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Cefixime with enhanced solubility, a better alternative in management of Typhoid fever: A randomized controlled clinical study

Arvind Vaish[1], Ashish Mungantiwar[2], Ruchi Agarwal[3], Shalmali Ambekar[2], Samanta Gour [4], Arun Singh[4]

1.Dept. of Medicine, CSM Medical University, Lucknow, India
2.Medical services department, Macleods Pharmaceutical ltd, Mumbai
3.Macleods Pharmaceutical ltd, Mumbai
4. Formulation and development department, Macleods Pharmaceutical ltd, Mumbai

ABSTRACT

Cefixime has bioavailability of 40-50%, which could be attributed to its low solubility in GI tract. The objective of this pilot study was to compare the efficacy and safety of improved formulation of cefixime 200 mg tablet (CEFOLAC) versus conventional marketed cefixime 200 mg tablet in patients with typhoid fever (TF). Patients with clinical diagnosis of TF were randomized to receive either treatment twice daily for 10 days. Primary efficacy end point was reduction of clinical symptoms score on day 5 and number of patients with absence of clinical symptoms. Secondary endpoints include microbiological cure and clinical relapse on day 10 and 21. Total 22 patients completed study successfully and were subjected to analysis**.** Percentage improvement in total clinical symptoms score from baseline to day 5 was greater in improved formulation of cefixime (70 %) than conventional cefixime 200 mg tablet (58 %). On day 5, numbers of patients with complete cure of clinical symptoms were greater in group A as compared to group B. All patients in both the groups were cured based on clinical symptoms and microbiological evaluation on day 10 and day 21. No case of clinical relapse was observed. Both the formulations of cefixime were well tolerated by patients. Improved formulation of cefixime offers faster and greater improvement in clinical symptoms than conventional cefixime tablet in patients with TF. Improved formulation of cefixime is a better option for the treatment of patients with TF than conventional cefixime tablet.

Keyword: Typhoid fever, Cefixime, Bioavailability, Solubility

*Corresponding Author Email: rnd@macleodspharma.com
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INTRODUCTION

Typhoid fever (TF), also known as enteric fever, is caused by a gram-negative bacterium *Salmonella typhi*. Typhoid fever was defined by fever >38.5ºC for longer than three days and the isolation of *S. typhi* from blood or bone marrow culture. It is characterized by a continuous fever for 3-4 weeks, relative bradycardia and considerable constitutional symptoms. The disease is mainly associated with low socio-economic status and poor hygiene [1, 2].

Every year throughout the world, there are at least 13-17 million cases of typhoid fever, resulting in 600,000 deaths. 80% of these cases and deaths occur in Asia alone. In South East Asian nations, 5% or more of the strains of the bacteria may already be resistant to several antibiotics [1].

Traditionally, chloramphenicol has been the antibiotic of choice for the treatment of typhoid fever, particularly in developing countries, with ampicillin and trimethoprim-sulfamethoxazole as alternative drugs. High rate of relapse, the unacceptable risk for aplastic anemia induced by Chloramphenicol and the emergence of multi-drug resistance (MDR) made it necessary to search new drugs that would address above concerns & produce quick remission of the fever with the smallest number of daily doses [3]. To date, fluoroquinolones have been the agents of choice for the treatment of MDR typhoid fever. However, due to controversial role of these agents in paediatric population (damage to articular cartilage) & rising prevalence of Nalidixic acid resistant *S .typhi* (NARST)[3, 4] alternative drugs for the treatment of TF are required.

Third generation Cephalosporin's have shown good activity against *S. typhi*[5, 2] Cephalosporins exert bactericidal activity by interfering with bacterial peptidoglycan synthesis after binding to the penicillin binding proteins. Cephalosporins are also thought to play a role in the activation of bacterical cell autolysins which may contribute to bacterial cell lysis [6, 2]. However, only Cefixime and Cefpodoxime proxetil allow oral administration for use in ambulatory patients. Cefixime is a third generation cephalosporin, for oral use in children and adults, administered once or twice daily with good antimicrobial activity against *S. typhi* [2].

The therapeutic efficacy of a drug product intended to be administered by the oral route mainly depends on its absorption in the gastrointestinal tract. However, for a drug substance to be absorbed, it needs to be solubilised. Solubility is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and low permeability. By improving the solubility of a drug, it is possible to enhance bioavailability and improve the efficacy of drug [7].

Cefixime is not soluble in acidic medium. After its oral administration; it is slowly and

incompletely absorbed from the gastrointestinal tract, which results into poor bioavailability, around 40-50% and therefore cefixime is reported as a BCS (Biopharmaceutical classification system) class II drug[8]. Therapeutic effect of Cefixime can be improved by increasing its bioavailability; with this objective a technologically advanced formulation of cefixime has been developed. This novel formulation involves addition of specific bio-modifiers that significantly enhance solubility of cefixime in the gastric lumen, which may significantly enhance its bioavailability and have a favourable impact on the efficacy & safety profile. A patent application for the said technology has been filed and is under consideration with the patent office. Cefixime in test groups (CEFOLAC 200mg) was manufactured by Macleods Pharmaceutical ltd using solubility enhancing technology which enhances solubility of cefixime; we therefore named CEFOLAC 200mg as improved formulation of cefixime in this study. Improved formulation of cefixime has shown 40% higher bioavailability than conventional cefixime formulation available in market [9].

It has been hypothesized that improved bioavailability of cefixime will result in better efficacy profile as compared to conventional formulation of cefixime tablet. Further, cefixime induced diarrhoea is due to insoluble cefixime in the intestine which changes the composition of intestinal normal flora. Improved solubility of cefixime will help in reducing cefixime induced diarrhoea. The objective of this pilot clinical study was to compare the efficacy and safety of improved formulation of cefixime 200mg tablet versus conventional cefixime 200 mg tablet in patients with typhoid fever.

MATERIAL AND METHODS:

In this prospective, randomized, open label active controlled phase-IV clinical study, out patients of either sex aged 18-65 years, with clinical diagnosis of enteric fever were enrolled from Dept. of Medicine, CSM Medical University, Lucknow, India. The study was conducted according to the protocol approved by ethics committee. The study was conducted in compliance with the ethical standards laid down in the Declaration of Helsinki, 1964 and its later amendments; Good Clinical Practice (GCP) guidelines issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India; Ethical guidelines for biomedical research on human participants, Indian Council of Medical Research (2006), New Delhi. All patients were explained the procedure clearly and written informed consent was obtained from each participant before their participation in the study. At the time of screening, medical history, clinical signs and symptoms were obtained; microbiological evaluation for presence of *S. typhi* was performed

using blood and stool culture.

Patients with known hypersensitivity or contraindications to cefixime or any cephalosporin or other β-lactam antibiotic and having a history of complications like lymphadenitis, arthritis, multifocal osteomyelitis, brain abscesses, pneumonia or sepsis and signs of severe typhoid (shock, deep jaundice, encephalopathy, convulsions, bleeding, suspicion or evidence of gut perforation) were excluded. Patients requiring intravenous antibacterial administration and patients suffering from HIV infection were excluded from the study. Lactating women and women of child bearing age not using medically approved contraceptives were excluded in the present study.

Patients who fulfill eligibility criteria were enrolled in the study after signing written informed consent form. Enrolled patients were equally divided into two groups as per computer generated simple randomization sheet. One group received improved formulation of cefixime 200 mg tablet (manufactured by Macleods Pharmaceuticals Ltd, Mumbai, India) orally twice daily (Group A) and another group received conventional cefixime 200 mg tablet orally twice daily (Group B) for 10 days. Each patient was asked to rate symptoms of typhoid (headache, abdominal pain, poor appetite, generalized aches and pain, lethargy and diarrhoea or constipation) on 0 to 3 severity scale where 0 indicates absent, 1 indicates mild, 2 indicates moderate and 3 indicates severe symptoms. Body temp. was measured using thermometers (^{o}F).

Patients were instructed to stop treatment after day 10, and were advised to visit on day 21 to evaluate relapse of TF. Fever and other symptoms of TF from each patient were assessed at baseline (before study drug administration), day 5, day 10 and day 21. Clinical relapse was defined as return of fever on and after day 21. Blood and stool samples were collected before initiation of therapy and on day 10 and day 21 for microbiological evaluation. Microbiological evaluations were performed to detect the presence or absence of *S. typhi*. Score of each symptom from each patient was recorded in case record form (CRF). Total score of all symptoms and individual symptoms score was compared between both the treatment groups. Each patient was observed for adverse event (AE) during study period and if any AE occurred, the same was also recorded in CRF.

Primary efficacy end point was reduction in total score of clinical symptoms on day 5 and number of patients with absence of clinical symptoms. Secondary endpoints include microbiological cure on day 10 and clinical relapse on day 21.

Quantitative data are presented as mean ± Standard deviation (SD), whereas categorical data are expressed as absolute number/proportion of patients. Quantitative data of both the treatment

groups was analyzed by unpaired "t" test or Mann Whitney test based on the distribution of data. Chi-square test or fisher exact test was used to compare the categorical data of both the treatment groups. P value of less than 0.05 was considered as statistically significant difference between both the treatment groups. All statistical analysis was performed using software, SAS® version 9.2. Patients with absence of *S. typhi* were considered as microbiological cure or success of therapy. Patients having bacterial infection on day 10 after treatment were considered as failure of therapy. Only patients who received treatment and visited study centre on day 5 (follow up visit) and rated their symptoms were included in efficacy analysis. Patients with absence of *S. typhi* at baseline & subsequent visit (day 10) will be excluded from analysis of microbiological evaluation. All patients who have received single dose of study drug were included in safety analysis.

RESULTS AND DISCUSSION:

Out of 25 patients screened, 22 were found eligible for enrolment. The enrolled patients were equally distributed (1:1) in both the groups. Eleven patients in each group completed study without any deviation and were subjected to statistical analysis. Demographic data showed equal distribution of patients in both the arms as no statistically significant difference was found between both the groups. Also there was no significant difference in baseline clinical symptoms between both the treatment groups (Table 1).

Table 1: Demographic and baseline characteristic

Characteristic	Cefixime 200 mg tablet (Improved formulation)	Cefixime 200 mg tablet (Conventional)	P value
Age (yrs)	28.27 ± 9.18	24.36 ± 7.45	0.2857*
Weight (Kg)	51.82 ± 11.16	55.27 ± 12.15	0.4959*
Height (Cm)	155.09 ± 10.00	154.73 ± 9.57	0.9321*
Gender (Male/Female)	06/05	03/08	>0.05**
Clinical Symptoms			
Fever (°F)	101.73 ± 0.92	102.0 ± 0.83	0.4782*
Headache	1.45 ± 0.69	1.73 ± 0.65	0.3390*
Abdominal Pain	1.27 ± 0.65	1.273 ± 0.90	0.9929*
Poor Appetite	1.64 ± 0.81	1.36 ±0.67	0.3875*
Lethargy	1.64 ± 0.50	1.27 ± 1.0	0.2854*
Diarrhoea or constipation	1.27 ± 0.65	1.182 ± 1.16	0.8285*

Values are expressed as Mean ± SD for age, weight and clinical symptoms. Absolute number for gender. *Data was analyzed by unpaired "t" test; **Data was analyzed by Chi square test

Cefixime has been used for more than ten years throughout the world in various indications. Cefixime is becoming first choice of antibiotic for treatment of respiratory and urinary tract infections. Due the emergence of MDR & Nalidixic acid resistant *S. typhi* in endemic countries,

alternative drugs for the treatment of TF are required. Cefixime has good antimicrobial activity against *S. typhi* with no reports of resistance. Several line of clinical evidences suggested Cefixime as first line treatment in TF.

The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints and flexibility in the design of dosage form. Major challenge with the design of oral dosage forms lies in their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and pre-systemic metabolism. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability[2].

Cefixime is a BCS Class II drug which has low solubility and reasonable permeability. This study was conducted to evaluate whether improvement in solubility of cefixime oral tablet enhances its efficacy in treating TF.

In this study, both the study drugs significantly reduce symptoms of typhoid on day 5 from baseline. However, between group comparisons for total clinical symptoms score suggested that reductions in clinical symptoms were significantly higher in patients treated with improved formulation of cefixime than conventional cefixime tablet on day 5. Percentage improvement in total clinical symptoms score from baseline to day 5 was also significantly greater in patients treated with improved formulation of cefixime than conventional cefixime 200 mg (Table 2).

Table 2. Comparison for total score of clinical symptoms

Visit	Cefixime 200 mg tablet (Improved formulation)	Cefixime 200 mg tablet (Conventional)	P value
Baseline	8.45± 1.29	7.91± 2.07	0.4713
Day 5	2.55 ± 0.82	3.36 ± 1.80	0.1895
Change from baseline (improvement from baseline)	5.91 ± 1.30	4.55 ± 1.69	0.0471
% improvement from baseline to day 5	70 %	58 %	NA

Values are expressed as Mean ± SD. N = number of patients in treatment group. Data was analyzed by unpaired "t" test.

On day 5, comparisons for individual symptoms score suggested that greater reduction in clinical symptoms were observed in patients treated with improved formulation of cefixime as compared to conventional cefixime tablet but difference was not statistical significant (Table 3). Percentage

improvement in individual clinical symptoms on day 5 from baseline was more in patients treated with improved formulation of cefixime than conventional formulation of cefixime (Table 4). Greater efficacy of improved formulation of cefixime on day 5 may be attributed due to its higher bioavailability

Table 3. Comparison for clinical symptom's score on day 5

Clinical Symptoms	Cefixime 200 mg tablet (Improved formulation)	Cefixime 200 mg tablet (Conventional)	P value
Fever	99.22 ± 0.81	99.09 ± 0.61	0.6752
Headache	0.64 ± 0.67	0.72 ± 0.46	0.7475
Abdominal Pain	0.45± 0.52	0.63 ± 0.67	0.4754
Poor Appetite	0.36 ±0.50	0.45 ±0.52	0.6834
Lethargy	0.27 ± 0.47	0.54 ± 0.82	0.3461
Diarrhoea or constipation	0.27 ± 0.47	0.54 ± 0.82	0.3461

Values are expressed as Mean ± SD. Data was analyzed by unpaired "t" test.

Table 4. Comparison for % improvement in each clinical symptom on day 5 from baseline

Clinical Symptoms	Cefixime 200 mg tablet (Improved formulation)	Cefixime 200 mg tablet (Conventional)
Fever	2.47 %	2.85 %
Headache	55.86 %	58.38 %
Abdominal Pain	64.57 %	50.04 %
Poor Appetite	78.05 %	66.91 %
Lethargy	83.64 %	57.09 %
Diarrhoea or constipation	78.74 %	53.89 %

Values are expressed as percentage improvement on day 5 from baseline score of each clinical symptoms

More number of patients treated with improved formulation of cefixime experienced complete absence of clinical symptoms than conventional formulation (Table 5).

Table 5. Number of patients with complete absence of clinical symptoms on day 5

Clinical Symptoms	Cefixime 200 mg tablet (Improved formulation)	Cefixime 200 mg tablet (Conventional)
Fever	04/11 (37 %)	04/11 (37 %)
Headache	5/11 (46 %)	3/11 (28 %)
Abdominal Pain	6/11 (55 %)	5/11 (46 %)
Poor Appetite	7/11 (64 %)	6/11 (55 %)
Lethargy	8/11 (73 %)	7/11 (64 %)
Diarrhoea or constipation	8/11 (73 %)	7/11 (64 %)

Values are expressed as absolute number/percentage of patients with complete absence of clinical symptoms on day 5

In improved formulation group (group A), four patients were infected by *S .typhi* at baseline visit. Whereas in conventional cefixime group (group B), five patients were infected by *S .typhi*

at baseline visit. On day 10 and 21, all the patients of both the treatment groups were cured based on bacteriological examination. No case of clinical relapse was observed in both the groups. Both the formulations of cefixime were well tolerated by patients with no case of any adverse events reported. The results of this study suggested that improved cefixime formulation is a better alternative in treatment of TF.

CONCLUSION:

Both the formulations of cefixime 200 mg tablet were effective in reducing clinical symptoms of TF. However, faster and greater improvements in clinical symptoms were observed in patients treated with improved formulation of cefixime than conventional cefixime. The results of this study suggested that improved formulation of cefixime 200mg tablet is a better alternative than conventional cefixime 200 mg tablet for treatment of TF.

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