Original Article

EFFECTS OF GENETIC & ENVIRONMENTAL FACTORS ON THE PHARMACOKINETICS OF CEFUROXIME FOLLOWING INTRAMUSCULAR ADMINISTRATION IN HEALTHY ADULT MALES FROM PAKISTAN

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Abstract:

Background: Cefuroxime is an extensively prescribed broad-spectrum beta-lactam antibiotic employed to treat a wide range of bacterial infections. Variability in drug response and pharmacokinetics due to genetic and environmental variations among population subsets during clinical trials necessitate the need for a comprehensive study of the drug's pharmacokinetics in the Pakistani population.

Materials & Methods: The pharmacokinetic study was carried out on eight adult male healthy volunteers at the dose of 10.7 mg/kg/intramuscular. Samples of blood were taken at predetermined time intervals 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours. High performance liquid chromatography (HPLC) was used to measure the cefuroxime concentration in plasma. Pharmacokinetics of cefuroxime, in the Pakistani population, were determined by plasma concentration time curve using two compartment open model without lag time.

Results: Pharmacokinetic parameters (mean±SD) were calculated and came out to be; maximum plasma concentration (Cmax) 31.35±0.90µg/ml, time to reach maximum plasma concentration (Tmax) 0.75±0.02h, volume of distribution (Vd) (0.28±0.02l/kg, half-life (t1/2) 1.4±0.1h, area under curve (AUC) 78.7±3.56µg h/mL.

Conclusion: In the Pakistani population it is suggested that minimum inhibitory concentration can be achieved by 1.5µg/mL of plasma level. The optimum dosage regimen of 7.31 mg/kg of body weight for the primary dose, and 7.16 mg/kg of body weight as the maintenance dose, to be repeated every 8 hours.

Keywords: Cefuroxime, Pharmacokinetics, Metabolism, Genetic Polymorphism, Environmental Factors

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INTRODUCTION:

The reliability of drug treatment in various genetic subsets of patients is the main goal of clinical trials during which a limited number of patients and lack of variability in genetic groups are the prime reasons for the failure to achieve this objective in clinical trials.[1] Lack of

clinical trial programs in developing countries due to various barriers such as limited research and development (R&D) facilities, and other operational barriers lead to inadequacy of literature describing therapeutic efficacy of developing country population.[2] Similarly, in Pakistan R&D of medicines is only limited to the development of pharmaceutical formulations and new lead compounds.[3] Several internal and external factors contribute to the variability in the response of drugs, including sex, race, age group, ethnic background, the status of liver and kidney functions, polymorphic isoforms of cytochrome-P 450 enzymes, and expressions of drug-membrane transporters. External factors include drug-food interactions, drug-drug interactions, and environmental factors such as xenobiotics.[4] Literature illustrates that almost 25–50% of patients show either inadequate or exaggerated responses to the drug due to these factors.[5] Genetic polymorphism causes phenotypic differences within individuals that not only cause variability in drug transport, distribution, and metabolism but also in observed pharmacodynamics. The inter-individual variability due to polymorphism in drug-metabolizing enzymes in different ethnicities is apparent even if equivalent doses of the same drug are administered. Therefore, this enzymatic polymorphism results in varied drug metabolism, which in turn is related to the unpredictability of drug response in a given population.[6] As a result of genetic and environmental factors and subsequent differences, the optimum therapeutic dosage regimen of imported drugs should be evaluated in the local population.[7]

Cefuroxime is a 2nd generation broad spectrum cephalosporin antibiotic that is resistant to β-lactamases. It can be administered via the intravenous, oral, or intramuscular routes. It is used to treat infections mainly caused by Gram-positive bacteria and a few Gram-negative bacteria. Cefuroxime is a bactericidal antibiotic, and its mechanism of action involves inhibition of the bacterial cell wall by binding to penicillin-binding proteins (PBPs).[8,9] Cefuroxime exhibits plasma protein binding ranging from 33-50% with a volume of distribution between 19.3 and 15.8 L per 1.73 m^2 of body surface area.[10] After administration, the drug is distributed across various body tissues, including the eye, gallbladder, kidneys, bones, and inflamed meninges. Effective concentrations are also attained in the amniotic fluid, umbilical cord blood, and the central nervous system. The oral dosage form was found to be less bioavailable due to the hampered absorption of the administered dose that has confined its use by the parenteral route compared to oral dosage forms.[11,12,13] As discussed earlier, the pharmacokinetic parameters of cefuroxime with various factors that ultimately affect the dosage regimen and may affect the prognosis of the disease for which it is being employed.

According to the analysis of unsuccessful antibiotic treatment, insufficient tissue concentrations of antibiotics were identified as the primary cause of their ineffectiveness.[34] The minimum inhibitory concentration of cefuroxime was reported to be between 0.5-2μg/mL, and ≥ 1μg/mL for the majority of susceptible pathogens.[35,36] In the current study, the recommended dose of cefuroxime (10.7 mg/kg) was insufficient to sustain therapeutic concentrations for 12 hours in healthy adult male subjects. The dosage regimen should be defined based on the pharmacokinetic parameters of drugs investigated in local populations where they are employed clinically Thus, to achieve maximum efficacy of a given drug, it is imperative to assess it in the local population and then modify the dosage regimen according to the obtained results.[14,15] This way, the dosage regimen and drug therapy can be tailored according to the indigenous population.

Therefore, the objective of the present study was to assess and evaluate the pharmacokinetic parameters of cefuroxime sodium in healthy local Pakistani volunteers. Furthermore, the study also evaluated whether genetic and/or

environmental factors had any effect on cefuroxime in the Pakistani population.

MATERIALS AND METHODS:

Eight healthy young male volunteers were included in this study. The investigation was conducted at the University of Agriculture, Faisalabad, within the Institute of Pharmacy, Physiology, and Pharmacology. The study was conducted over a day of one day in May 2020, during which a single dose of cefuroxime was administered to healthy male volunteers, and pharmacokinetics were assessed at predetermined time intervals. The study was performed in compliance with good clinical practices and was initially screened and accredited by the Ethical Committee of the University of Agriculture, Faisalabad. The experimental research was approved by the Graduate Studies and Research Board (GSRB) of The University of Agriculture Faisalabad. Complete information regarding the experiment was provided to all participants and informed consent was obtained before the beginning of the investigation.

Volunteers were selected based on their previous medical history and laboratory investigations, including hematological parameter screening, blood chemistry, and urinalysis. Healthy individuals without the evidence of any acute or chronic hepatic & renal disease, and/or beta-lactam antibiotic allergy were included in the study. The volunteers were advised and monitored for not taking any medication two weeks before and during the investigation period. Obesity, cefuroxime sensitivity, known allergy to beta-lactam antibiotics, smoking, and exposure to any drug one week before study onset time, and missing informed consent were decided as exclusion criteria. All subjects were maintained on the same diet throughout the study period. The demographic characteristics of the male participants in the study were as follows: the average age was 26.87 years, with standard deviation (SD) of 0.29 years. The mean weight was 70.87 kg, with a SD of 0.63 kg. The average height of the subjects was 165.37 cm, with a SD of 1.1 cm.

A single dose study design was used as described by R. D. Foord (1976) to investigate the effects of genetic and environmental factors on the pharmacokinetics of cefuroxime in the Pakistani population.[18] After overnight fasting, a single dose of cefuroxime sodium 750 mg was administered intramuscularly to all the subjects. The same breakfast and lunch were given to the subjects according to their schedule. Beverages and foods containing caffeine were not allowed during the study period. A sterile cannula (24G) was used to withdraw 5ml blood samples in heparinized vacutainers at pre-selected or pre-determined time intervals of 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6h. Plasma was made from the blood samples. This was performed by centrifuging the vacutainers at 2500 rpm for 15 min. Once the plasma was separated, it was kept at -20°C till further analysis.

A reference standard powder of cefuroxime was provided by GlaxoSmithKline Laboratories Limited, Karachi, Pakistan. Zinacef® injection vials (cefuroxime sodium 750mg) of GlaxoSmithKline Laboratories Limited, Karachi. HPLC-grade acetic acid, methanol, and dimethylformamide (DMF) were purchased from Merck Chemical Laboratories (Germany).

Plasma samples for cefuroxime sodium were analyzed using high-performance liquid chromatography (HPLC), as described and validated by Olguin et al.[16] Separation of cefuroxime separation was carried out in a BDS thermohypersil (4.6×250 mm; 5µm) C18 column. The mobile phase, consisting of acetic acid/water/methanol at a ratio of 1:69:30 (v/v), was eluted at a flow rate of 1.5mL/min and the effluent was analyzed using a UV detector (Sycum S32012) at a wavelength of 281 nm, whereas the column temperature was fixed at 35 °C.

Control samples with known concentrations of cefuroxime were prepared by dissolving 1 mg of cefuroxime sodium in 1000µL distilled

water to obtain concentrations of 1µg/µL which were further used to prepare dilutions of the cefuroxime standard at concentrations of 1, 10, 20, 40, 50, 60, 100 and 500µg/mL.

Cefuroxime was extracted from the plasma samples by adding 1mL of dimethylformamide to 1mL of plasma. The mixture was vortexed for 5 min, followed by centrifugation at 400 g for 10 min. The supernatant (0.8mL) was diluted with an equal amount of water to allow it to pass through 0.45 µ filters.

The retention time for cefuroxime was 7.5 minutes without any significant interfering peaks. The calibration curve showed a linear relationship over the concentration range of 0.5-500µg/ml. The detection limit of cefuroxime was 0.5µg/mL and the limit of quantification was 1µg/mL. The regression equation was *y=24.2x+427.85* and the correlation coefficient was R_2= 0.9992.

A semi-logarithmic graph paper was used to plot a graph between plasma concentrations and time. Data was analyzed using two-compartmental open model. Drug concentration was calculated from plasma samples using individual plasma drug concentration-time curves. Cefuroxime Half-life (t1/2), peak plasma concentration (Cmax), time to peak plasma concentration (Tmax), and area under the curve (AUC) were the pharmacokinetic parameters that were calculated. The pharmacokinetic parameters of cefuroxime were calculated using MW/PHRAM software, version 3.02 (copyright 1987–1991) by F. Rombout. This MEDI WARE product was developed in collaboration with the University Centre for Pharmacy, Department of Pharmacology and Therapeutics at the University of Groningen, and Medi/Ware.

RESULTS:

Pharmacokinetic parameters of cefuroxime were analyzed by two-compartmental open model without lag time and are described in Table 2. The mean plasma concentration of cefuroxime in healthy subjects following a single intramuscular administration of cefuroxime at 10.7mg/kg is shown in Figure 1. Time to peak plasma concentration (T_{max}) was calculated to be 0.75±0.02 hr at 10.7 mg/kg/IM. In the present study, absorption of cefuroxime was found to be rapid and the drug was detected in plasma after 0.25h. Maximum plasma concentration (C_{max}) was calculated to be 31.35±0.90µg/mL. The elimination half-life was calculated to be 1.4±0.1h.

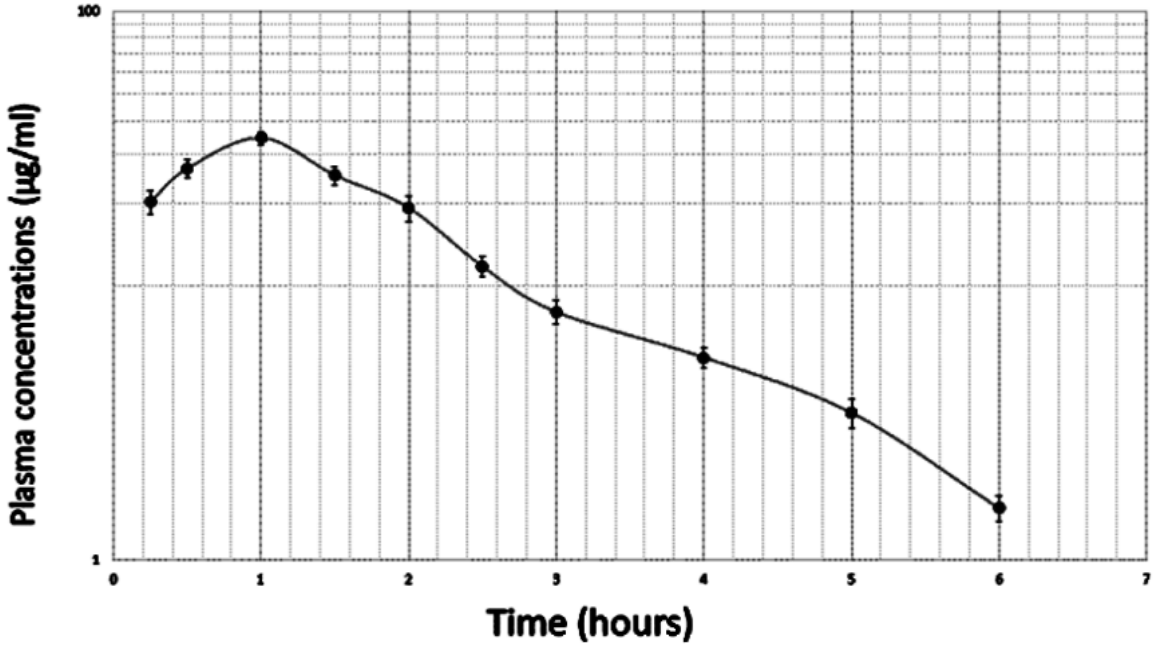

Figure 1: Mean ± SD plasma concentration time curve of cefuroxime

Parameter	C_{max} (µg/ml)	T_{max} (hr)	K_a (hr^{-1})	$t_{1/2\alpha}$ (hr)	A (µg/ml)	α (hr^{-1})	B (µg/ml)	β (hr^{-1})	$t_{1/2\beta}$ (hr)	V_c (l/kg)	V_d (l/kg)	K_{el} (hr^{-1})	K_{12} (hr^{-1})	K_{21} (hr^{-1})	Cl (l/hr/kg)
Mean	31.35	0.75	1.63	0.43	48.74	1.52	22.97	0.49	1.4	0.15	0.28	0.91	0.28	0.83	0.13
±SD	0.90	0.02	0.12	0.03	7.32	0.23	5.6	0.03	0.1	0.01	0.02	0.07	0.05	0.16	0.01

*maximum plasma concentration (**C_{max}**)*
*time to peak plasma concentration (**T_{max}**)*
*absorption rate constant (**Ka**)*
*distribution half-life (**$t_{1/2\alpha}$**)*
*zero-time drug concentration at distribution phase (**A**)*
*the distribution rate constant (**α**),*
*zero-time drug concentration at elimination phase (**B**)*
*the elimination rate constant (**β**)*
*elimination half-life (**$t_{1/2\beta}$**)*
*the volume of distribution of the central compartment (**V_c**)*
*volume of distribution (**V_d**)*
*the elimination rate constant (**K_{el}**)*
*first order transfer rate constant for distribution from central to peripheral compartment (**K_{12}**)*
*first order transfer rate constant for distribution from peripheral to central compartment (**K_{21}**)*
*clearance (**Cl**)*

DISCUSSION:

The values of maximum plasma concentration, time to peak plasma concentration, AUC, volume of distribution, t1/2, and clearance were compared to those reported in other studies conducted in various population subsets, as referenced in the literature. The differences in maximum plasma concentration and time to reach peak plasma concentration of the drug are influenced by physiological factors such as age, diet, sex, enzymatic polymorphism, and pharmaceutical factors that are related to drug such as particle size, crystal shape or salt form, and the nature of excipients, which ultimately affect the rate and extent of drug absorption from the site of administration.[7, 18] Both C_{max} and T_{max} are also influenced by the dose, dosage form, and route of administration.

The peak plasma concentration time (T_{max}) for the 10.7 mg/kg dose administered intramuscularly was 0.75 hours ± 0.02, which was consistent with a prior study conducted on the American population that used the same dosage.[17] In contrast, an Arab population study at a 7 mg/kg dose found a T_{max} of 1.92 hours ± 0.62.17 A study by Barbour et al. (2009) reported a T_{max} of 0.60 hours ± 0.22, which was similar to the current study's T_{max}.[20]

The maximum plasma concentration (C_{max}) for the present study, at 31.35 µg/mL ± 0.90, was lower than the C_{max} of 34.90 µg/mL observed at the same dosage in the prior study. The C_{max} in the current study was also lower than the C_{max} of 66.8 µg/mL ± 18.9 µg/mL observed in a study at a much higher dose of 20 mg/kg that was administered intravenously.[17, 19] The C_{max} of the suspension dosage form was 7µg/mL at a dose of 20mg/kg given orally, which was lower compared to the C_{max} in the present study.[19] In the Arab population, C_{max} was 4.28±1.47 and

4.48±1.18µg/mL at a dose of 7mg/kg of two different formulation.[17]

The elimination half-life ($t_{1/2\beta}$) of the drug depends on clearance and volume of distribution. It changes as a function of clearance and volume of distribution. An Iraqi study reported a half-life of 1.5 ± 0.62h for cefuroxime at a dose of 7mg/kg given orally while it was 1.4h in our study.[22] A study also found the same half-life of cefuroxime in children at a dose of 15mg/kg given orally.[21] However, it was 1.8h at a dose of 15mg/kg given intravenously (IV) in a study by Nascimento et al., which was longer than the present study.[23] The elimination half-life of cefuroxime was reported to be 3.07±0.37h in foreign neonates, which could be due to under-developed excretory organs that result in slow elimination of the drug from the body.[22] In the Arab population, the elimination half-life of two different brands of oral cefuroxime at a dose of 4mg/kg was 1.22±0.25h and 1.13±0.18h, which was shorter than the present study.[17] Similarly, a shorter half-life of cefuroxime in the Polish healthy population had been reported at a dose of 7mg/kg.[24,25] The half-life of cefuroxime was found 1.50±0.63h in dogs at a dose of 10mg/kg given intramuscularly (IM), while in rats was 37.5±8.5 min at a dose of 2.02mg/oral.[26,27] In goats, cefuroxime half-life was longer at a dose of 40mg/kg IM was 2.11h, which was considerably longer than the present study.[28] The difference in half-life might be due to differences in drug administration, elimination rate constants, and differences in species.

The average volume of distribution (Vd) in the Pakistani population was less than the reported Vd of cefuroxime at 25mg/kg/IV in neonates.[21,22] Nascimento et al. reported a reduced volume of distribution (Vd) for cefuroxime (0.19 L/kg) in patients undergoing cardiopulmonary bypass surgery.[23] The Vd in children with mild, moderate, and severe disease conditions was 1.5,1.9 and 3.1/kg, respectively, which was higher than the present study. This above-mentioned difference in Vd may be due to the drug-disease interaction.[17]

A study reported clearance of cefuroxime of 0.08 ± 0.016/kg/h in neonates while it was 0.14±0.01/kg/h in the present study.[24] The clearance of cefuroxime was calculated to be 6.01/h and 8.6/h in the Swedish and Dutch healthy population, respectively, which were comparable to the present study conducted in the Pakistani population.[29,30] The total plasma clearance of cefuroxime in goats and dogs was 29.08±2.61 at 20mg/kg/IM dose and 0.31±0.03/kg/h at 20mg/kg/IV dose, respectively, which was much higher than the present study.[26,31] The difference in total body clearance of cefuroxime in comparison to other population subsets and species may be due to differences in cefuroxime plasma protein binding and renal perfusion rate.[32,33]

Al-Said et al. reported a lower Kel of cefuroxime in the Arab population as compared to the findings of the present study.[19] No significant difference was found between the Kel in the current study and other studies conducted in varied subsets of the healthy population of different ethnicities.[20,22] Therefore, no effect of genetics and environment was found on the elimination rate constant of cefuroxime.

CONCLUSION:

Cefuroxime, a beta-lactam antibiotic, exhibits time-dependent killing. The dosing interval should be adjusted so that the plasma drug concentration remains above the minimum inhibitory concentration for the duration of the dosing interval. Based on results obtained and subsequent analysis from the present investigation, the recommended dosage regimen for cefuroxime in the Pakistani population is recommended to be 7.31 mg/kg and 7.16 mg/kg as priming and maintenance dose, respectively, to be administered every 8 hours.

AUTHOR'S CONTRIBUTION:

SS: Conceptualization

MHUR: Statistical Data Analysis, Manuscript writing
MR: Manuscript Writing and Editing
SY: Manuscript Editing
QAI: Supervision, Critical Review
SR: Data Collection

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