analyses

The R and SPSS 25 software were utilized for statistical analyses. Cohort's demographic characteristics (age, weight & height), signs & symptoms, and treatment details at the start of therapy, end of therapy, and post-treatment follow-up were reported using descriptive statistics. Continuous variables were represented using mean and standard deviation, while categorical variables were presented as frequencies and percentages. The correlation between key categorical variables was investigated with Pearson's Chi-Square test. The relationship between adverse events and symptom resolution was also assessed. A $p < 0.05$ and 95% confidence interval (CI) demonstrated statistical significance.

Ethical considerations

This study adhered to the principles of good clinical practice (GCP) in addition to standard Indian Council of Medical Research (ICMR) guidelines. Independent ethics committee approval was taken before conducting initiating the study. Given its retrospective design, anonymized data from existing medical records were utilized, waiving the need for informed consent from patients. Rigorous measures were implemented to safeguard data confidentiality throughout the study.

Results

Baseline demographic and characteristics

The patient's baseline demographics and characteristics are demonstrated in Table I. An interim data of 6,726 participants were analysed in the study. Following clinical confirmation, 6,274 (93.28%) patients were diagnosed with typhoid fever, while 452 (6.72%) patients with other diagnoses were excluded from the final analysis. The analysis thus included 6,274 typhoid-confirmed cases, comprising 1,751 (27.9%) females and 4,523 (72.1%) males. Mean age of the study population was 37.72 (13.93) years. Mean height and weight were 157.87 (16.61) cm and 61.44 (14.18) kg respectively.

Fever was the most commonly reported symptom, present either alone or in combination in 5,754 patients (91.71%). Most patients (n = 4,446; 70.9%) presented with a single symptom such as fever, body pain, or headache. The remaining 1,761 patients (28.1%) exhibited a combination of symptoms, including fever, body pain, cough and cold, headache, diarrhoea, and vomiting. Regardless of the symptom presentation, all the patients were treated with cefixime. Cefixime 200mg tablets were prescribed to 6114 (97.4%) patients. The average duration of therapy among patients was 8.21 (3.68) days, while the mean duration of hospital stay was 7.60 (3.84) days.

Clinical outcomes

WIDAL test results were available for a small proportion of the patient population (Figure I). Out of a total population of 6,274 patients, 134 (2.14%) patients tested positive with the WIDAL test at the start of therapy, which reduced to 76 (1.21%) at 7±2 days and further reduced to 28 (0.45%) at 14±2 days. Additionally, symptom resolution (defined as cure on clinical assessment) was observed in 96.68% of patients by day 7 ± 2, increasing to 99.35% by day 14 ± 2 (Figure II).

Adverse Events

Adverse events were rare. Only six patients (0.09%) reported adverse events related to cefixime at day 7 ± 2, and four patients (0.06%) reported such events at day 14 ± 2.

Microbiological Data

Microbiological data was available for a subset of patients. At baseline, Salmonella enterica subsp. enterica serovar Typhi was isolated in 224 patients (3.6%). This number decreased to 116 (1.8%) at 7 ± 2 days and further to 54 (0.9%) at 14 ± 2 days.

Associations

Bivariate analysis showed no significant association between cefixime use and adverse events at either follow-up point (p = 1.000). Similarly, no significant correlation was observed between cefixime use and clinical symptoms at day 7 ± 2 (p = 0.091) or day 14 ± 2 (p = 0.309) (Table II).

Table I: Patient baseline demographic and characteristics (n = 6274)

Parameters	Mean (Standard Deviation), n (%)
Age (years)	37.72 (13.93)
Gender	
Female	1751 (27.9)
Male	4523 (72.1)
Height (cm)	157.87 (16.61)
Weight (kg)	61.44 (14.18)
Duration of Current Illness (Days)	3.84 (2.34)
Total Duration of Therapy (Days)	8.21 (3.68)
Duration of Hospital Stay (Days)	7.60 (3.84)
Cefixime 200mg tablets prescribed	
Yes	6114 (97.4)
No	160 (2.6)
Signs and symptoms	
Combination	1761 (28.1)
Single	4446 (70.9)
NA	67 (1.1)

Table II: Change in signs and symptoms at end of therapy (7±2 days) and follow-up therapy (14±2 days)

		Signs and Symptoms noted at 7±2 days			Total
		Cure	Improvement	Worsening	
Cefixime 200mg tablets	**No**	159 (2.53%)	1 (0.02%)	0 (0.0%)	160
	Yes	5907 (94.15%)	206 (3.28%)	1 (0.02%)	6114
Total		6066 (96.68%)	207 (3.3%)	1 (0.02%)	6274

p-value = 0.091 (Fisher's Exact test)

		Signs and Symptoms noted at 14±2 days				Total
		Cure	Improvement	Mortality	Worsening	
Cefixime 200mg tablets	**No**	158 (2.52%)	2 (0.03%)	0 (0.0%)	0 (0.0%)	160
	Yes	6075 (96.83%)	36 (0.57%)	1 (0.02%)	2 (0.03%)	6114
Total		6233 (99.35%)	38 (0.61%)	1 (0.02%)	2 (0.03%)	6274

p-value = 0.309 (Fisher's Exact test)

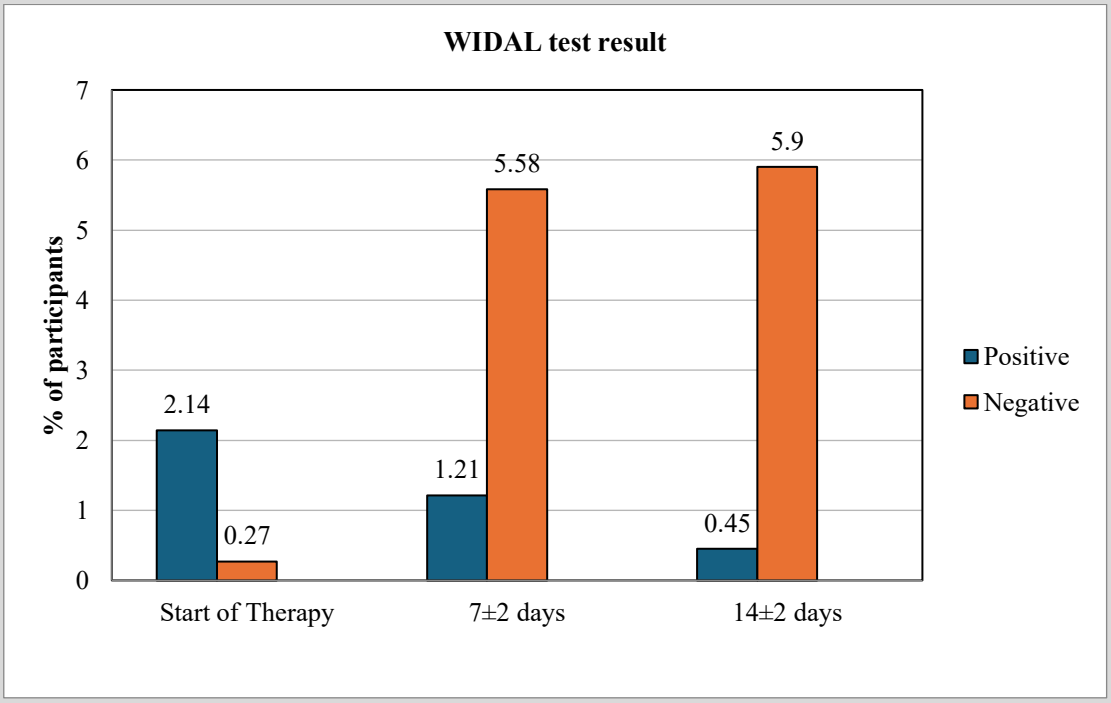

Fig. I: Serological testing results (WIDAL test) at different time points (start of therapy, at 7±2 days, and at 14±2 days) for the patients included in the study.

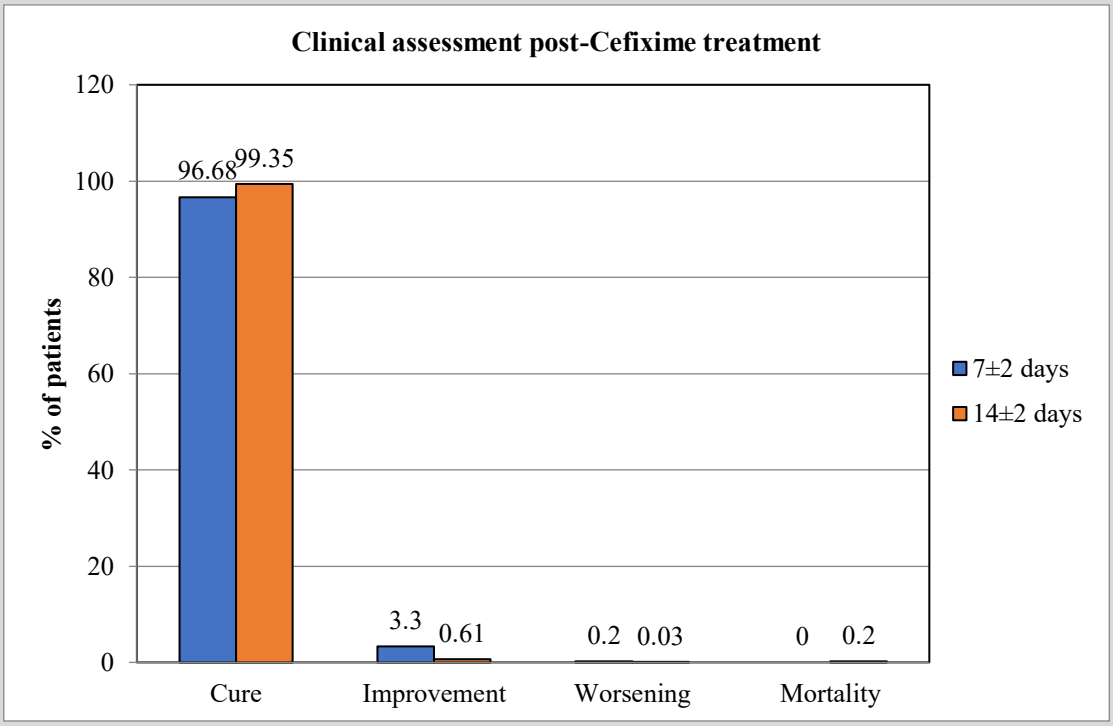

Fig. II: Clinical response post-treatment with cefixime at 7±2 days and 14±2 days

Discussion

This large-scale retrospective study provides compelling evidence for the effectiveness and safety of cefixime in managing typhoid fever. Cefixime, when administered to typhoid fever patients, resulted in clinical cure in over 99% of the patients within two weeks. This demonstrates high activity of cefixime against the causative agent, S. typhi. Serological testing using the WIDAL method showed a progressive decline in positive results throughout the treatment course, further confirming the antimicrobial action of cefixime. Notably, the therapeutic regimen was associated with a low incidence of adverse events. The mortality rate was negligible with only a single fatality reported. Overall, cefixime had a favorable safety profile in the Indian patient population.

Cefixime is a third-generation cephalosporin, and is considered a first-line therapeutic agent [18,19]. In the present study cefixime demonstrated high therapeutic effectiveness in the present study cohort, consistent with earlier clinical investigations. A single-center, prospective study on typhoid fever patients in tertiary care in Nepal reported a 96% clinical cure in typhoid fever with no incidence of infection relapse with the use of 200 mg cefixime [20]. Another multicenter study in Nepal assessed the efficacy of cefixime in managing typhoid fever in adults and children [4]. Post-treatment with 200 mg cefixime for a period of either 5 days or 7 days, a 92.5% clinical cure was reported. Bhargava *et al*. (2014) observed an efficacy of 83% [21]. A small cohort, interventional, prospective study on Egyptian children receiving 20mg per kg per day for a duration of 1 week observed clinical and bacteriological cure in 90% of the participants, with a single case of infection relapse [22]. Thapa *et al*. (2020) conducted an in-vitro analysis on Salmonella typhi strains obtained from patients from three hospitals in India to evaluate the susceptibility of the bacteria to cefixime and azithromycin [23]. The findings of the study indicate a zone of inhibition in all the strains increasing with the increasing concentration of cefixime. Furthermore, the antibacterial potency of cefixime was higher than azithromycin [23]. Reported clinical cure for the present population was over 99% at 2 weeks from therapy initiation, higher than existing reports, which may be attributed to early treatment initiation, or lower infection with MDR strains.

The potent activity of cefixime against Salmonella typhi is particularly important, as antibiotic-resistant strains cause treatment failures to existing antibiotics. Presence of transferable MDR plasmids encoding resistance genes against various antibiotics including ampicillin, cotrimoxazole, and chloramphenicol has been long documented in different regions across the globe [24,25]. In an earlier study by Matsumoto *et al*. (1999), 25% of tested strains exhibited resistance to chloramphenicol and cotrimoxazole, with many also resistant to amoxicillin due to TEM-1 β-lactamase production [26]. In contrast, cefixime has demonstrated stability against hydrolysis by several β-lactamases, including TEM-1, [27,28] allowing it to retain activity against these resistant strains [29].

Although cephalosporins were initially considered ineffective against intracellular pathogens due to limited cellular penetration [26]. Subsequent clinical studies have validated the efficacy of third-generation agents, such as cefixime, in systemic infections like typhoid fever [30-32]. Some studies have found azithromycin as a better therapeutic option for typhoid fever [33,34], but may be associated with a risk of severe cardiac adverse events [35]. A systematic review suggested that fluoroquinolones are more effective than cefixime,[36] however, they are contraindicated in pediatric patients due to the potential risk of adverse events [37]. In contrast, β-lactam antibiotics, while generally safe for pediatric use, present challenges such as the higher costs associated with parenteral administration and hospitalization, along with the inconvenience compared to oral formulations [26]. Therefore, cefixime has emerged as a feasible, safe, and effective pharmacological option in managing typhoid fever.

The incidence of adverse events in the present study was rare, with the severity of the events ranging from mild to moderate. This finding aligns with previous investigations, where mild adverse events including nausea, diarrhea, stomatitis, skin reactions, and fatigue were incident in 14.2% and 21% of the study population in two individual studies [4,21]. Tally *et al*. (1987) performed a pioneering large-scale study, reporting safety outcomes in adults and children [38]. The most frequently reported drug-related adverse

reaction was diarrhea, followed by headaches, nausea, abdominal pain, and flatulence. Hypersensitivity reactions including rashes, pruritis, urticaria, and serum sickness were also documented [38]. However, these adverse reactions are comparable to those found in existing cephalosporins and other antibiotics [39,40].

Furthermore, the study identified the lack of association between the use of cefixime 200 mg and the presence of adverse events or improvements in the symptoms, This implies that the risk of developing adverse reactions or achieving a clinical cure is not dependent on the 200 mg dose, with the drug showing similar efficacy and safety at other doses as well. This could help tailor treatments for diverse patient populations, including those with varying degrees of infection severity or underlying health conditions. However, the proportion of cefixime doses other than 200 mg per day was significantly lower, suggesting that further studies with a more balanced distribution of dosing levels could provide additional insight into the dose-response relationship.

The present retrospective analysis has several strengths. First, the large population size strengthens the reliability and generalizability of the results to the diverse Indian population, providing robust evidence to support the clinical efficacy and safety of cefixime. Furthermore, lack of updated data in the literature, particularly in adult populations and in the Indian context, underscores the significance of the current study, as it fills a critical gap in research. The retrospective design allowed capturing data from real-world clinical practice, reflecting the actual use of cefixime outside of controlled experimental conditions. This makes the findings more applicable to routine clinical settings in India.

Several limitations should also be acknowledged. The retrospective design introduces the potential for confounding bias, as patient selection and treatment decisions may not be randomized or controlled. Additionally, the study lacks microbiological assessments of majority of the study population, which may have led to an overestimation of cure rates. Lastly, the study did not account for resistance profiling or susceptibility testing for the majority of patients. This prevents a definitive conclusion about cefixime's effectiveness in cases of confirmed MDR S. Typhi infections.

In conclusion, cefixime demonstrated high effectiveness in improving signs and symptoms of typhoid fever, with over 99% of the patients showing clinical cure at the post-therapy follow-up assessment. The occurrence of adverse events due to cefixime was extremely rare, indicating a favourable safety profile among Indian patients with typhoid fever. Future randomized controlled trials to compare cefixime with other antibiotics and determine relative efficacy, safety, and patient adherence are recommended. Studies including patients infected with MDR S. Typhi can validate the efficacy in such strains. Longitudinal surveillance programs to monitor the emergence of cefixime resistance in S. Typhi should be established.

Declaration

Conflict of interest

Authors AP, DP and AS are full time employees of the Medical Affairs Department, Alkem Laboratories Ltd., Mumbai, India.

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Ethical Clearance

Reviewed and approved by a registered Independent Ethics Committee (IEC).

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