Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20141236

Research Article

Open-label, randomized, crossover comparative bioavailability study of cefixime from two tablet formulations after single oral administration

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Received: 10 November 2014
Accepted: 22 November 2014

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ABSTRACT

Background: Cefixime is an oral extended spectrum third generation cephalosporin, which has marked in vitro bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms, effective in the treatment of community-acquired infections such as respiratory tract infection and urinary tract infection. The objective of this randomized, crossover study was to compare the bioequivalence (BE) of two tablets of test (Milixim® 200 mg, containing 200 mg of cefixime) with Reference formulation (Cefixime, 400 mg).

Methods: A total of 12 healthy volunteers were randomly assigned to crossover, single-dose treatment regimens. Serial blood samples were collected, and plasma concentrations of cefixime were analyzed using the high-performance liquid chromatographic technique. Pharmacokinetic parameters and BE limits were calculated using non-compartmental methods.

Results: The mean C_{max} for the test and reference formulations were 4435.0298±149 and 4408.2150±1021 ng/mL, respectively. The mean area under the serum concentration curve $(AUC)_{0-t}$ were 38108.2614±8583.6535 and 38457.5791±8105.2529 ng/hr/mL The mean ratios (test: reference) for C_{max}, AUC_{0-t}, were 99.7% and 98.5%, respectively. There were no significant differences in pharmacokinetic parameters between groups. Overall, the 90% confidence interval for the intra-individual ratios of the log-transformed C_{max} and AUC values of the two formulations were within the BE interval of 80-125%.

Conclusion: The study has demonstrated the BE of milixim and reference formulation of cefixime.

Keywords: Cefixime, Bactericidal, Bioequivalence, High-performance liquid chromatographic

INTRODUCTION

Generic drugs are important options that allow greater access to health care. Generic drugs are copies of innovator (reference) drugs and are the same as those innovator drugs with respect to safety, strength, route of administration, quality, performance characteristics, and intended use.[1] Within a jurisdiction, generic drugs are generally multisource drug products, defined as products marketed by more than one manufacturer and containing the same active pharmaceutical ingredient in the same dosage form intended to be administered by the same route of administration.[2]

Cefixime is an oral extended spectrum third generation cephalosporin, which has marked in vitro bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms. It is particularly active against many *Enterobacteriaceae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Branhamella catarrhalis*.[3,4] Cefixime has been shown to be effective in the treatment of otitis media in children[5] and good choice for community-acquired infections like respiratory tract infection and urinary tract infection.[6] Cefixime is resistant to β-lactamase enzymes that inactivate oral penicillins and cephalosporins and it has a longer elimination half-life (3-4 hr vs. 1 hr) and larger dose-adjusted area under the serum concentration curve (AUC) than other oral cephalosporins.[7] Despite its poor lipophilicity and ionization at physiological pH, cefixime is significantly absorbed unchanged after oral administration.[8] The calculated absolute bioavailability of cefixime was 40% for 400 mg capsules, 48% for 200 mg capsules and 52% for oral solution.[3] Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals. Following oral dosing, cefixime attains peak serum levels in approximately 4 hr.[8] Typically the peak serum levels

following the recommended adult or pediatric doses are between 1 and 4 µg/ml.[9] The drug has an elimination half-life of 3-4 hr after single oral dose and a relatively low proportion (15-20%) of a dose is excreted by the renal route.[9] Little or no accumulation of cefixime occurs following multiple dosing. Cefixime is excreted by renal and biliary mechanisms. Serum protein binding is well characterized for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30%. Protein binding of cefixime is concentration dependent in human serum only at very high concentrations that are not seen following clinical dosing.[8]

Cefixime tablets in India are made and marketed by many pharmaceutical manufacturers. The method of preparation and the final formulation of the drug can markedly affect the bioavailability of the drug.[8]

The aim of this study was to demonstrate that the rate and extent of absorption of a generic tablet formulation of cefixime (Milixim®) intended for marketing by Glenmark Pharmaceutical Company, India and the reference tablet formulation are bioequivalent to each other based on the obtained plasma concentration data following oral administration in healthy volunteers.

METHODS

Twelve healthy adult Indian male volunteers participated in the study. The ages of the subjects ranged from 24 to 38 years and their body weights ranged from 55 to 75 kg. After the approval from the local Research, Ethics Committee had been obtained, and the participants' written informed consent was available, the volunteers underwent pre-study general physical and biomedical tests. They were free to withdraw from the study at any time. The study was performed in accordance with the relevant national and international guidelines, regulations and recommendations.

The test formulation cefixime (Milixim® 200 mg tablets, batch no. WC1016) and the reference formulation (Cefixime 400 mg tablets, batch no. MTD1010A) were administered to the subjects by an open, randomized, single-blind two-sequence, two-period crossover design with a washout period of 1 week. After an overnight fast for at least 10 hr, the participants received a dose of 400 mg cefixime, as one of the two treatments: treatment A (test formulation, 2 tablets) and treatment B (reference formulation, 1 tablet) with 240±5 ml of water. They were given a standard lunch 4 hr, snacks 6 hr and dinner at 13 hr post dose (comprising 2600-2800 kcal) in both periods. Water was not provided 1 hr before and 1 hr after dosing except at the time of dose administration, after which it will be provided ad libitum. Multiple venous blood samples 10ml each were collected in K_2EDTA vacutainers at pre-dose (−1 to 0 hr) and 5 ml were collected in K_2EDTA vacutainers from all subjects prior to the dosing and at 0.5, 1, 1.5, 2, 2.33, 3, 3.33, 4, 4.33, 5, 5.50, 6, 7, 10, 14, 18 and 24 hr after drug administration. The samples were centrifuged at 3000 rpm for 10 mins at 6°C to separate plasma and plasma was separated in two aliquots in labeled radioimmunoassay vials and stored in the deep freezer at −20°C.

Concentrations of cefixime in serum were determined using the high-performance liquid chromatographic method, which was sensitive, accurate, selective and validated. The pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $T_{1/2}$, and K_{el} were estimated. These parameters were calculated by non-compartmental models, using WinNonlin Enterprise Software – Version 5.3 (Pharsight Corporation, USA).

Statistical analysis was carried out employing PROC GLM of SAS® Version 9.3. Analysis of variance (ANOVA) and 90% confidence interval for log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf} were calculated. Ratio of least square means of untransformed and log-transformed C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ were calculated.

RESULTS

All the 12 volunteers well-tolerated both of the formulations and completed the study until the end. No adverse reactions were seen throughout the study period. The mean serum concentration-time profiles after single oral dose administration of reference and test formulations are depicted in Figure 1. As it is seen, the mean serum concentration-time curves from two formulations are almost superimposable. Moreover, there was no significant difference between cefixime serum concentrations at each time point following oral administration of the two formulations. At the first sampling time (0.5 hr), the drug was measurable in all subjects following the administration of both formulations. The resulting pharmacokinetic parameters are shown in Table 1. Mean maximum serum concentrations of 4435.0298±1149 and 4408.2150±1021 ng/mL, were obtained

Table 1: Pharmacokinetic parameters of cefixime after single oral dose of the test and reference formulation.

Parameters (units)	Arithmetic mean±SD	
	Test (T)	Reference (R)
C_{max} (ng/ml)	4435.0298±1149	4408.2150±1021
AUC_{0-t} (ng/hr/ml)	38108.2614±8583	39457.5791±8105
$AUC_{0-\infty}$ (ng/hr/ml)	39264.8558±8882	39727.7618±8405
T_{max} (hr)	4.5700±1.04997	4.3208±1.26345
$T_{1/2}$ (hr)	4.0965±0.49683	3.9582±0.78266
K_{el} (1/hr)	0.1714±0.01937	0.1821±0.03905

AUC: Area under the serum concentration curve, SD: Standard deviation

Table 2: ANOVA results.

Pharmacokinetic parameter	ANOVA (p value) Variation source			90% CI for the ratios
	Treatment	Period	Sequence	
C_{max}	0.9701	0.1515	0.5590	88.35-112.61
AUC_{0-t}	0.7221	0.7145	0.7361	91.21-106.30
$AUC_{0-\infty}$	0.5590	0.2842	0.2404	91.28-105.69

AUC: Area under the serum concentration curve, CI: Confidence interval, ANOVA: Analysis of variance

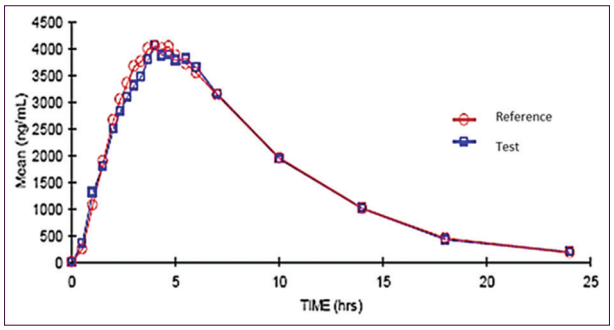

Figure 1: Mean plasma concentration versus time plot of reference and test formulations.

for the test and reference formulations, respectively. T_{max}, the time required to reach the maximum serum concentration, was 4.57±1.04 hr and 4.32±1.26 hr, for the test and reference formulations, respectively. These calculated ratios were 11.29% and 11.09% for the test and reference formulations. The AUC_{0-t} and $AUC_{0-\infty}$ for the test formulation were 38108.2614 ng/hr/ml and 39264.8558 ng/hr/ml, respectively. The calculated values for the reference formulation were 38457.5791 ng/hr/ml and 39727.7618 ng/hr/ml in the order mentioned.

DISCUSSION

The establishment of bioequivalence (BE) is fundamental in successful applications for generic drug products. BE is established in order to demonstrate therapeutic equivalence between the generic (test) drug product and corresponding reference drug product.[10]

Results from previous studies have shown that the pharmacokinetic profile of cefixime is similar after single oral doses ranging from 50 to 400 mg and after multiple dosing of 200 mg twice a day or 400 mg once a day for 15 days.[11] Furthermore, it has been shown by Faulkner et al. that capsule and tablet formulations of the drug were bioequivalent to each other.[7] The parameters used to measure bioavailability were AUC_{0-t}, $AUC_{0-\infty}$, for the extent of absorption and C_{max}, T_{max}, $C_{max}/AUC_{0-\infty}$ for the absorption rate.[12] Results from the present study show that the Milixim® (test) formulation used during study was bioequivalent with cefixime reference formulation. The confidence limits shown in Table 2 reveal that these values are entirely within the BE acceptable range of 80-125% proposed by Food and Drug Administration and European Medicines Agency.[13] The calculated pharmacokinetic parameters of cefixime are in agreement with previously reported values.[7,8]

The multivariate analysis accomplished through ANOVA indicated that there were no statistical differences between the two formulations with any of the pharmacokinetic parameters.

CONCLUSION

In conclusion, Milixim® (cefixime test) is bioequivalent to cefixime reference formulation, with good safety profile and can be used interchangeably in clinical practice.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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doi: 10.5455/2319-2003.ijbcp20141236
Cite this article as: Patil S, Hajare AL, Krishnaprasad K. Open label, randomized, crossover comparative bioavailability study of cefixime from two tablet formulations after single oral administration. Int J Basic Clin Pharmacol 2014;3:943-6.