

Original Article

Pharmacokinetics and bioequivalence study of two formulations of Cefixime Suspension

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ABSTRACT

Cefixime is a broad-spectrum oral antibiotic used for treating a wide variety of bacterial infections. This investigation was aimed to study the pharmacokinetics and bioequivalence of a new generic suspension containing 100 mg cefixime trihydrate per 5 ml as a test product against the reference formulation Suprax® suspension after administration to 28 Arabic healthy male adult subjects under fasting condition. Ten milliliters of each formulation (equivalent to 200 mg cefixime) were administered as a single dose applying a two-treatment, two-period, two-sequence, randomized crossover design with a one-week washout interval between dosing. Eighteen serial blood samples were collected from each subject before dosing and then up to 24.0 hours post-dosing. All the calculated pharmacokinetic parameters, including C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $K_{elimination}$ (λ_z), T_{half} , and MRT were statistically analyzed by ANOVA tests. Ln-transformed values of the primary parameters used for bioequivalence evaluation, namely C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were also statistically analyzed by ANOVA and 90% confidence interval tests. The ranges of 90% confidence interval tests for the Ln-transformed C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ were 88.90-108.71, 89.71-109.30, and 89.83-109.23, respectively. Both products were well tolerated by all subjects. Based on FDA and EMEA criteria on bioequivalence, the results obtained from the present study exhibited bioequivalence between the test and the reference formulations of cefixime. Hence, the new generic suspension may be considered interchangeable with the reference product and prescribable in therapy with cefixime.

Keywords: Cefixime, Pharmacokinetics, Bioequivalence, Arabic subjects

Introduction

Cefixime is an orally administered broad-spectrum antibiotic with high resistance to degradation by beta-lactamase [1]. Cefixime is indicated for the treatment of acute bronchitis and

acute exacerbations of chronic bronchitis, otitis media, pharyngitis/tonsillitis, uncomplicated gonorrhea (cervical/urethral), uncomplicated urinary tract infections [1-6], and recently for early and acute syphilis [7-9]. The available dosage forms of cefixime are 100 and 200 mg tablet, chewable tablet and powder for oral suspension containing 100 mg per 5 ml cefixime, and 400 mg capsule [1]. Cefixime is distinguished by its relatively longer terminal elimination half-life (approximately 3 hours) in comparison to 1.5 hours for cefalexin and 0.5 hours for cefaclor which allows twice or, in many cases, once-daily administration [1]. Attempts were made to escalate the antimicrobial activity of cefixime by nanotechnology [10], spray drying [11] and mucoadhesion [12] pharmaceutical technologies.

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The terminal plasma elimination half-life of cefixime is independent of the dosage form and the dose given. About 50 % of the drug is excreted unchanged with urine within 24 hours and about 10% with stool [1]. The disposition characteristics including C_{max} , T_{max} , AUC, and T_{half} of cefixime obtained from pharmacokinetic, bioavailability, and bioequivalence studies after administration of different dosage forms at therapeutic doses of 200-400 mg indicating that cefixime demonstrates linear (dose-proportional) pharmacokinetics and its disposition characteristics are comparable after different oral dosage forms [1-4].

The use of generic drug formulations for therapeutically well-established active ingredients must be justified by a well-designed, conducted, and evaluated bioequivalence study [13]. Documentation of bioequivalence, especially for generic antimicrobial products, possesses special concern in therapy since it is important to obtain the necessary therapeutic plasma concentrations of the drug, which produce the optimal effect and minimal adverse effect and consequently assure the complete extermination of the microorganisms which cause the infections. On most occasions, when the antimicrobial plasma concentrations fall below the needful levels to ensure the entire destruction of the microorganisms, this would lead to failure of therapy in addition to boosting the potential for the risk of developing resistance to the drug [14]. Therefore, numerous bioequivalence studies were conducted for cefixime in different countries and their populations to prove the bioequivalence of their marketed generic drug formulations in comparison to the brand drug products [15-21]. Among these bioequivalence studies were conducted for German [15], French [16], Arabic [17, 18], Persian [19, 20] and Pakistani populations [21].

The purpose of the present investigation was to determine the pharmacokinetic characteristics and to assess the bioequivalence of a new generic suspension containing 100 mg cefixime trihydrate per 5 ml as a test product in comparison to the reference Suprax® suspension produced by Hikma Pharmaceuticals, Jordan after administration to 28 Arabic healthy male adult subjects under fasting condition. The performance of both drug products was compared using the pharmacokinetic parameters obtained from the plasma concentrations-time data of each subject, including C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $K_{elimination} (\lambda_z)$, T_{half} , and MRT.

Materials and Methods

Investigational drug products

The test formula was a new generic suspension containing 100 mg cefixime trihydrate per 5 ml. The reference formula was Suprax® suspension containing 100 mg cefixime trihydrate per 5 ml manufactured by Hikma Pharmaceuticals, Jordan.

Study protocol

The study protocol was approved by the clinical investigator and the institutional review board (IRB) before study conduct.

The protocol described all details of the project, i.e., design of the study, clinical procedures, bioanalysis of blood samples obtained from the participants, pharmacokinetic and statistical data analysis, bioequivalence evaluation, the informed consent form, and ultimately documentation and final report issuance [13].

Ethical considerations

The study was carried out adhering to ICH guidelines for good clinical practice (GCP) [22] and the declaration of Helsinki provisions [23]. Each subject was given the informed consent form at the screening phase before starting the study. A meeting was arranged to the subjects by the principal and clinical investigators together with the clinical staff to explain all details of the study, including the purposes, risks, advantages, procedures, and the right as a research subject to withdraw at any time during the study, and the compensation in case of any harm caused by the study.

Study design

A randomized, two-way crossover, open-labeled, laboratory-blind, single-dose, fasting, two-treatment, two-sequence two-period design was applied in this study. An equal number (14 subjects) were randomly assigned to each dosing sequence of the investigational drug products (test and reference formulations). Hence. At the first period, 14 participants were administered 200 mg of the test formulation as a single dose (10 ml containign100 mg cefixime per 5 ml), while the other 14 participants were administered 200 mg of the reference formulation as a single dose (10 ml containign100 mg cefixime per 5 ml) according to a randomization table established in the study protocol. In the second period, the order of the test and reference products administration was reversed. The second period was carried out after a washout interval of one week.

Inclusion criteria for participation in the study

The subjects were regarded eligible for participation in this research based on the following inclusion criteria: adult male subjects with ages between 18-48 years and body mass index (BMI) ranges from 18 – 30 kg/m², non-smokers or light smokers (less than 10 cigarettes per day) with no illicit drug or alcohol abuse, no history of hypersensitivity or contraindication to cefixime and related compounds, no history of using chronic medications, have normal physical condition and medical examinations involving vital signs, ECG, respiratory, cardiac, hepatic, renal, gastrointestinal and psychiatric, have normal clinical laboratory tests including hematology, biochemistry, routine urine analysis, negative for HIV and for hepatitis B and C, have not taken any medications for the last two weeks prior the study other than paracetamol, no hospitalization or blood donation or involvement in any clinical trials including

pharmacokinetics, bioavailability or bioequivalence within the last 2 months prior the current study.

Drug products administration

The subjects were admitted to the clinical site before almost 14 hours pre-dosing and they were confined until the end of each study period (24.0 hours post-dosing). The subjects were served standard dinners at 12 hours before drug intake, then lunches after 4 hours, and dinners after 12 hours of drug intake. The meals were the same in both periods of the study and the participants were asked to have all the served meals each time. Any sorts of fluids and meals were entirely prohibited other than those served. Products containing xanthine were banned 12 hours before and 12 hours after dosing. Besides, any products containing grapefruit were prevented one week before dosing and until the end of the study. After overnight fasting of 12 hours, the test and reference drug formulations were administered with 240 ml of tap water. Water was not permissible 2 hours pre- and 2 hours post-dosing, water intake was free thereafter. The participants were not permitted to lie or sleep during the first 4 hours of drug administration, they were remained seated upright and ambulatory but prohibited from strenuous activity. Any medication other than the investigational drug was not permitted to be given and for any reason unless as decided by the clinical investigator.

Blood samples collection

In each study period, 5 ml blood samples were obtained from each subject by indwelling venous cannula placed into the antecubital vein. Blood samples were obtained from each individual prior to cefixime administration of the test and the reference formulations (zero time) and then at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 12.0, 16.0 and ultimately at 24.0 hours following cefixime intake. Eighteen blood samples were obtained from each subject at each period. The blood samples were placed directly in pre-labeled heparinized tubes and then promptly centrifuged at 4000 rpm for 5 minutes. The separated plasma was directly placed in Eppendorf tubes and then promptly stored at $-30 \pm 5^{\circ}\text{C}$ until the day of bioanalysis for assay of cefixime concentrations in plasma.

Safety and tolerability assessments

Physical and medical examinations involving vital signs (blood pressure, pulse, and temperature), in addition to clinical laboratory tests including hematology, biochemistry and routine urinalysis, were carried out during the screening phase for the selection of healthy eligible subjects to participate in the study. Besides, the medical examinations and the clinical laboratory test were performed after drug administration of period 1, the day before drug intake of period 2, and eventually at the end of period 2 upon subject discharged. Vital signs were registered before about 1.0 hours of drug administration at periods 1 and

2, and then at 2.0, 4.0, 6.0, 8.0, 12, and finally at 24.0 of drug dosing.

Bioanalysis of cefixime in plasma

A sensitive, selective, accurate, and precise, high-performance liquid chromatography with UV detection method modified from previous researches was used for the determination of cefixime plasma concentrations [24-28]. The method was developed and validated following FDA guidance on bioanalytical method validation [29]. The standard calibration curve gave acceptable linearity with a correlation coefficient (r) equal to 0.9989 over concentrations range from 4-5000 ng/ml cefixime in plasma using least-squares linear regression analysis. The lower limit of quantification (LLOQ) was 4 ng/ml. The precision and accuracy were within the acceptable ranges for intra-day and inter-day assay. The analytical batch/run for each subject (including standard calibration curve, quality control (QC) samples (low, mid, and high), and the unknown authentic plasma samples obtained from both periods of the study) was performed after completing the clinical phase of the study. No determination was done by extrapolation above the upper limit of quantitation (ULOQ) or below the LLOQ of the standard calibration curve. Therefore, plasma samples with cefixime concentrations above the ULOQ (5000 ng/ml) were diluted as recommended by FDA guidance [29].

Pharmacokinetic calculations and statistical analysis

The software Kinetica was used for calculating the pharmacokinetic parameters, statistical analysis, and bioequivalence testing. Microsoft Excel was used for data plotting and for measuring the descriptive statistics involving geometric mean, arithmetic mean, the ratio of means, relative bioavailability, maximum and minimum values, median, standard deviation (SD), and coefficient of variation (CV). The pharmacokinetic parameters of cefixime obtained from plasma concentration-time data of each subject, including C_{\max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{\max} , $K_{\text{elimination}}$ (λ_z), T_{half} , and MRT were determined by standard methods applying non-compartmental data analysis [30, 31].

The maximum concentration of the drug in plasma (C_{\max}) and the time attain C_{\max} (T_{\max}) were obtained from the concentration-time profile of each subject. The terminal elimination rate constant ($K_{\text{elimination}}/\lambda_z$) was determined by linear regression of at least the last three concentrations at the terminal phase of the log-concentration-time curve of each subject. The terminal elimination half-life (T_{half}) was measured from $0.693/\lambda_z$. The AUC_{0-t} is the area under the plasma concentration-time curve from time zero, and up to the last blood sampling time withdrawal (t_{last}) was calculated by the Trapezoidal rule. The $AUC_{t-\infty}$ ($AUC_{\text{extrapolated}}$), which is also called residual area (AUC_{residual}), is the extrapolated area under plasma concentration-time curve from t_{last} to infinity was

estimated as C_{last}/λ_z . The C_{last} is the last measurable cefixime concentration which equals to or above the LLOQ of cefixime in plasma. The $AUC_{0-\infty}$ is the area under plasma concentration-time curve from time zero to infinity was measured from the summation of AUC_{0-t} and $AUC_{t-\infty}$. The % $AUC_{extrapolated}$ was calculated from $(AUC_{t-\infty}/AUC_{0-\infty}) \times 100$. The MRT is the mean residence time of the drug in the body was calculated as the ratio of area under moment curve $AUMC/AUC$ [30, 31].

Statistical analysis applying ANOVA tests were used to evaluate the difference between the data obtained from the test product versus the corresponding data obtained from the reference product, including concentration-time data and all calculated pharmacokinetic parameters C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $K_{elimination}(\lambda_z)$, T_{half} and MRT. Moreover, the non-parametric [32] Friedman design and Kruskal-Wallis test were used for statistical analysis of T_{max} and MRT values of the test versus the reference products. Furthermore, ANOVA and 90% confidence interval (90% CI) tests were used for the Ln-transformed values of the pharmacokinetic parameters used for bioequivalence evaluation, namely C_{max} , AUC_{0-t} , and $AUC_{t-\infty}$ as recommended by FDA and EMEA guidance [13]. The average bioequivalence of the test versus reference formulations was concluded if 90 % CI interval for Ln-transformed values of each parameter C_{max} , AUC_{0-t} , and $AUC_{t-\infty}$ are within 80.00-125.00 %. Differences between test versus reference products are declared statistically not significant at 5% significance level ($\alpha = 0.05$) when $P \geq 0.05$. Schuirmann's two one-sided t-tests were used as further support to 90% CI for evaluation of bioequivalence [13].

Results and Discussion

Study design

According to the knowledge obtained from the above-mentioned literature concerning the low inter-and intraindividual differences in cefixime pharmacokinetics [15-21], the participation of 24 individuals was found to be enough to get adequate power for bioequivalence testing of cefixime. Thus, 36 individuals were screened in this study to account for any withdrawal and/or drop out, which may happen at the screening phase and during study conduct which is common in clinical trials. Six subjects were excluded from the study at the screening phase since they were not eligible to participate in the study according to the inclusion/exclusion criteria established in the study protocol. Two more subjects withdrew from the study for personal reasons before drug products administration

of the first period. The remaining 28 subjects exhibited good compliance and completed the entire study. The average and the ranges for the demographic characteristics of the participants were as follow: age 23 years (range 19-30), height 1.8 meters (range 1.7-1.9), bodyweight 71 kg (range 60-94), and body mass index was 23 kg/m² (range 20-27).

Tolerability and safety assessments

The average and the ranges for the baseline vital sign for the participants were as follow: systolic blood pressure was 116 mmHg (range, 105-130), diastolic blood pressure was 74 mmHg (range, 60-85), pulse was 70 beats per minute (range 60-82), and the temperature was 36.8 °C (range 36.6-37.2). Both cefixime formulations were well tolerated by all subjects, and all the participants were discharged from the study without significant changes in their clinical baseline properties involving vital signs and clinical laboratory tests (hematology, biochemistry, and routine urine analysis).

Plasma concentrations of cefixime

The bioanalytical method used in the present study for measuring cefixime concentrations in plasma was found to be selective, sensitive, precise, and accurate based on FDA bioanalytical method validation criteria [29]. Cefixime was not detected (plasma levels were below LLOQ of 4 ng/ml) in the plasma samples obtained before drug products administration at period 2 for all individuals and for both the test and the reference formulations indicating the absence of carryover effects from previous dosing (period 1) and confirming that one-week washout interval between dosing is very sufficient for bioequivalence study of cefixime with a terminal elimination half-life of about 3.5 hours. The concentrations of the drug in the general circulation were above the LLOQ in all subjects and for both products after 0.5 hours post-dosing, which indicates rapid absorption of the drug from the suspension. Comparing all plasma concentrations of cefixime at each time point from 0.5 up to 24 hours post-dosing (17 data points) for the test product against the corresponding concentrations for the reference product applying ANOVA tests demonstrated no significant differences ($P > 0.05$) between the concentration-time profiles of both products. Furthermore, the concentration-time curves of both products are nearly superimposable, as appear in **Figure 1**. Thus, these findings indicate a good similarity in the concentration-time profiles and disposition properties of both products, including cefixime absorption, distribution, and elimination (**Figure 1**).

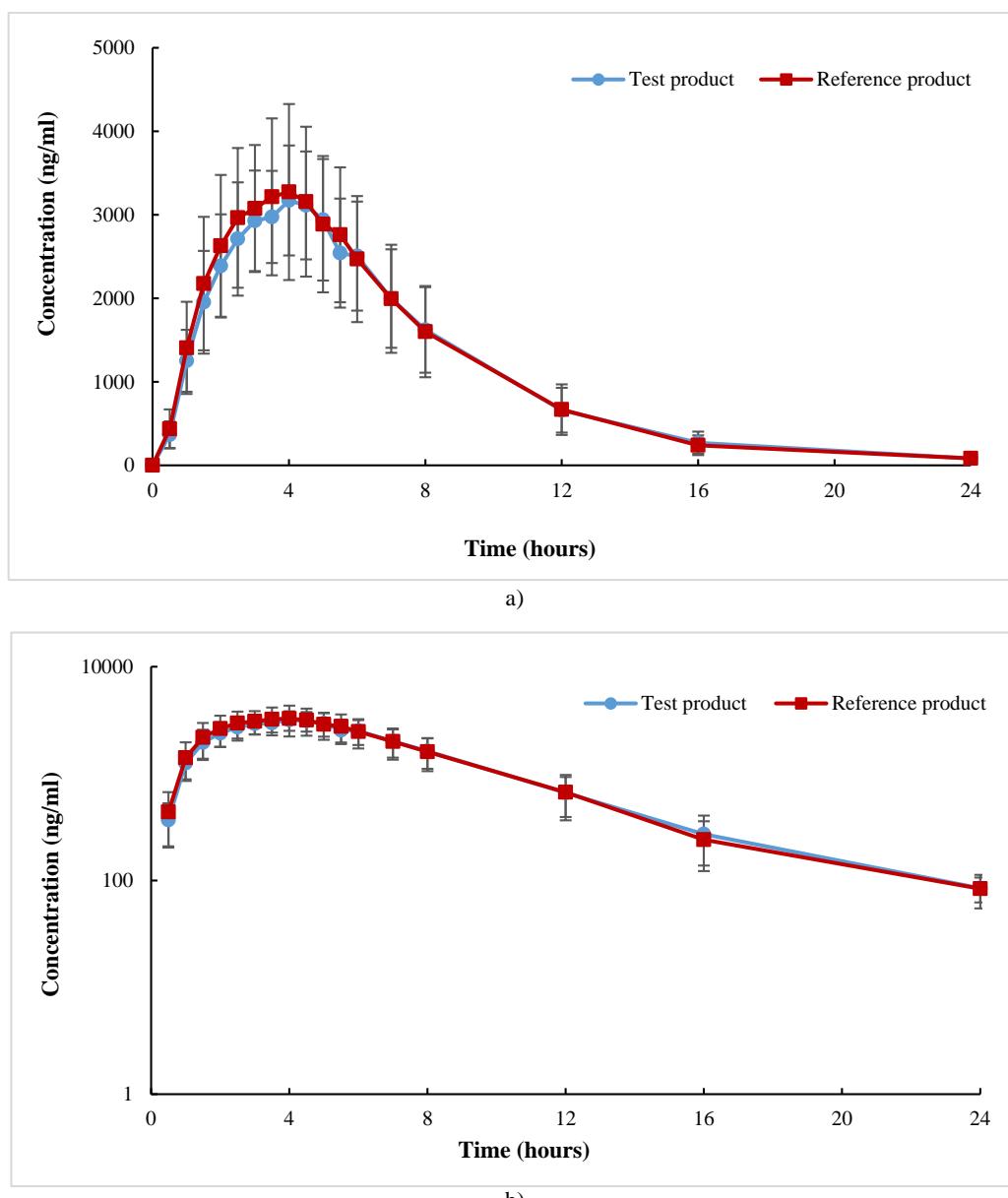


Figure 1. Plasma concentrations-time profiles (Mean \pm SD) of cefixime after administration of 200 mg suspension as a single dose of the test and the reference products in (a) linear scale and (b) semilog scale.

Pharmacokinetic results

The drug was assessed in blood at 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 12.0, 16.0 and lastly at 24.0 hours post-dosing. This blood sampling strategy applied in this investigation ensures a reliable determination of all cefixime pharmacokinetic parameters C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $K_{elimination}$ (λ_z), T_{half} , and MRT since blood sampling were early enough, for frequent time intervals and for an adequate period. The pharmacokinetic parameters obtained after administration of the test and the reference cefixime formulations are presented in **Table 1**. It is obvious from visual observation of **Table 1** that both formulations exhibit similar pharmacokinetic properties since the mean values of all the calculated pharmacokinetic parameters C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $K_{elimination}$ (λ_z), T_{half} , and MRT were comparable. Besides, all the pharmacokinetic parameters of both drug products demonstrated low and similar interindividual differences with a

mean %CV of about 20% and a range of 11-29% (**Table 1**). Cefixime in both formulations attained its C_{max} in plasma within about 4 hours (range 2-5.5 hours). Thereafter, the drug concentrations in plasma showed a mono-exponential decline with a mean T_{half} of about 3 hours (range 2-5 hours). Moreover, the secondary pharmacokinetic parameter, which reflects the residence of the drug in the body (MRT), confirms the similarity in the calculated T_{half} for both products since the MRT was found to be 6.6 hours (range 5.4-8.4 hours) as appear in **Table 1**. The $\%AUC_{extrapolated}$ possessed a very low contribution to the total AUC ($AUC_{0-\infty}$) since the mean value was 2% (range 0.8-4.3%), as displayed in **Table 1**. Hence, collection of blood samples for 24 hours post-dosing and using 4 ng/ml as LLOQ of cefixime in plasma applied in the present investigation are very enough for studying the disposition kinetics of the drug. Interestingly, the values of all the pharmacokinetic parameters obtained in this research for Arabic individuals are almost comparable to all data presented in the literature [15-17, 19-

21], which were conducted in different populations and for different oral dosage forms of cefixime, which suggest that

ethnicity and the type of dosage form have no remarkable impact on cefixime pharmacokinetics.

Table 1. Pharmacokinetic parameters of cefixime suspension administered as a single dose (200 mg) of the test and the reference product

Test product						
Parameters	Mean	±SD	%CV	Min	Max	Geomean
C _{max} (ng/ml)	3340.1	694.5	20.8	2183.0	4410.2	3268.3
AUC _{0-t} (ng·hr/ml)	24852.3	5897.0	23.7	12466.5	35446.7	24122.9
AUC _{0-∞} (ng·hr/ml)	25310.6	5898.6	23.3	12932.7	35822.6	24596.9
T _{max} (hr)	4.16	0.667	16.0	2.5	5.5	*
λ _z (hr ⁻¹)	0.2134	0.0366	17.2	0.1593	0.2979	**
T _{0.5} (hr)	3.33	0.527	15.8	2.33	4.35	**
MRT (hr)	6.75	0.749	11.1	5.37	8.43	**
%AUC _{extrapolated}	1.924	0.743	38.6	0.942	3.605	**
Reference product						
Parameters	Mean	±SD	%CV	Min	Max	Geomean
C _{max} (ng/ml)	3473.4	1012.0	29.1	1285.7	5831.7	3324.6
AUC _{0-t} (ng·hr/ml)	25511.2	7428.9	29.1	8417.1	43432.4	24360.8
AUC _{0-∞} (ng·hr/ml)	25961.5	7448.8	28.7	8796.3	44269.1	24831.7
T _{max} (hr)	3.98	0.811	20.4	2.0	5.5	*
λ _z (hr ⁻¹)	0.2274	0.0457	20.1	0.1584	0.3523	**
T _{0.5} (hr)	3.16	0.574	18.2	1.97	4.79	**
MRT (hr)	6.56	0.776	11.8	5.46	8.31	**
%AUC _{extrapolated}	1.892	0.896	47.4	0.752	4.31	**

* Median, **Geomean calculations for these parameters are statistically not recommended for bioequivalence testing.

Statistical analysis and bioequivalence testing

ANOVA tests for all the pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-∞}, T_{max}, K_{elimination} (λ_z), T_{half}, and MRT of the test formula against their corresponding values of the reference formula showed no statistically significant differences (P > 0.05) in the source of variations including formulation (which has the most important effect), sequence and period (**Table 2**). A similar result was found for the Ln-transformed values of C_{max}, AUC_{0-t}, and AUC_{0-∞} (**Table 2**). In addition to that, non-parametric Friedman design and Kruskal-Wallis tests demonstrated no statistical differences between T_{max} and MRT values of the test against their corresponding values for the reference formulations. Furthermore, the geometric mean ratio and the relative bioavailability of each of the primary parameters used in bioequivalence evaluation (C_{max}, AUC_{0-t}, and AUC_{0-∞}) were approximately equal to one (**Table 3**). The above-mentioned statistical tests suggest the close similarity between the pharmacokinetic properties of the test and the reference formulations in terms of extent and rate of cefixime absorption

and total drug exposure. Moreover, 90% CI ranges for Ln-transformed values C_{max}, AUC_{0-t}, and AUC_{0-∞} of the test against the corresponding values of the reference formulations (**Table 3**) were well within the bioequivalence acceptance ranges of 80.00-125% based on FDA and EMEA guidance on bioequivalence [13]. Over and above, Schuirmann's two one-sided t-tests support the results obtained from 90% of tests, as displayed in **Table 4**. Hence, it can be concluded from these findings that the newly formulated generic suspension containing 100 mg/5 ml cefixime is bioequivalent to the reference formulation Suprax® suspension containing 100 mg/5 ml cefixime produced by Hikma pharmaceuticals, Jordan. Therefore, both formulas may be interchangeable in clinical practice, and the generic product may be prescribable with adequate safety and efficacy as the reference product.

Table 2. ANOVA tests for the pharmacokinetic parameters

Parameters	Source of variations and their P values		
	Formulation	Sequence	Period
C _{max}	0.5018	0.3201	0.2637

AUC_{0-t}	0.6353	0.3767	0.6460
AUC_{0-∞}	0.6428	0.3872	0.6648
Ln C_{max}	0.7746	0.1844	0.2189
Ln AUC_{0-t}	0.8667	0.1881	0.5295
Ln AUC_{0-∞}	0.8697	0.1962	0.5463
T_{max}	0.3091	0.2243	0.8373
λ_z	0.1004	0.6050	0.7213
T_{0.5}	0.1162	0.5939	0.8041
MRT	0.1231	0.7088	0.7119

Table 3. Geometric mean ratio, relative bioavailability, and 90 % confidence interval (90% CI) for the test versus the reference products.

Parameter	Geometric ratio	Relative* bioavailability	90% CI lower limit	90% CI upper limit
C _{max}	0.98	0.96	88.90	108.71
AUC _{0-t}	0.99	0.97	89.71	109.30
AUC _{0-∞}	0.99	0.98	89.83	109.23

*Relative bioavailability=arithmetic mean test/arithmetic mean reference

Table 4. Schuirmann two one-sided t-test for pharmacokinetic parameters of the test versus reference drug products.

Pharmacokinetic Parameter	Lower t(26df)	Upper t(26df)	Accepted T _L & T _U ≥ t(0.05-26 df)
C _{max}	3.4948	4.0735	1.7056
AUC _{0-t}	3.6844	4.0234	1.7056
AUC _{0-∞}	3.7266	4.0580	1.7056

Conclusion

The current research displays the pharmacokinetic properties of cefixime 100/5 ml suspension after therapeutic oral dose (200 mg) of a new test generic formulation in comparison to the reference Suprax® suspension administered to Arabic healthy adult male subjects. Based on FDA and EMEA guidance on bioequivalence, the new generic formulation is bioequivalent to Suprax® and may be interchangeable with Suprax® and prescriptive in therapy with cefixime.

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Conflict of interest: None

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Ethics statement: The study was conducted in compliance with ICH guidelines for good clinical practice (GCP) and ethical principles for medical research involving human subjects stated in the declaration of Helsinki.

References

1. Brogden RN, Campoli-Richards DM. Cefixime. A review of its antibacterial activity. Pharmacokinetic properties and therapeutic potential. Drugs. 1989;38(4):524-50.
2. Kristie LC, Ann EE, Carolina G, Blaire LO, Magnus U, Ann EJ. Pharmacokinetic data are predictive of In Vivo efficacy for cefixime and ceftriaxone against susceptible and resistant Neisseria gonorrhoeae strains in the gonorrhea mouse model. Antimicrob Agents Chemother. 2019;26;63(3):e01644-18.
3. Lindley AB, Seema UN, Jeffrey LB, Mary AOR, Wesley G, Jonathan MZ, et al. A Phase 1 Pharmacokinetic and Safety Study of Extended-Duration, High-dose Cefixime for Cephalosporin-resistant Neisseria gonorrhoeae in the Pharynx. Sex Transm Dis. 2018;45(10):677-83.
4. Alicia RG, Amaia AQ, Andrés CB. Are oral cefuroxime axetil, cefixime and cefditoren pivoxil adequate to treat uncomplicated acute pyelonephritis after switching from intravenous therapy? A pharmacokinetic/pharmacodynamic perspective. Enferm Infect Microbiol Clín. 2020;38(7):306-11.
5. Lilith KW, Peter JW, Xavier D. Estimating the fitness cost and benefit of cefixime resistance in Neisseria gonorrhoeae to inform prescription policy: A modelling study. PLOS Med. 2017;14(10): e1002416.
6. Faraj LA, Alrawithi DS, Alkhatabi SA, Alotaibi SB, Nooli ME, Alharthi RS, et al. Evaluation of the Recent Updates Regarding Diagnosis and Management of Bronchiolitis: Literature Review. Arch Pharm Pract. 2020;11(3):48-51.
7. Chrysovalantis S, Kori K, David T, Pamela B, Carl M, Jeffrey DK. Clinical Efficacy of Cefixime for the Treatment of Early Syphilis. Clin Infect Dis. 2021;26;ciab187.
8. Shivani NM, Chrysovalantis S, David MT, Pamela LB, Cliff MO, Carl EM, et al. Clinical trial protocol to evaluate the efficacy of cefixime in the treatment of early syphilis. Trials. 2020;21(1):1009.
9. Melanie MT, Edna OK, Maria ALA, Mariangela FS, Angelica EM, Ivo CC, et al. Phase II trial evaluating the clinical efficacy of cefixime for treatment of active syphilis in non-pregnant women in Brazil (CeBra). BMC Infect Dis. 2020;20(1):405.
10. Khan FA, Zahoor M, Islam NU, Hameed R. Synthesis of cefixime and azithromycin nanoparticles: an attempt to enhance their antimicrobial activity and dissolution rate. J Nanomater. 2016;2016.

11. Mogal P, Derle D. Optimization and Formulation Development of Cefixime Complex Using Spray Drying Technique: DOE Approach. *J Appl Pharm.* 2017;9:3,10000245.
12. Prashanta KP, Prasanna KD, Uma SM. Formulation development and evaluation of cefixime Mucoadhesive tablets using natural polymers. *Eur J Mol Clin Med.* 2021;8(1):1995-2008.
13. Elambharathy E. Bioequivalence Guidelines Requirements for Orally Administered Generics (IR Products) in Gulf Cooperation Council Countries, European Union and United States of America. *J Bioequivalence Bioavailab.* 2019;11(1):6-13.
14. Tiwari R, Sandil S, Nain P, Kaur J. Bacteriological Analysis with Antimicrobial Sensitivity and Resistance Pattern in Blood Culture of Septicemic Patient from Different Wards of a Tertiary Care Hospital in India. *Int J Pharm Phytopharmacl Res.* 2020;10(4):112-9.
15. Kees F, Naber KG, Sigl G, Ungethüm W, Grobecker H. Relative bioavailability of three cefixime formulations. *Arzneimittelforschung.* 1990;40(3):293-7.
16. Eveno E, Brault M, Monique M, Sibille M, Montay G, Vital D. Bioequivalence Study of Two Formulations (Sachet and Tablet) of Cefixime after Single Oral Doses of 200mg in Healthy Male Volunteers. *Clin Drug Investig.* 2001;21(4):287-94.
17. Asiri YA, Al-Said MS, Al-Khamis KI, Niazy EM, El-Sayed YM, Al-Rashood KA, et al. Comparative bioavailability study of cefixime (equivalent to 100 mg/5 ml) suspension (Winex vs Suprax) in healthy male volunteers. *Int J Clin Pharmacol Ther.* 2005;43(10):499-504.
18. Ahmad Al-S, Samir HA, Adil A Al-S. A randomized, single dose, two treatment, two period, crossover bioequivalence study of cefixime (as trihydrate) suspension in healthy participants comparing Acacime® suspension produced by ACAI / Iraq to Suprax® suspension produced by Hikma / Jordan. *Al-Mustansiriyah J Pharm Sci.* 2017;1(1):163-9.
19. Zakeri-Milani P, Valizade H, Islambulchilar Z. Bioavailability study of two cefixime formulations administered orally in healthy male volunteers. *Arzneimittelforschung.* 2008; 58(2):97-100.
20. Hossein D, Mehrdad H. Pharmacokinetics and Bioequivalence Study of Two Formulations of Cefixime in Healthy Male Volunteers. *Iran J Pharm Res.* 2016;12(4):1-14.
21. Mudassar AM, Ljaz J, Bilal A, Tanweer K. Cefixime; disposition kinetics and bioavailability comparison of two formulations of cefixime in healthy adult male subjects. *Prof Med J.* 2015;22(7):959-65.
22. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonized Guidance: Guidance for Good Clinical Practice E6(R2), Current Step 4 version dated 9 November 2016.
23. WMA Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
24. Khan A, Iqbal Z, Khan MI, Javed K, Khan A, Ahmad L, et al. Simultaneous determination of cefdinir and cefixime in human plasma by RP-HPLC/UV detection method: Method development, optimization, validation, and its application to a pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011;879(24):2423-9.
25. Raveendra B, Lakshmana AR, Rao J. Bioanalytical Method Development and Validation for Simultaneous Estimation of Paracetamol and Cefixime by using RP-HPLC in Rabbit Plasma. *Orient J Chem.* 2016;32(1):701-7.
26. Mohamed MA. Efficient UPLC and spectrophotometric MC methods for simultaneous determination of cefixime and sodium benzoate in their dosage form and in its degradation product of cefixime-E Isomer. Application of lean six sigma and in-vitro dissolution studies. *Sci Chromatogr.* 2019;11(4):167-85.
27. Ahmadreza A, Ali N. Partial Least Square and Parallel Factor Analysis Methods Applied for Spectrophotometric Determination of Cefixime in Pharmaceutical Formulations and Biological Fluids. *Iran J Pharm Res.* 2018;17(4):1191-200.
28. Bashir E, Mohammad AA. Determination of Cefuroxime Axetil and Cefixime Trihydrate in Pharmaceutical Dosage Forms by RP-HPLC Method. *Pharm Anal Chem.* 2016;2(2):1-5.
29. Bioanalytical Method Validation Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), 2018.
30. Leon S, Andrew BCY, Murray D. Shargel and Yu's Applied Biopharmaceutics & Pharmacokinetics, 8th ed. McGraw-Hill Education/Medical: New York, NY, USA. 2021.
31. Hartmut D, Stephan S. Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications, 5th ed. LWW: Philadelphia, PA, USA. 2019.
32. Patrick S, Thomas RV. Nonparametric Statistical Methods in Medical Research. *Anesth Analg.* 2020;131(6):1862-3.