

## Disposition kinetics, renal clearance and urinary excretion of cefixime in adolescent Pakistani boys

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### Abstract

**Objectives:** To investigate the role of environmental variation, genetic differences and age on disposition kinetics, renal clearance and urinary excretion of oral cefixime 400mg in healthy boys.

**Methods:** The cross-sectional study was conducted at the University of Agriculture, Faisalabad, Pakistan, from August 2014 to July 2015, and comprised healthy boys aged 12-17 years after oral administration of cefixime capsule 400mg. Serum and urine samples were collected before and after drug administration and were stored at -20°C until evaluation of cefixime concentration in each sample by high performance liquid chromatography. Drug concentration versus time data was used for pharmacokinetic calculations using one compartment model. Data obtained for urinary excretion and renal clearance of cefixime was analysed using regression-correlation analysis.

**Results:** There were eight boys in the study. Mean values for elimination half-life, volume of distribution and total body clearance were  $2.4 \pm 0.2$  hours,  $0.9 \pm 0.0L/kg$  and  $0.3 \pm 0.0L/h/kg$ , respectively. The ratio of renal clearance of cefixime ( $0.7 \text{ ml/min/kg}$ ) to that of endogenous creatinine ( $0.8 \text{ ml/min/kg}$ ) was 0.9. Cumulative mean percentage of cefixime excreted from young adolescent boys was  $11.6 \pm 0.5\%$ .

**Conclusions:** Other than filtration, back-diffusion was also involved in renal handling of cefixime. There was enough indication that major portion of cefixime was excreted from a young body through bile.

**Keywords:** Cephalosporins, Diffusion, Diuresis, Differences, Elimination, Kinetic. (JPMA 69: 367; 2019)

### Introduction

It is essential that the concentration of antibiotic must be adequate at the site of infection and must be retained for a suitable time.<sup>1</sup> Developmental changes during the first few days, months, or years of life influence both the rate and extent of oral drug absorption in paediatric patients. Stomach acidity is decreased in paediatric patients by frequent intake of milk. Thus, weak acidic drugs are absorbed more slowly than weak basic drugs in paediatric patients compared to adults. Distribution of drugs in the body is related to body composition. Neonates have a much high proportion of body mass in the form of water than older children or adults. Total body water (TBW) in infants is about 75% of the body mass whereas it is about 85% of the body mass in small premature infants. The TBW level gradually decreases with age; adult value (55% TBW) is attained by 12 years of age.<sup>2</sup> Therefore, volume of drug distribution, which is parallel to body water contents, is mostly higher for children than adults.

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Permeability of cell membranes is also greater in immature infants, and, therefore, drug entry into some compartments is enhanced. Brain-plasma ratios of anticonvulsant drugs are higher in infants and children compared to adults.<sup>3</sup> The important factor of influencing drug distribution is the extent of drug protein binding. Albumin concentration directly increases with gestational age. Neonate serum contains approximately 80% protein.<sup>4</sup> So, binding affinity to albumin for many drugs appears lower in neonates than in adults. The enzymatic system, which is responsible for drug metabolism, is immature (less active) at birth and its capacity increases with advancing age.<sup>5</sup> Inhibition of drug metabolising enzymes by co-administered drugs also play important role in drug biotransformation and bioavailability.<sup>6</sup> This low activity may be due to low levels of hepatic uptake, low concentrations of intracellular carrier or low levels of bile production.<sup>7</sup> However, it was found that the activity of metabolic enzymes in neonates, infants and children is about 20% to 70% of adults, revealing that actual enzyme activity does increase with age.<sup>4</sup> Conjugation activity of endogenous substances and drugs is low at birth, but increases to reach adult levels (in children) by three years of age.<sup>3,7</sup> Drugs which are mainly excreted through bile may become toxic in neonates and infants due to low

activity of the enzymatic system responsible for their detoxification and elimination. Similarly, blood flow, glomerular filtration rate (GFR), ability to manage concentration, acidity and tubular functions (including re-absorption and secretion), are lower in children and infants compared to adults. Thus, renal function in infants and children is lower compared to adults. It was found that GFR is low in neonates then increases gradually to adult values.<sup>8</sup>

Cephalosporins are  $\beta$ -lactam antibiotics with a broad antibacterial spectrum and are being widely used. Cefixime is an orally active third-generation cephalosporin and is well stable to inactivation by  $\beta$ -lactamase enzyme. Cefixime is available for paediatric as well as for adult patients in different formulations and strengths.<sup>9,10</sup>

Pakistan imports raw material and finished products for clinical use in human beings and animals. It has been reported that genetic make-up in human beings and animals is different in different countries. Thus, pre-clinical and clinical studies must be performed for imported drugs too.<sup>9-11</sup>

The literature available on pharmacokinetics and excretion of cefixime in young and local population is scanty. The current study was planned to assess the pharmacokinetics, renal clearance and urinary excretion of cefixime in healthy young volunteers to understand the contribution of factors such as age, genetic and environmental variability in the pharmacokinetics, renal clearance and urinary excretion of cefixime in indigenous conditions.

## Methods

The cross-sectional study was conducted at the University of Agriculture, Faisalabad, Pakistan, from August 2014 to July 2015, and comprised healthy boys aged 12-17 years after oral administration of cefixime capsule 400mg. After approval was obtained from the institutional review board, weight and height of all the volunteers was measured. After laboratory investigations and clinical history, all the young bodies were declared healthy and fit for the study. Volunteers were found to be non-allergic to any  $\beta$ -lactam antibiotic. They were given the same diet on the day of sampling and no carbonated drink, ice creams and tea/coffee were allowed to be taken till the collection of the last sample. Written informed consent was taken from parents/guardians of each volunteer.

Cefixime capsule 400mg was administered to each healthy young boy after a washout period of seven days. A blank urine and blood sample was collected prior to

drug administration. Further blood samples were taken at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hours post-administration. Urine samples were obtained at 45, 75, 105, 135, 165, 240, 480, 600 and 720 min post-administration of cefixime. A potential of hydrogen (pH) meter (Beckman HS, Germany) was used to determine pH of each fresh sample with a glass electrode at 37°C. Each collected blood sample was processed for centrifugation to separate the plasma. All the samples were properly stored at -20°C until assayed.

Concentration of cefixime in plasma and urine samples was analysed by high performance liquid chromatography (HPLC) method with an ultra-violet (UV)-visible detector. Column of thermo-hypersil keystone (C-18) was used and flow rate was set at 1ml/min.<sup>9,10</sup>

Concentration of endogenous creatinine in all the samples was determined by using spectrophotometer (Spectronic 212, Bausch and Lomb, Germany) according to the method described in literature.<sup>11</sup>

Plasma concentration of cefixime versus time data was used for calculating parameters of disposition kinetic by one compartment model using MW/PHARM version 3.02 computer programme. Kidney functions of cefixime were estimated after calculation of diuresis, renal clearance of cefixime and creatinine, clearance ratio and cumulative percentage of dose excreted.

Plasma concentration versus time interval data was plotted on a semi-logarithmic scale and analysed by one compartment open model<sup>9</sup> using plasma concentration versus time profile data of cefixime. Mean  $\pm$  SE value for peak concentration of drug in plasma ( $C_{max}$ ), time required to attain  $C_{max}$  ( $T_{max}$ ), area under concentration (AUC) versus time curve, mean residence time (MRT), extrapolated zero time cefixime concentration (B), volume of distribution ( $V_d$ ), rate of absorption ( $K_{abs}$ ), elimination rate constant ( $\beta$ ), absorption half-life ( $t_{1/2abs}$ ), elimination half-life ( $t_{1/2\beta}$ ) and total drug clearance from body (CLB). Least square regression analysis was applied to discriminate the best model and correlation coefficient was taken as measure of goodness-of-fit. The pharmacokinetic parameters were computed with the help of APO version 3.02 a computer programme.<sup>12</sup> The concentration of cefixime and creatinine in urine and plasma samples were used to calculate renal clearance of cefixime and creatinine. Influence of plasma drug concentration, diuresis and urine pH on renal clearance of the cefixime was analysed by regression/correlation method at  $p < 0.05$  level of significance. The urinary excretion of drug was expressed as cumulative percentage of dose excreted. Microsoft Excel version 2010

was used for statistical analysis of data and for calculating mean value with standard error (mean ± SE) for each concentration and parameter.

**Results**

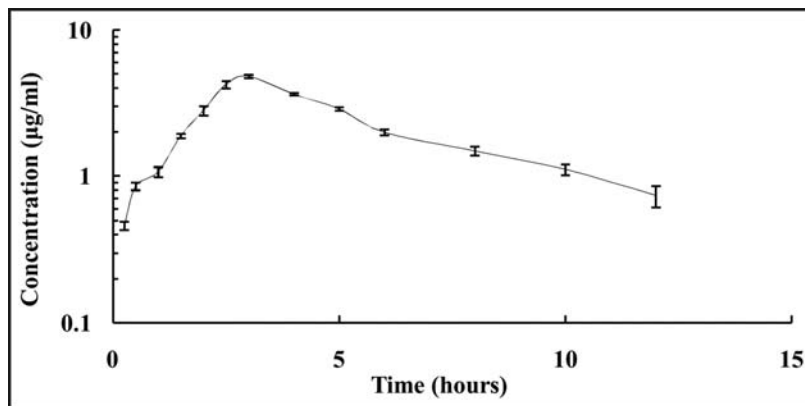
There were eight volunteers in the study with a mean body weight of 54.75±1.73kg. Mean plasma concentration of cefixime reached its peak level 4.8±0.1µg/mL, at 3 hours and then declined progressively to 0.7±0.1 at 12 hours after the oral administration (Figure-1).

Pharmacokinetic parameters were determined using plasma concentration versus time profile data of cefixime (Table-1).

Renal clearance of endogenous creatinine, which is an index of GFR, and of cefixime was investigated in each volunteer (Table-2).

Effect of plasma drug concentration, diuresis and urinary pH on renal clearance of cefixime was also noted (Figure-2). There

was a non-significant negative correlation between plasma drug concentration and renal clearance (p>0.05) (Figure-2a), a non-significant positive correlation with the renal clearance of cefixime (p>0.05) (Figure-2b). Urine pH also showed non-significant positive correlation with the renal clearance of the drug (Figure-2c).



**Figure-1:** Mean ± Standard Error (SE) plasma concentration versus time curve of cefixime 400mg on semi logarithmic scale following single oral administration in healthy young boy.

**Table-1:** Mean ± Standard Error (SE) pharmacokinetic parameters of cefixime 400 mg following oral administration in healthy young volunteers.

Volunteer No	C <sub>max</sub> (µg/ml)	T <sub>max</sub> (hr)	AUC (hr.ug/ml)	MRT (hr)	B (µg/ml)	V <sub>d</sub> (l/kg)	K <sub>abs</sub> (hr <sup>-1</sup> )	t <sub>1/2abs</sub> (hr)	β (hr <sup>-1</sup> )	t <sub>1/2β</sub> (hr)	Cl <sub>B</sub> (l/hr/kg)
1	2.60	3.92	23.60	6.70	7.04	1.03	0.30	2.37	0.30	3.20	0.31
2	2.86	4.89	34.79	8.94	7.78	0.95	0.22	3.10	0.22	3.10	0.21
3	2.90	3.03	27.88	7.07	7.87	0.90	0.28	2.45	0.28	2.50	0.25
4	2.74	4.16	22.85	6.15	7.43	0.91	0.33	2.12	0.33	2.13	0.29
5	2.86	3.56	25.76	6.64	7.76	0.85	0.30	2.30	0.30	2.30	0.26
6	2.94	3.23	24.25	6.06	7.97	0.94	0.33	2.10	0.33	2.10	0.31
7	2.92	3.70	24.59	6.21	7.92	0.87	0.32	2.15	0.32	2.15	0.28
8	2.86	3.92	22.58	5.81	7.77	0.99	0.35	2.01	0.34	2.01	0.34
Mean ± S.E	2.83 ± 0.04	3.80 ± 0.20	25.79 ± 1.42	6.70 ± 0.35	7.69 ± 0.36	0.93 ± 0.02	0.30 ± 0.01	2.33 ± 0.12	0.30 ± 0.01	2.44 ± 0.16	0.28 ± 0.01

C<sub>max</sub> = Maximum plasma drug concentration; T<sub>max</sub> = Time to attain C<sub>max</sub>; AUC = Area under plasma concentration Vs time curve; MRT = Mean residence time; B = Extrapolated zero time drug concentration; V<sub>d</sub> = Volume of distribution; K<sub>abs</sub> = Absorption rate constant; t<sub>1/2abs</sub> = Absorption half life; β = Elimination rate constant; t<sub>1/2β</sub> = Elimination half life; Cl<sub>B</sub> = Renal clearance.

**Table-2:** Mean ± Standard Error (SE) values for body weight, diuresis, pH, plasma and urine concentrations and renal clearance of endogenous creatinine and cefixime in healthy young boys following a single oral dose of cefixime 400 mg.

Volunteer No.	Body weight (kg)	Diuresis ml/min/kg	pH		Creatinine conc. µg/ml		Drug conc. µg/ml		Renal clearance ml/min/kg		Ratio Cef/Creat
			Blood	Urine	Plasma	Urine	Plasma	Urine	Creat.	Cef	
1	45	0.030	7.43	6.403	9.00	270.00	2.02	63.44	0.90	0.94	1.05
2	54	0.021	7.40	6.30	12.00	250.00	2.45	60.55	0.44	0.52	1.19
3	57	0.023	7.45	6.61	10.00	240.00	2.33	62.65	0.55	0.62	1.12
4	59	0.024	7.41	6.29	9.00	250.00	2.34	68.72	0.67	0.71	1.06
5	60	0.027	7.44	6.36	8.00	230.00	2.48	63.71	0.77	0.69	0.90
6	53	0.032	7.44	6.68	9.00	280.00	2.99	79.69	0.99	0.84	0.86
7	58	0.023	7.43	6.072	8.00	270.00	2.49	75.62	0.77	0.69	0.90
8	52	0.031	7.41	6.39	7.00	260.00	2.86	73.22	1.15	0.79	0.69
Mea±S.E	54.75±1.73	0.03±0.00	7.43±0.01	6.39±0.07	9.00±0.53	256.25±5.96	2.49±1.11	68.45±2.48	0.78±0.08	0.73±0.05	0.97±0.06

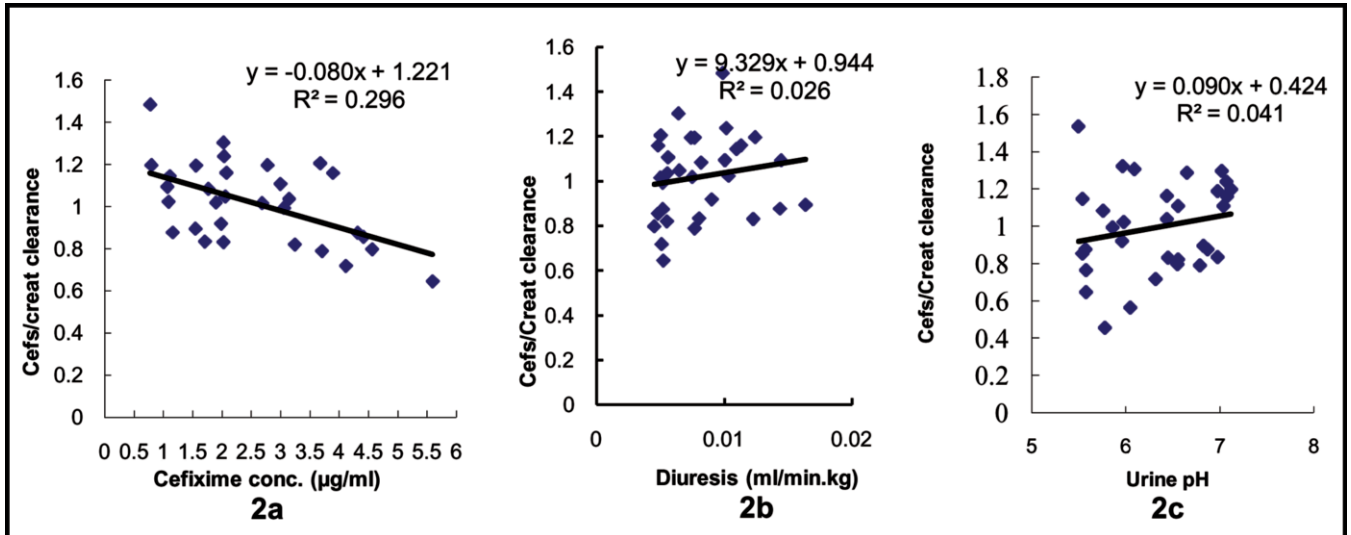


Figure-2: Effect of plasma drug concentration (2a), diuresis (2b) and urine pH (2c) on renal clearance of cefixime 400 mg after oral administration in healthy young male subjects.

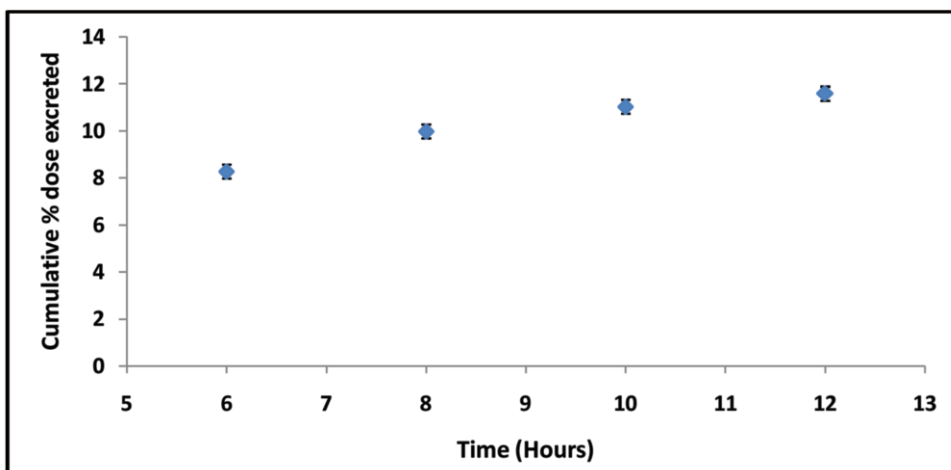


Figure-3: Cumulative percentage of the dose excreted in young boys after an oral administration of cefixime 400 mg.

Mean cumulative percentage of cefixime dose excreted in individuals via urine up to 12 hours after the drug administration was  $11.6 \pm 0.5\%$  (Figure-3).

## Discussion

An antibiotic should maintain its therapeutic level or minimum inhibitory concentration (MIC) in plasma or serum during the course of antimicrobial therapy. Cefixime is effective against most pathogenic bacteria at 0.1-1.0  $\mu\text{g/ml}$ .<sup>12</sup>

In healthy young boys in the current study, an upper limit of cefixime MIC 1.0  $\mu\text{g/ml}$  was maintained in plasma for 10 hours after the drug administration. However, plasma levels of the drug did not fall below the lower limit of MIC

0.1  $\mu\text{g/ml}$  even after 12 hours of sampling. The results are in close agreement with previous studies in which cefixime 400mg was administered orally in adult male subjects and the plasma levels of it were maintained above the lower limit of MIC 0.1  $\mu\text{g/ml}$  throughout the experimental period.<sup>9</sup>

The elimination half-life (2.4 hours) of cefixime in healthy young boys of aged 12-17 years old in present study was shorter than 5.0 and 4.7 hours,<sup>9</sup> 4.2 hours<sup>13</sup> and 3.5 hours<sup>14</sup> after oral administration of cefixime

400mg in healthy adult male subjects. The shorter elimination half-life of cefixime in local young boys compared to their foreign counterparts may be attributed to the lower value of  $V_d$  in the young boys of the present study.

The apparent  $V_d$  (0.9 l/kg) of cefixime in the present study was higher than 0.004 l/kg for cefixime in sheep and 0.01 l/kg in cattle<sup>15</sup> and 0.3 L/kg in human subjects.<sup>16</sup> However, the present  $V_d$  values were lower than 1.3L/kg<sup>9</sup> and 1.1 L/kg<sup>17</sup> after 400mg oral administration and 1.7 L/kg after 200mg intravenous administration<sup>18</sup> of cefixime in adult counterparts. Further, higher values of 2.2 and 2.8 L/kg were recorded in dogs following oral doses of 6.3 and 25 mg/kg cefixime, respectively.<sup>19</sup> A possible explanation for

the lower value of  $V_d$  in the present study may be linked to the higher extrapolated zero time drug concentration (B) compared to its lower values in the above cited studies.

In the current study, the  $Cl_B(0.3 \text{ l/hr/kg})$  in local young boys was comparable to  $0.2 \text{ l/hr/kg}$  for ceforal-3 and higher than  $0.16 \text{ l/hr/kg}$  for cefspan<sup>9</sup> and  $0.1 \text{ l/hr/kg}$  for cefixime<sup>17</sup> 400mg in healthy adult subjects. A higher value of  $Cl_B$  in local young boys than the values reported in literature may be related to the higher value of  $\beta$  and  $V_d$  or shorter  $t_{1/2\beta}$  in the present study than that of the values reported above.

The urine flow rate in young boys ( $0.03 \pm 0.0 \text{ ml/min/kg}$ ) recorded in the present study was similar to the values of urine flow reported as  $0.01 \text{ ml/min/kg}$ ,<sup>10</sup> and  $0.02 \text{ ml/min/kg}$ .<sup>11</sup> Water intake, environmental conditions, metabolic status of experimental subjects and several other factors may affect the rate of urine flow.

In the present study, pH of blood was  $7.4 \pm 0.0$  and of urine it was  $6.4 \pm 0.1$ . These pH values were comparable to pH of blood (7.4 and 7.6) and pH of the urine (6.3 and 6.2), respectively.<sup>11</sup> In another study pH of blood was recorded as  $7.5$ .<sup>10</sup>

Renal clearance ( $0.8 \pm 0.1 \text{ ml/min/kg}$ ) of endogenous creatinine in the present study was higher than  $0.4 \text{ ml/min/kg}$ <sup>20</sup> but lesser than the previous reported values i.e.  $1.7 \text{ ml/min/kg}$ <sup>21</sup> and  $1.03 \text{ ml/min/kg}$  in healthy volunteers.<sup>10</sup>

Plasma and urine concentrations of cefixime in the present study were  $2.5 \pm 0.1$  and  $68.5 \pm 2.5 \text{ } \mu\text{g/ml}$ , respectively. The renal clearance of cefixime was  $0.7 \pm 0.1 \text{ ml/min/kg}$  which was lower than  $0.2 \text{ ml/min/kg}$  reported previously.<sup>10</sup> Similarly, clearance ratio ( $0.9 \pm 0.1$ ) of the present study was greater than the ratio ( $0.3 \pm 0.1$ ) reported previously.<sup>10</sup> The lesser value of clearance ratio of cefixime indicates reabsorption or back-diffusion of the drug.

Negative correlation between concentration of cefixime in plasma and ratio of renal clearance of cefixime to renal clearance of creatinine showed the saturation of excretory mechanism at higher plasma concentration of drug which reveals the involvement of active secretion at tubular level. The positive correlation between diuresis and clearance ratio means that with increase in the rate of urine flow, the rate of cefixime clearance also increased. It means that at lower diuresis, the drug will have more time to stay in the renal tubules from where it would be reabsorbed. It was concluded that reabsorption or back-diffusion was also involved in renal handling of cefixime besides its glomerular filtration. The positive correlation between urine pH ( $6.4 \pm 0.1$ ) and ratio of renal clearance of cefixime and renal clearance of creatinine indicated ionization of drug at basic urine. As cefixime is an acidic drug having acid dissociation constant (pKa) of 2.5, its excretion

increases when pH value of the urine is increased.<sup>22</sup> The sample size was small that could have resulted in statistical tests with P values being underpowered as a limitation.

Similar positive correlations of urinary pH and diuresis and negative correlation of plasma drug concentration with that of clearance ratio of cefixime were observed earlier.<sup>10,23</sup>

Urinary excretion of substances (endogenous/ exogenous) is manipulated by different mechanisms i.e. glomerular filtration, active tubular secretion and passive reabsorption. Drugs are regarded as interfering with homeostasis and, thus, must be excreted by means of existing mechanisms.<sup>23</sup>

The duration of drug action in the body is dependent on its elimination through metabolism and excretion. Cumulative percentage of dose excreted of cefixime via urine after 12 hours after oral administration in our subjects was 11.6%. A higher value of 40.9%<sup>24</sup> was observed in healthy males after 24hr. In another study, 16-20% of oral dose (200 mg) of cefixime was recovered unchanged in urine.<sup>25</sup> In a dose-comparative pharmacokinetic study of cefixime, the urinary recovery values at 24 hour were observed as  $21.2 \pm 2.9$ ,  $19.3 \pm 2.1$ ,  $20.0 \pm 1.8$  and  $16.1 \pm 1.3\%$  after oral doses of 400, 200, 100 and 50mg, respectively.<sup>26</sup> Similarly, after 24 hr of cefixime administration, percentage of total dose excreted in urine was 13.4.<sup>10</sup> The lower urinary excretion of cefixime in local subjects may be due to environmental or seasonal variation and due to differences in the genetic makeup. Besides cefixime, higher urinary excretion has also been reported for other cephalosporins, like in a previous study, urinary excretion of cefotaxime after 48 hours of drug administration was 22.9%.<sup>27</sup>

Lesser bioavailability of cefixime in the present study compared to that in the adults in previous studies may be linked to less acidic environment of the stomach of non-adults because children/non-adults use more milk than adults in their diet.<sup>22</sup>

TBW decreases and body fat increases with age.<sup>4</sup> Therefore, lipid-soluble drugs like cefixime was less distributed in our subjects compared to adults of studies cited above, due to less adipose tissue and high extracellular water contents in young boys.

As renal function becomes more and more developed with age and are lower in infants and children compared to adults, so, urinary excretion of cefixime in young boys was lower than urinary excretion of cefixime in adult persons studied previously and reported above. Greater total body clearance and lower urinary excretion of cefixime in the present study compared to previous ones reported above indicate more biliary excretion of cefixime



in young boys.

In terms of limitations, the current study dealt with pharmacokinetic and urinary excretion profile of cefixime in young male subjects. However, several clinical examples indicate that physiological changes in the body are dependent and/or independent of developmental age, genetic polymorphisms and physicochemical properties of drugs and some environmental factors may exert a significant effect on the first-time assessment of kinetic parameters of drug absorption, disposition and excretion after a single-dose administration in children.<sup>29</sup>

## Conclusions

Cefixime maintained its therapeutic level in plasma of healthy young volunteers throughout the study period. Comparison with literature, as cited above, indicates that age, species, genetic and environmental differences affect results.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Source of Funding:** The Higher Education Commission of Pakistan.

## References

- Naz U, Ashraf MM, Javed I, Aslam B, Khan JA, Muhammad F, et al. Comparative pharmacokinetics of cefspan and ceforal.3 in adult human healthy female subjects. *Lat Am J Pharm.* 2017;36:776-82.
- Cheek DB. Body water, height, and weight during growth in normal children. *Arch Pediat Adol Med.* 1966;112:312.
- Assael BM. Pharmacokinetics and drug distribution during postnatal development. *Pharmacol Ther.* 1982;18:159-7.
- Boreus LO, Chateau PU. Terbutaline in breast milk. *Br J Clin Pharmacol.* 1982;13:731-2.
- Juchau MR, Chao ST, Omiecinski CJ. Drug metabolism by the human fetus. *Clin Pharmacokinet.* 1980;5:320-39.
- Zafar S, Muhammad MA, Asghar A, Nosheen A, Asma A, Sara Z, et al. Effect of caffeine on anti-clotting activity of warfarin in healthy male albino rabbits. *Pak J Pharm Sci.* 2018;31:611-6.
- Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants age-related differences and therapeutic implications. *Clin Pharmacokinet.* 1980;5:485-527.
- Finney H, Newman DH, Thakkar H, Fell JM, Price CP. Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. *Arch Dis Child.* 2000; 82:71-5.
- Ashraf MM, Javed I, Aslam B, Khaliq T. Cefixime; disposition kinetics and bioavailability comparison of two formulations of cefixime in healthy adult male subjects. *Professional Med J.* 2015;22: 959-65.
- Anwar M, Aslam B, Ashraf MM, Raza A. Renal clearance and urinary excretion of cefspan® in healthy male volunteers. *Scholar's Adv Anim Vet Res.* 2015;2:117-22.
- Aziz A, Aslam B, Ashraf MM, Naz U, Ashraf N, Raza A, et al. Pharmacokinetic study of glimepiride alone and in combination with atorvastatin in healthy male volunteers. *Lat Am J Pharm.* 2016;35:2331-6.
- Javed I, Iqbal Z, Rahman ZU, Khan MZ, Muhammad F, Aslam B, et al. Disposition Kinetics and Optimal Dosage of Ciprofloxacin in Healthy Domestic Ruminant Species. *Acts Vet Brno.* 2009;78:155-62.
- Knapp CC, Sierra-Madero J, Washington JA. Antibacterial activities of cefpodoxime, cefixime, and ceftriaxone. *Antimicrob Agents Chemother.* 1988;32:1896-8.
- Liu X, Xie L, Gao J, Liu GQ. Cefixime absorption kinetics after oral administration to humans. *Eur J Drug Metab Pharmacokinet.* 1997;22:185-8.
- Jieying H, Min H, Xianglan Z. comparative study on pharmacokinetics in volunteers of domestic and imported cefixime in 3 dosage forms. *Chin New Drugs J.* 1996;6: 48-53.
- ElDalo A, Ali A, Shaddad S, Mohammed AH. Pharmacokinetic study of cefixime in the sheep the and cattle. *J Anim Vet Adv.* 2004;3:36-8.
- Ziv G, Lavy E, Glickman A, Winkler M. Clinical pharmacology of cefixime in unweaned calves. *J Vet Pharma Therapeutics.* 1995;18:94-100.
- Guay DR, Meatherall RC, Harding GK, Brown GR. Pharmacokinetics of cefixime (CL 284,635; FK 027) in healthy subjects and patients with renal insufficiency. *Antimicrob Agents Chemother.* 1986;30:485-90.
- Duverne C, Bouten A, Deslandes A, Westphal JF, Trouvin JH, Farinotti R, et al. Modification of cefixime bioavailability by nifedipine in humans: involvement of the dipeptide carrier system. *Antimicrob Agents Chemother.* 1992;36:2462-7.
- Bialer M, Wu WH, Look ZM, Silber BM, Yaqobi A. Pharmacokinetics of cefixime after oral and intravenous doses in dogs: bioavailability assessment for a drug showing nonlinear serum protein binding. *Res Commun Chem Pathol Pharmacol.* 1987;56:21-32.
- Nawaz M. Geometrical factors affecting biodisposition of drugs. *Can J Physiol Pharmacol Abst.* 1994;257:12.
- Boehncke E. Creatinine excretion in veal calves, and endogenous creatinine clearance in young bulls. *Zentralbl Veterinarmed A.* 1980;27: 421-8.
- Rao NR, Ram P, Kulkarni U. Formulation and evaluation of gas powered system of cefixime tablets for controlled release using hydrophillic polymers. *Int J Res Pharm Biomed Sci.* 2010;1:82-91.
- Sana T, Bilal A, Muhammad MA, Nosheen A, Asma A, Tahir AM, et al. Therapeutic effect of atorvastatin on kidney functions and urinary excretion of glimepiride in healthy adult human male subjects. *Pak J Pharm Sci.* 2016;29:2321.
- Hong Z, Wang Y, Xu N, Zhang H, Liang D. Pharmacokinetics of ciprofloxacin injection in healthy volunteers. *Hua His Ko Ta Hsueh Hsueh Pao.* 1995;26:315-8.
- Leroy A, Oser B, Grise P, Humbert G. Cefixime penetration in human renal parenchyma. *Antimicrob Agents Chemother.* 1995;39:1240-2.
- Brittain DC, Scully BE, Hirose T, Neu HC. The pharmacokinetic and bactericidal characteristics of oral cefixime. *Clin Pharmacol Ther.* 1985;38:590-4.
- Pandota J. Limitations in the clinical usefulness of single-dose pharmacokinetic studies of drugs and a bayesian approach for the estimation of kinetic parameters. *Am J Ther.* 2004;11:295-301.