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. 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. Therefore, volume of drug distribution, which is parallel to body water contents, is mostly higher for children than adults.

Disposition kinetics, renal clearance and urinary excretion of cefixime in adolescent Pakistani boys
Muhammad Waqas Khadam, Muhammad Mudassar Ashraf, Umbreen Naz, Nadeem Irfan Bukhari, Imtiaz Mahmood Tahir, Dawood Asghar

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±0.2 hours, 0.9±0.0L/kg and 0.3±0.0L/h/kg, respectively. The ratio of renal clearance of cefixime (0.7 ml/min/kg) to that of endogenous creatinine (0.8ml/min/kg) was 0.9. Cumulative mean percentage of cefixime excreted from young adolescent boys was 11.6 ± 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)
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.\textsuperscript{8}

Cephalosporins are β-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 β-lactamase enzyme. Cefixime is available for paediatric as well as for adult patients in different formulations and strengths.\textsuperscript{9,10}

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.\textsuperscript{9,11}

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 β-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 1 ml/min.\textsuperscript{9,10}

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.\textsuperscript{11}

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\textsuperscript{8} using plasma concentration versus time profile data of cefixime. Mean ± SE value for peak concentration of drug in plasma (C\textsubscript{max}), time required to attain C\textsubscript{max} (T\textsubscript{max}), area under concentration (AUC) versus time curve, mean residence time (MRT), extrapolated zero time cefixime concentration (B), volume of distribution (V\textsubscript{d}), rate of absorption (K\textsubscript{abs}), elimination rate constant (β), absorption half-life (t\textsubscript{1/2abs}), elimination half-life (t\textsubscript{1/2β}) and total drug clearance from body (Cl\textsubscript{B}) were used for calculating parameters of disposition kinetic. 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.\textsuperscript{12} 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±0.1μgmL⁻¹ 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.](image)

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

<table>
<thead>
<tr>
<th>Volunteer No</th>
<th>Cmax (μg/ml)</th>
<th>Tmax (hr)</th>
<th>AUC (hr.ug/ml)</th>
<th>MRT (hr)</th>
<th>Vd (L/kg)</th>
<th>Kobs (hr⁻¹)</th>
<th>t½abs (hr)</th>
<th>β (hr⁻¹)</th>
<th>t½β (hr)</th>
<th>Cib (L/hr/kg)</th>
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<tr>
<td>1</td>
<td>2.60</td>
<td>3.92</td>
<td>23.60</td>
<td>6.70</td>
<td>7.04</td>
<td>1.03</td>
<td>0.30</td>
<td>2.37</td>
<td>0.30</td>
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<td>2</td>
<td>2.86</td>
<td>4.89</td>
<td>34.79</td>
<td>8.94</td>
<td>7.78</td>
<td>0.95</td>
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<tr>
<td>3</td>
<td>2.90</td>
<td>3.03</td>
<td>27.88</td>
<td>7.07</td>
<td>7.87</td>
<td>0.90</td>
<td>0.28</td>
<td>2.45</td>
<td>0.28</td>
<td>2.50</td>
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<tr>
<td>4</td>
<td>2.74</td>
<td>4.16</td>
<td>22.85</td>
<td>6.15</td>
<td>7.43</td>
<td>0.91</td>
<td>0.33</td>
<td>2.12</td>
<td>0.33</td>
<td>2.13</td>
</tr>
<tr>
<td>5</td>
<td>2.86</td>
<td>3.56</td>
<td>25.76</td>
<td>6.64</td>
<td>7.76</td>
<td>0.85</td>
<td>0.30</td>
<td>2.30</td>
<td>0.30</td>
<td>2.30</td>
</tr>
<tr>
<td>6</td>
<td>2.94</td>
<td>3.32</td>
<td>24.25</td>
<td>6.06</td>
<td>7.97</td>
<td>0.94</td>
<td>0.33</td>
<td>2.10</td>
<td>0.33</td>
<td>2.10</td>
</tr>
<tr>
<td>7</td>
<td>2.92</td>
<td>3.70</td>
<td>24.59</td>
<td>6.21</td>
<td>7.92</td>
<td>0.87</td>
<td>0.32</td>
<td>2.15</td>
<td>0.32</td>
<td>2.15</td>
</tr>
<tr>
<td>8</td>
<td>2.86</td>
<td>3.92</td>
<td>22.58</td>
<td>5.81</td>
<td>7.77</td>
<td>0.99</td>
<td>0.35</td>
<td>2.01</td>
<td>0.34</td>
<td>2.01</td>
</tr>
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</table>

Mean ± SE 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

Cmax = Maximum plasma drug concentration; Tmax = Time to attain Cmax; AUC = Area under plasma concentration Vs time curve; MRT = Mean residence time; Vd = Extrapolated zero time drug concentration; Vd = Volume of distribution; Kobs = Absorption rate constant; t½abs = Absorption half life; β = Elimination rate constant; t½β = Elimination half life; Cib = 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.

<table>
<thead>
<tr>
<th>Volunteer No</th>
<th>Body weight (kg)</th>
<th>Diuresis ml/min/kg</th>
<th>Blood</th>
<th>Urine</th>
<th>Creatinine conc. μg/ml</th>
<th>Drug conc. μg/ml</th>
<th>Renal clearance ml/min/kg</th>
<th>Ratio Cef/Creat</th>
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<td>0.030</td>
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<td>9.00</td>
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<tr>
<td>2</td>
<td>54</td>
<td>0.021</td>
<td>7.40</td>
<td>6.30</td>
<td>12.00</td>
<td>250.00</td>
<td>2.45</td>
<td>60.55</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>0.023</td>
<td>7.45</td>
<td>6.61</td>
<td>10.00</td>
<td>240.00</td>
<td>2.33</td>
<td>62.65</td>
</tr>
<tr>
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<td>0.024</td>
<td>7.41</td>
<td>6.29</td>
<td>9.00</td>
<td>250.00</td>
<td>2.34</td>
<td>68.72</td>
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<tr>
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<td>60</td>
<td>0.027</td>
<td>7.44</td>
<td>6.36</td>
<td>8.00</td>
<td>230.00</td>
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</tr>
<tr>
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<td>53</td>
<td>0.032</td>
<td>7.44</td>
<td>6.68</td>
<td>9.00</td>
<td>280.00</td>
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<tr>
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<td>0.023</td>
<td>7.43</td>
<td>6.072</td>
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<td>270.00</td>
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<td>75.62</td>
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<tr>
<td>8</td>
<td>52</td>
<td>0.031</td>
<td>7.41</td>
<td>6.39</td>
<td>7.00</td>
<td>260.00</td>
<td>2.86</td>
<td>73.22</td>
</tr>
</tbody>
</table>

Mean ± SE 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
Mean cumulative percentage of cefixime dose excreted in individuals via urine up to 12 hours after the drug administration was 11.6 ± 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 μg/ml.12

In healthy young boys in the current study, an upper limit of cefixime MIC 1.0 μg/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 μg/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 μg/ml throughout the experimental period.9

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,9 4.2 hours13 and 3.5 hours14 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 Vd in the young boys of the present study.

The apparent Vd(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 cattle15 and 0.3 L/kg in human subjects.16 However, the present Vd values were lower than 1.3L/kg9 and 1.1 L/kg17 after 400mg oral administration and 1.7 L/kg after 200mg intravenous administration18 of cefixime in adult counterfeits. 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.19 A possible explanation for
the lower value of Vd 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 ClB(0.3 l/hr/kg) in local young boys 
was comparable to 0.2 L/hr/kg for ceforal-3 and higher than 
0.16 L/hr/kg for cefspan9 and 0.1 L/hr/kg for cefixime17 
400mg in healthy adult subjects. A higher value of Cls in 
local young boys than the values reported in literature may 
be related to the higher value of β and Vd or shorter t1/2β 
in the present study than that of the values reported above.

The urine flow rate in young boys (0.03±0.0 ml/min/kg) 
recorded in the present study was similar to the values of 
urine flow reported as 0.01 ml/min/kg,10 and 0.02 
ml/min/kg.10 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±0.0 and of urine it 
was 6.4±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.11 In 
another study pH of blood was recorded as 7.5.10

Renal clearance (0.8±0.1 ml/min/kg) of endogenous 
creatinine in the present study was higher than 0.4 
ml/min/kg20 but lesser than the previous reported values i.e. 
1.7 ml/min/kg21 and 1.03 ml/min/kg in healthy volunteers.10

Plasma and urine concentrations of cefixime in the present 
study were 2.5±0.1 and 68.5±2.5 μg/ml, respectively. The 
renal clearance of cefixime was 0.7±0.1 ml/min/kg which 
was lower than 0.2 ml/min/kg reported previously.10 
Similarly, clearance ratio (0.9±0.1) of the present study was 
greater than the ratio (0.3±0.1) reported previously.10 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 in the present study was similar to the 
values of urinary clearance of cefixime observed earlier.10 
Drug concentration in plasma and ratio of renal clearance 
shows the saturation of excretory mechanism at higher plasma concentration of drug which 
related to the involvement of active secretion at tubular level. 
The positive correlation between diuresis and clearance 
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±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.22 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 
and negative correlation of plasma drug concentration with that 
of clearance ratio of cefixime were observed earlier.10,23

Urinary excretion of the 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.23

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%24 was 
observed in healthy males after 24 hr. In another study, 16- 
20% of oral dose (200 mg) of cefixime was recovered 
unchanged in urine.25 In a dose-comparative 
pharmacokinetic study of cefixime, the urinary recovery 
values at 24 hour were observed as 21.2±2.9, 19.3±2.1, 
20.0±1.8 and 16.1±1.3% after oral doses of 400, 200, 100 
and 50mg, respectively.26 Similarly, after 24 hr of cefixime 
administration, percentage of total dose excreted in urine 
was 13.4.10 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%.27

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.22

TBW decreases and body fat increases with age.4 
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 
extacellular 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.29

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.

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Conflict of Interest: None.

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References