Pharmacokinetics of Ofloxacin in Male Volunteers Following Oral Administration

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Abstract: Ofloxacin a synthetic fluoroquinolone analog of nalidixic acid is a broad spectrum antibiotic. This study was designed to find pharmacokinetics of ofloxacin in healthy male volunteers under indigenous conditions. A total of 15 healthy male volunteers were included in this study. Ofloxacin (200 mg) was administered orally and blood samples were collected at different time intervals. The blood samples were analyzed for drug concentration by microbiological assay. The plasma concentration versus time data was used to determine pharmacokinetics parameters by one compartment model kinetic analysis. The mean (SD) values for different parameters were, absorption rate constant (ka) 7.833 (8.683) h⁻¹, area under curve (AUC) 14.545 (4.304) h, mg⁻¹, total body clearance (CL) 14.813 (4.379) l h⁻¹, volume of distribution (Vd) 130.76 (25.589) l, elimination half life (t₁/₂) 6.419 (1.785) h, elimination rate constant (kₑ) 0.164 (0.133) h⁻¹, mean residence time (MRT) 10.104 (2.284) h, absorption half life (tₐ₁/₂) 0.212 (0.161) h, time to maximum concentration (tₚ) 1.397 (0.599) h and maximum concentration (Cₚ) 1.416 (0.305) micrograms ml⁻¹. Values of parameters like Vd, AUC and CL were comparable with foreign studies. While t₁/₂, ka were higher, and Cₚ, tₚ were lower in local population as compared with the foreign studies.

Keywords: Male volunteers, ofloxacin, oral dose, pharmacokinetics, elimination half life

Introduction
The concentration of drug attained at the site of its action depends upon the extent and rate of its absorption, distribution, binding or localization in tissues, biotransformation and excretion. Pharmacokinetic parameters describe the rate and extent of movement of a drug in a biosystem (Gillman et al., 1985). The factors that modify the absorption of a drug can change its bioavailability. Pharmacokinetics parameters like half-life, distribution and body clearance provide information about the rate of elimination of drug from the body in a specific time period. The distribution is influenced by blood flow to the tissue. Depending on the ionization constant of drugs (pKa values) the biodisposition is determined in different body fluid compartments by the value of pH. There are many factors, which can affect biodisposition and fate of drugs under indigenous conditions. These include blood proteins, drug metabolism and excretion (Bagat, 1977). In view of these influences of different parameters on bioavailability and biodisposition of drugs, it is important that imported drugs be evaluated under local environmental conditions.

Ofloxacin a 4-quinolone synthetic fluorinated analog of nalidixic acid is a broad-spectrum antibacterial agent. Ofloxacin inhibit bacterial topoisomerase II (DNA gyrase) and topoisomerase IV (Katzung, 1998). The drugs used in Pakistan for health programs of man and animals are being imported from abroad either in the raw or finished form. The studies conducted over several years under indigenous conditions have revealed difference between the foreign and local species explained by an original term “geometrics” geographical influence on genetics manifested by dissimilar biochemical, physiological and pharmacological parameters (Navaz and Shah, 1985; Nawaz et al., 1988; Nawaz, 1994). The present project was therefore planned to study pharmacokinetics of ofloxacin in healthy male volunteers under local environmental conditions.

Materials and Methods
The Pharmacokinetics of ofloxacin following single 200 mg oral dose was investigated in a controlled, randomized, study. Ofloxacin manufactured by Boehr Pharmaceuticals (Pvt) Limited Pakistan was purchased from local market. The sampling for analysis was done in the month of December. The 15 healthy male volunteers for this study were the students. Each volunteer was apprised of the design of the study, dosing and sampling protocol. The volunteers were kept fasting for last 12 hours and after that normal or blank blood samples were taken. To each volunteer one oral tablet of 200 mg was administered with 100 ml tap water at 8 a.m. under fasting conditions. On study days eating was not allowed up to 4 h after drug administration. Drinking water was given after this time.

The blood samples (approximately 5 ml) of each volunteer were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 7, 8 and 12 h. The activated charcoal tubes were shaken to precipitate the protein. Heparinized plasma samples were analyzed by microbiological assay using disc agar diffusion method (Arret et al., 1971). Staphylococcus aureus was used as test organism. Zone of inhibition and log concentration were plotted on semi logarithmic graph. A linear curve was obtained. Simple linear regression equation Y = a + bX was fitted by taking concentration as X and zone of inhibition as Y which is as follows:

\[ Y = 10.93 \times + 16.116 \]

Ofloxacin concentration in plasma samples was calculated using this equation from different drug sensitivity zone sizes. The plasma concentration time data was used to determine pharmacokinetics parameters and was analyzed by single compartment model (Bagat, 1977) using computer program MW/PHARM version 3.02 (Rombout, 1987). The mean value and standard deviation (SD) for each pharmacokinetics parameter were calculated.

Results
Ofloxacin was well tolerated throughout the study. All volunteers completed the period of study. There were a few adverse events reported for the subjects; all were mild in nature. Two cases of headache were reported. The mean values for the plasma concentration of ofloxacin against time have been shown for 115 volunteers (Fig. 1). The mean (SD) values of pharmacokinetics parameters are given (Table 1). The absorption rate constant (ka) of ofloxacin ranged from 1.214 to 23.93 h⁻¹ and mean (SD) was 7.833 (8.683) h⁻¹. AUC ranged from 8.744 to 22.93 h mg⁻¹ and mean (SD) was 14.545 (4.304) h mg⁻¹.

The clearance in h⁻¹ ranged between 6.722 to 22.870 and mean (SD) 14.913 (4.373 h⁻¹). The mean (SD) value of Vd was 130.76 (25.589) and ranged between 92.61 and 168.7.
Table 1: Pharmacokinetics parameters of ofloxacin after 200 mg oral dose in male volunteers.

<table>
<thead>
<tr>
<th>Pharmacokinetics parameters</th>
<th>Mean (N = 15)</th>
<th>SD</th>
</tr>
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<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>1.397</td>
<td>0.598</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg L$^{-1}$)</td>
<td>1.416</td>
<td>0.305</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>0.212</td>
<td>0.151</td>
</tr>
<tr>
<td>$k_{e}$ (L h$^{-1}$)</td>
<td>7.833</td>
<td>8.683</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>6.419</td>
<td>1.768</td>
</tr>
<tr>
<td>$k_{e}$ (L h$^{-1}$)</td>
<td>0.154</td>
<td>0.139</td>
</tr>
<tr>
<td>AUC (mg h L$^{-1}$)</td>
<td>14.545</td>
<td>4.304</td>
</tr>
<tr>
<td>Cl (L h$^{-1}$)</td>
<td>14.913</td>
<td>4.373</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>130.70</td>
<td>25.998</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>10.104</td>
<td>2.384</td>
</tr>
</tbody>
</table>

$t_{\text{max}}$ (time to maximum concentration), $C_{\text{max}}$ (maximum concentration), $t_{1/2}$ (half life), $k_{e}$ (excretion rate constant), $t_{1/2}$ (elimination half life), $k_{e}$ (elimination rate constant), AUC (area under curve), Cl (total body clearance), Vd (volume of distribution), and MRT (mean residence time).

Fig. 1: Mean plasma concentration of ofloxacin at various time intervals following 200 mg oral dose

The mean (SD) value of the elimination half-life of ofloxacin was 6.419 (1.768) hours and ranged between 3.918 and 10.710 h. The elimination rate constant ($k_{e}$) of ofloxacin ranged from 0.083 to 0.847 h$^{-1}$ with mean value (SD) 0.154(0.139) h$^{-1}$. The mean residence time (MRT) ranged from 6.064 to 15.88 h and mean (SD) was 10.104 (2.364). The absorption half-life ranged from 0.026 to 0.571 h and mean (SD) 0.212 (0.151) hours. The values for $t_{\text{max}}$ ranged between 0.678 to 2.395 h mean (SD) 1.397 (0.599) h, $C_{\text{max}}$ ranged between 1.067 and 2.149 mg ml$^{-1}$ with mean (SD) 1.406 (0.305) mg ml$^{-1}$.

Discussion
Most of the developing countries like Pakistan are importing raw or finished drugs for their human or veterinary health programmes. In most cases, the genetic make up of man and animals and environmental conditions are different from their foreign counterparts. The studies have shown that amongst the genetic factors affecting biodisposition and fate of drugs, pH (blood, urine and stomach etc.) is an important parameter which differs amongst local and foreign species (Navaz, 1984). The other factors, which differ and can affect the biodisposition kinetics and fate of drugs under indigenous conditions, include blood protein, drug metabolism, and excretion. pH is an important parameter which differs amongst local and foreign species (Navaz and Shah, 1986; Navaz et al., 1988; Navaz, 1994). Such influences have been reported for blood and urine pH, blood proteins, drug metabolism and kidney function in buffaloes, cows, sheep and goats (Navaz et al., 1988). Therefore it is very important that imported drugs should be evaluated under local environment to determine their dosage regimes.

Pharmacokinetics of ofloxacin was described by one compartment model that showed its goodness to fit over data. The mean (SD) values for $t_{\text{max}}$ was 1.397(0.598) hours and is less than 1.74 (0.57) (Yuk et al., 1991), 1.6 (Stein et al., 1991), 1.7 (Fior et al., 1993), 2 (Eboa et al., 1997) and is greater than 1 h (Malerczk et al., 1987).

In present study $C_{\text{max}}$ ranged between 1.067 to 2.149 mg ml$^{-1}$ with mean (SD) 1.406 ± 0.305 mg ml$^{-1}$ which is less than 3.14 µg ml$^{-1}$ (Yuk et al., 1991), 1.74 µg ml$^{-1}$ (Stein et al., 1991), 3.5 µg ml$^{-1}$ (Malerczk et al., 1987) 1.56 µg ml$^{-1}$ (Eboa et al., 1997), 1.9 µg ml$^{-1}$ (Zhou et al., 1993) and 4.4 µg ml$^{-1}$ (Fior et al., 1991), 2 to 3 µg ml$^{-1}$ (Lamp et al., 1992), 6.5 µg ml$^{-1}$ (Israel et al., 1993), 4.44 µg ml$^{-1}$ (Eichols et al., 1994) 1.99 µg ml$^{-1}$ (Verho et al., 1996) after 400 mg dose reported previously. The lower values for $C_{\text{max}}$ and $t_{\text{max}}$ in endogenous conditions may be due to different environmental conditions (Navaz and Shah, 1985; Navaz et al., 1988; Navaz, 1994).

The mean (SD) volume of distribution of ofloxacin was 130.70 (25.69) liter similar to 121 to 136 liters after 200 mg intravenous dose (Guay et al., 1991) and greater than 88, 58, 94 liters (Zhou et al., 1993) reported previously. The mean (SD) area under curve (AUC) was 14.545 ± 4.304 h mg$^{-1}$ which is comparable with 15.22 µg ml$^{-1}$h (Eboa et al., 1997), 15.91 mg h$^{-1}$ (Zhou et al., 1993) and 14.6 h mg$^{-1}$ (Verho et al., 1996).

In present study mean (SD) total body clearance was 14.913 ± 4.373 h$^{-1}$. This value is similar to 15.08 h$^{-1}$ (Corvisier et al., 1999), 16.87 h$^{-1}$ (Guay et al., 1991), 13.98 h$^{-1}$ (Molinaro et al., 1992), 14 h$^{-1}$ (Zhou et al., 1993) and 16.06 h$^{-1}$ (Stein et al., 1991). Mean (SD) elimination half life of ofloxacin was 6.419 ± 1.768 h which is greater than 5.6 (Stein et al., 1991), 5.29 h (Guay et al., 1991), 5.4 h (Farinotti et al., 1988), 6.2 h (Molinaro et al., 1992), 5 h (Zhou et al., 1993), 4.98 h after 200 mg intra venous dose (Guay et al., 1992) and 4.9 h (Orlando et al., 1992). For human beings after 400 mg oral dose elimination half life of ofloxacin was reported as 6.54 h (Israel et al., 1993) and in some studies ranging from 5 to 8 h (Lamp et al., 1992), 5.06 to 6.67 after 400 mg intravenous dose (Guay et al., 1992). Longer half-life of ofloxacin may be related to lower glomerular filtration rate (GFR) in local population.

The absorption rate constant 0.833 (0.633) h$^{-1}$ was higher than 2.28 h$^{-1}$ (Yuen et al., 1992) and 2.68 h$^{-1}$ (Corvisier et al., 1999). So absorption rate constant in present study is very high as compared to the value in other studies this difference may be due to indigenous conditions (Navaz and Shah, 1985; Navaz et al., 1988; Navaz, 1994).

In conclusion values of parameters like, volume of distribution, AUC, and total body clearence were comparable, elimination half life, absorption rate constant were higher, and $C_{\text{max}}$, $t_{\text{max}}$ were lower in local population as compared with foreign studies. In view of these differences, it is very essential that imported drugs be evaluated under local environment.

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References
Hameed et al.: Pharmacokinetics of ofloxacin in male volunteers


Rombout, F., 1987. Incorporation with university center for pharmacy, Department of Pharmacology and Therapeutics University of Gronigen and Medi Ware.


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