PHARMACOKINETIC STUDY AFTER SINGLE ORAL DOSE OF BETA-LACTAM AND FLUOROQUINOLONE ANTIMICROBIALS IN BANGLADESHI HEALTHY MALE VOLUNTEERS

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ABSTRACT

The variability of response to antimicrobial has been inadequately explained because of lack of pharmacokinetic data. The present pharmacokinetic study was designed to provide information beneficial to formulate a population pharmacokinetic model appropriate for Bangladeshi population. Among the beta-lactams, amoxicillin (500 mg), flucloxacillin (250 mg), cefuroxime (500 mg) and among the fluoroquinolones, ciprofloxacin (500 mg), levofloxacin (500 mg), gatifloxacin (400 mg) were studied in 15 healthy Bangladeshi male volunteers. The C\text{max}, AUC\text{0–\infty}, T\text{max}, T\text{1/2} and C\text{trough} were studied with all antimicrobials. Later, the C\text{max} and AUC\text{0–\infty} were adjusted for bodyweight and dose. Among the studied antimicrobials, the C\text{max} varied to great extent even after adjustment for bodyweight and dose. The C\text{max} after adjustment was highest in case of flucloxacillin and lowest in case of ciprofloxacin, indicating excellent absorption of flucloxacillin in Bangladeshi population. The information obtained through this study generates necessity of new cut-off value for the antimicrobials.

Key words: Pharmacokinetics, Beta-lactam, Fluoroquinolones, Bangladeshi volunteer (Bangladesh J Physiol Pharmacol 2014;30(1):16-24.)

INTRODUCTION

Least developed countries like Bangladesh differs greatly from the developed countries especially in disease pattern. Bacterial infections are the principal reason of morbidity and mortality in these countries. Consequently, antimicrobials became the group of medicine that contributing mostly in medicine consumption of country like Bangladesh.¹⁻⁷ Though antimicrobial susceptibility surveillance data is required to support the selection of appropriate antimicrobial agents, there availability is generally poor.⁸

Plasma concentration of medicine is the most important factor in clinical response to pharmacotherapy and therefore, even when any medicine administered at one particular dose, some patients suffer from toxicity and some other fail to exhibit desired therapeutic effect.⁹⁻¹² There are several factors that influence the pharmacokinetic variability of medicines, which include ethnicity, gender, age, body weight, disease status, pregnancy, hepatic impairment, drug-drug interactions, binding to plasma proteins and host genetic factors.¹¹,¹³-¹⁴

The variability of response to antimicrobial is now only partially explained by the available sensitivity data, though detailed understanding about their pharmacokinetic parameters is required to explain such variability. Studies conducted in different countries provide information about the pharmacokinetic behavior of that studied population like Cambodia¹⁵, China¹⁶, Japan¹⁷, Denmark¹⁸, Switzerland¹⁹, Uganda²⁰ and Jordan²¹. The great differences observed in findings of different studies indicate necessity of obtaining pharmacokinetic data from the population for whom the dose of a medicine needs to be optimized. The extrapolation of data obtained from other sources is not possible because of high inter-individual variation as well as difference in ethnic, racial, social and cultural origin. Bangladeshi populations are ethnically, socially and genetically different from the studied population of different studies conducted so far.

In this backdrop, the pharmacokinetic behavior of Bangladeshi population warrants immediate detail evaluation in order to get the understanding adequate to generate new ideas. There have been efforts to correlate plasma concentration with clinical outcome, though very little progress has been made so far.

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Though some initiative and effort was made towards understanding the pharmacokinetics of antimicrobials in Bangladeshi children and adult population, very little development has been achieved. There were different challenges like selection of volunteers, laboratory facilities, establishment of laboratory methods and hospitalization of volunteers, for which this type of pharmacokinetic study could not be conducted before in this region. Inadequate information about the pharmacokinetic status of Bangladeshi people led to the necessity of research to enable scientists to understand these issues. The present pharmacokinetic study was designed to provide information beneficial to formulate a population pharmacokinetic model appropriate for Bangladeshi population.

Study period
The study was conducted from January 2010 to December 2010.

Place of study
The study was conducted in the Department of Clinical Pharmacy and Pharmacology, University of Dhaka, Department of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU) and ZH Sikder Women’s Medical College & Hospital, Dhaka.

Subject of the study
This study included 15 (fifteen) Bangladeshi male healthy volunteers, aged 20–30 years (24.80 ± 2.43 years), weighing between 51–60 kg (55.93 ± 3.33 kg), height between 160.00 - 172.00 cm (166.00 ± 4.00 cm), Body Mass Index (BMI) between 19.10 - 22.31 (20.39 ± 0.94), serum creatinine between 0.60 - 0.80 mg/dL (0.73 ± 0.07 mg/dL), serum ALT between 30.00 - 45.00 U/L (35.87 ± 4.73 U/L) and prothrombin time between 9.00 - 12.00 sec (10.07 ± 0.88 second). Volunteers were screened to ensure that they have no cardiac, renal, hepatic, hematological, neurological, gastrointestinal and pulmonary disorders and allergy to ciprofloxacin. The volunteers were requested to stay away from any medication for two weeks prior to the study and up to its completion. Moreover, they were requested not to take any beverages like alcohol, coffee and tea in 48 h prior to first dose and until the collection of last blood sample. 

Medicines (beta-lactam)
Among the commonly used beta-lactams of Bangladesh, following were included in the study:
1. Commercially available pioneer brand of amoxicillin 500 mg capsules
2. Commercially available pioneer brand of flucloxacillin 250 mg capsules

Medicines (fluoroquinolones)
Among the commonly used fluoroquinolones of Bangladesh, following were included in the study:
1. Commercially available pioneer brand of ciprofloxacin 500 mg tablets
2. Commercially available pioneer brand of levofloxacin 500 mg tablets
3. Commercially available pioneer brand of gatifloxacin 400 mg tablets

Medicine administration schedule
This study was conducted in an open label design with one-week washout period between oral doses of different medicines. At the time of study, the healthy volunteers were hospitalized at Z H Sikder Women’s Medical College & Hospital, Dhaka, Bangladesh for collection of blood samples. The volunteers were observed by experienced physician to detect adverse effects (if any) during the study.

Amoxicillin: All volunteers received single oral dose of 500 mg amoxicillin capsule.
Flucloxacillin: All volunteers received single oral dose of 250 mg flucloxacillin capsule.
Cefuroxime: All volunteers received single oral dose of 500 mg cefuroxime tablet.
Ciprofloxacin: All volunteers received single oral dose of 500 mg ciprofloxacin tablet.
Levofloxacin: All volunteers received single oral dose of 500 mg levofloxacin tablet.
Gatifloxacin: All volunteers received single oral dose of 400 mg gatifloxacin tablet.

Blood sample collection
For collection of blood samples, a catheter in situ was placed in one arm by the researcher with all aseptic precaution. The catheter was removed immediately if phlebitis develops, otherwise normally after the study period. Blood samples (3 ml at each occasion) were obtained at appropriate intervals as follows:

Amoxicillin
Zero (immediately before the first dose), 30, 60, 120, 180, 360, 480, 960 and 1440 minutes after first dose of medicine

Flucloxacillin
Zero (immediately before the first dose), 30, 60, 120, 180, 360, 720, 1080 and 1440 minutes after first dose of medicine
RESULTS

All volunteers completed the study without any event, which was ascertained by thorough medical examination by experienced physician after study completion.

In addition to the actual plasma concentration and the calculated different pharmacokinetic parameters based on those obtained values, an adjustment was done to minimize the variation in weight of the volunteers and dose of the administered medicines. For that purpose, the obtained actual plasma concentration was adjusted for bodyweight and expressed as per mg of antimicrobial/kg of body weight.

\[ \text{Concentration of antimicrobial in plasma (µg/mL)} \times \left[ \frac{\text{[amount of antimicrobial administered (mg)/bodyweight of volunteer (kg)]}}{223.05 ± 0.07 \text{µg/mL per kg}} \right] \]

The values were then used for calculation of different pharmacokinetic parameters. Therefore, the AUC\(_0\)–\(\infty\), and C\(_{\text{max}}\) were calculated with two values, one with the original plasma concentration of antibiotics detected in HPLC and the other was with value obtained after adjustment for dose and bodyweight.

Table 1 shows that after single oral administration of amoxicillin (500 mg), the C\(_{\text{max}}\), AUC\(_0\)–\(\infty\), T\(_{\text{max}}\), T\(_{\text{1/2}}\), and C\(_{\text{trough}}\) were 6.57 ± 0.53 µg/mL, 1265.20 ± 203.07 µg min/m, 72.00 ± 24.84 min, 89.95 ± 17.22 min and 0.29 ± 0.20 µg/mL respectively. When the values were adjusted for bodyweight and dose, the C\(_{\text{max}}\) and AUC\(_0\)–\(\infty\), 0.74 ± 0.04 µg/mL per mg/kg and 141.31 ± 14.22 µg min/mL per mg/kg respectively.

In case of flucloxacillin (250 mg), the C\(_{\text{max}}\), AUC\(_0\)–\(\infty\), T\(_{\text{max}}\), T\(_{\text{1/2}}\), and C\(_{\text{trough}}\) were 4.64 ± 0.62 µg/mL, 1005.88 ± 171.26 µg min/m, 76.00 ± 27.46 min, 81.59 ± 15.91 min and 0.46 ± 0.30 µg/mL respectively. When the values were adjusted for bodyweight and dose, the C\(_{\text{max}}\) and AUC\(_0\)–\(\infty\), 1.03 ± 0.12 µg/mL per mg/kg and 223.05 ± 25.99 µg min/mL per mg/kg respectively.

In case of cefuroxime (500 mg), the C\(_{\text{max}}\), AUC\(_0\)–\(\infty\), T\(_{\text{max}}\), T\(_{\text{1/2}}\), and C\(_{\text{trough}}\) were 3.70 ± 0.52 µg/mL, 806.68 ± 122.08 µg min/m, 104.00 ± 27.46 min, 88.34 ± 11.06 min and 0.64 ± 0.32 µg/mL respectively. When the values were adjusted for bodyweight and dose, the C\(_{\text{max}}\) and AUC\(_0\)–\(\infty\), 0.83 ± 0.07 µg/mL per mg/kg and 180.26 ± 16.44 µg min/mL per mg/kg respectively.
Pharmacokinetic Study after Single Oral Dose of Beta-Lactam and Fluoroquinolone Antimicrobials in Bangladeshi Healthy Male Volunteers

Table 1
Pharmacokinetic parameters following single oral administration of beta-lactam (amoxicillin 500 mg, flucloxacillin 250 mg, cefuroxime 500 mg) antimicrobials in Bangladeshi healthy male volunteers

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Cap. Amoxicillin (500 mg) Mean ± SD</th>
<th>Cap. Flucloxacillin (250 mg) Mean ± SD</th>
<th>Tab. Cefuroxime (500 mg) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL)</td>
<td>6.57 ± 0.53 (5.90 - 7.90)</td>
<td>4.64 ± 0.62 (3.21 - 5.35)</td>
<td>3.70 ± 0.52 (3.01 - 4.96)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0&lt;/sub&gt;–&lt;sub&gt;infinity&lt;/sub&gt; (μg min/mL)</td>
<td>1265.20 ± 203.07 (1011.03 - 1687.22)</td>
<td>1005.88 ± 171.26 (780.03 - 1247.88)</td>
<td>806.68 ± 122.08 (656.27 - 1002.93)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (min)</td>
<td>72.00 ± 24.84 (60.00 - 120.00)</td>
<td>76.00 ± 27.46 (60.00 - 120.00)</td>
<td>104.00 ± 27.46 (60.00 - 120.00)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (min)</td>
<td>89.95 ± 17.22 (46.31 - 113.17)</td>
<td>81.59 ± 15.91 (54.24 - 101.54)</td>
<td>88.34 ± 11.06 (74.97 - 110.33)</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt; (μg/mL)</td>
<td>0.29 ± 0.20 (0.00 - 0.52)</td>
<td>0.46 ± 0.30 (0.00 - 0.93)</td>
<td>0.64 ± 0.32 (0.28 - 1.19)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL per mg/kg)</td>
<td>0.74 ± 0.04 (0.67 - 0.81)</td>
<td>1.03 ± 0.12 (0.77 - 1.18)</td>
<td>0.41 ± 0.03 (0.36 - 0.51)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0&lt;/sub&gt;–&lt;sub&gt;infinity&lt;/sub&gt; (μg min/mL per mg/kg)</td>
<td>adjusted value</td>
<td>223.05 ± 25.99 (187.21 - 254.57)</td>
<td>90.13 ± 8.22 (78.75 - 102.30)</td>
</tr>
</tbody>
</table>

Adjusted value means the value obtained after adjustment of the original values expressed as mg of antimicrobial per kg bodyweight.

Table 2 shows that after single oral administration of ciprofloxacin (500 mg), the C<sub>max</sub>, AUC<sub>0</sub>–<sub>infinity</sub>, T<sub>max</sub>, T<sub>1/2</sub> and C<sub>trough</sub> were 2.11 ± 0.48 μg/mL, 585.92 ± 93.64 μg min/m, 72.00 ± 24.84 min, 206.91 ± 16.91 min and 0.07 ± 0.07 μg/mL respectively. When the values were adjusted for bodyweight and dose, the C<sub>max</sub> and AUC<sub>0</sub>–<sub>infinity</sub>, 0.23 ± 0.04 μg/mL per mg/kg and 65.00 ± 6.95 μg min/mL per mg/kg respectively.

In case of levofloxacin (500 mg), the C<sub>max</sub>, AUC<sub>0</sub>–<sub>infinity</sub>, T<sub>max</sub>, T<sub>1/2</sub> and C<sub>trough</sub> were 4.57 ± 0.65 μg/mL, 2326.69 ± 379.79 μg min/m, 76.00 ± 27.46 min, 377.04 ± 30.31 min and 0.53 ± 0.11 μg/mL respectively. When the values were adjusted for bodyweight and dose, the C<sub>max</sub> and AUC<sub>0</sub>–<sub>infinity</sub>, 0.48 ± 0.02 μg/mL per mg/kg and 247.00 ± 19.91 μg min/mL per mg/kg respectively.
## Table 2
Pharmacokinetic parameters following single oral administration of fluoroquinolones (ciprofloxacin 500 mg, levofloxacin 500 mg and gatifloxacin 400 mg) in Bangladeshi healthy male volunteers

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Tab. Ciprofloxacin (500 mg) Mean ± SD</th>
<th>Tab. Levofloxacin (500 mg) Mean ± SD</th>
<th>Tab. Gatifloxacin (400 mg) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/mL)</td>
<td>2.11 ± 0.48 (1.60 - 3.59)</td>
<td>4.57 ± 0.65 (3.13 - 5.60)</td>
<td>3.45 ± 0.34 (3.01 - 4.02)</td>
</tr>
<tr>
<td>$AUC_0-\infty$ (μg min/mL)</td>
<td>65.00 ± 6.95 (49.24 - 75.32)</td>
<td>2326.69 ± 379.79 (1610.58 - 2977.25)</td>
<td>1779.60 ± 247.00 (1490.40 - 2189.46)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (min)</td>
<td>72.00 ± 24.84 (60.00 - 120.00)</td>
<td>76.00 ± 27.46 (60.00 - 120.00)</td>
<td>80.00 ± 29.28 (60.00 - 120.00)</td>
</tr>
<tr>
<td>$T_{1/2}$ (min)</td>
<td>206.91 ± 16.91 (165.39 - 233.23)</td>
<td>377.04 ± 30.31 (311.96 - 421.29)</td>
<td>420.81 ± 32.79 (357.84 - 458.10)</td>
</tr>
<tr>
<td>$C_{\text{trough}}$ (μg/mL)</td>
<td>0.07 ± 0.07 (0.00 - 0.22)</td>
<td>0.53 ± 0.11 (0.36 - 0.74)</td>
<td>0.34 ± 0.11 (0.20 - 0.54)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (μg/mL per mg/kg) adjusted value</td>
<td>0.23 ± 0.04 (0.19 - 0.37)</td>
<td>0.53 ± 0.04 (0.45 - 0.59)</td>
<td>0.48 ± 0.02 (0.43 - 0.51)</td>
</tr>
<tr>
<td>$AUC_0-\infty$ (μg min/mL per kg adjusted value)</td>
<td>65.00 ± 6.95 (49.24 - 75.32)</td>
<td>269.42 ± 25.47 (231.19 - 313.18)</td>
<td>247.00 ± 19.91 (218.76 - 279.16)</td>
</tr>
</tbody>
</table>

Adjusted value means the value obtained after adjustment of the original values expressed as mg of antimicrobial per kg bodyweight.

**Fig 1. Amoxicillin**

**Figure 1:** Time concentration curve obtained by plotting the mean plasma concentrations of amoxicillin estimated at different point of time (after single oral administration of 500 mg)

**Fig 2. Flucloxacillin**

**Figure 2:** Time concentration curve obtained by plotting the mean plasma concentrations of flucloxacillin estimated at different point of time (after single oral administration of 250 mg)
Figure 3. Cefuroxime

Figure 4. Ciprofloxacin

Figure 5. Levofloxacin

Figure 6 Gatifloxacin

DISCUSSION

Pharmacokinetic parameters of amoxicillin have been investigated previously in different studies at different doses of 500, 875, 1000 and 2000 mg. The $C_{\text{max}}$ and $AUC_{0-8h}$ observed in the present study after single oral administration was lower than the findings of the previous study, which might be due to the dissimilarity in the studied population. Nevertheless, the $T_{\text{max}}$ observed in the present study was parallel to the values revealed by previous researchers using 500 mg and 1000 mg. The similarity in this finding reiterates the fact that different doses of the same medicine have little influence on $T_{\text{max}}$ values. The $T_{1/2}$ values, different studies revealed a range of 90 minutes to 180 minutes with a mean of 100 minutes and the present study finding is similar to those observations.

Flucloxacillin have been studied at different doses of 1500, 2000 and 2500 mg in Chinese volunteers. Regular dosing even while used intravenously, appears inadequate to treat the MSSA infections. The pharmacokinetic feature was inconsistent in comparison to one study conducted in neonates, which can be explained by the dissimilarity of the studied population. The plasma half-life ($t_{1/2}$) in the present study was higher than the previous study results, which might be due to the slower metabolic rate of Bangladeshi population. However, the most important finding of the present study was that the $C_{\text{trough}}$ was above than the minimum inhibitory concentration (MIC) for common strains of *Staphylococcus aureus*.66

In case of cefuroxime, the present study revealed that $C_{\text{max}}$ in Bangladeshi healthy volunteer are lower than the findings of the previous study conducted with different population. In spite of the lower $C_{\text{max}}$, the $AUC_{0-\infty}$ was almost equal to the previous result, which might be due to slower metabolic rate in subjects of the present study. The plasma half-life ($t_{1/2}$) higher
than the previous study, it reiterates the possibility of slower metabolic rate. The peak serum concentration was attained little earlier (Tmax) in the present study in comparison to previous study.44

Pharmacokinetic parameters of ciprofloxacin have been investigated at different doses of 250, 500, 750 and 1000 mg.50-53 The Cmax and AUC0-12h observed in the present study was modestly lower than the previous studies.53 The Tmax observed in the present study was parallel to the values revealed by previous researcher, both using same dose53 as well as different dose.54 However, the similarity in these findings reiterating the fact that different doses of the same medicine have no influence on Tmax values. The T1/2 similar to previous findings, which ranged between 2.9 hours to 5.4 hours with a mean of 100 minutes.49,50,54,55 The T1/2 values, the present study findings are above than the minimum inhibitory concentration of the targeted microbes.

In case of levofloxacin, the Cmax and AUC0-∞ was lower than the findings of the previous study,55-57 which might be due to dissimilar study population and different dose used.55 The plasma half-life (T1/2) was similar to that of previous study,47,48,55 though the peak serum concentration was attained little earlier (Tmax) in the present study in comparison to previous reports.45,59

In case of gatifloxacin, the Cmax and AUC0-∞ was similar to the findings of the previous studies.54,59,60 The plasma half-life (T1/2) was similar to one of previous study,53 however lower than other reports.44,59 The conflicting plasma half-life indicates that the study subjects were not uniformly comparable to any of the study conducted beforehand. Though the peak serum concentration was attained little earlier (Tmax) in the present study in comparison to previous report.45

Among the studied antimicrobials, the Cmax varied to great extent even after adjustment for bodyweight and dose. The Cmax after adjustment was highest in case of flucloxacillin and lowest in case of ciprofloxacin, indicating excellent absorption of flucloxacillin in Bangladeshi population.

CONCLUSION

The new understanding might restate the necessity of periodic pharmacokinetic study in some selected clinical cases. The information obtained through this study may provide idea about the necessity of new cut-off value for the antimicrobials.

REFERENCES


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Pharmacokinetic Study after Single Oral Dose of Beta-Lactam and Fluoroquinolone Antimicrobials in Bangladeshi Healthy Male Volunteers


