Biodisposition Kinetics of Clarithromycin Following Oral Administration of 250mg Tablet in Human Male Volunteers

Aftab Ahmad, Munir Ahmad Sheikh, 'Muhammad Nawaz, Muhammad Shahid, Abdul Ghaffar and Shakeela Naz

Biodisposition of drug was investigated in male volunteers following the oral dose of 250mg. Blood samples were collected after predetermined schedule and drug concentration was determined by microbiological assay. The two compartment model kinetics analysis of plasma clarithromycin concentration versus time data revealed that the average ± SD values of t₁/₂, clearance and volume of distribution are 1.36 ± 0.14h, 20.43 ± 3.04 l/h and 39.91 ± 1.461 l/kg respectively. The absorption rate constant, area under curve (AUC) and mean resident time with ± SD are 0.51 ± 0.05h, 12.36 ± 1.43 h.mg/l and 4.17 ± 43 h respectively.

Key words: Disposition kinetics, clarithromycin
Ahmad et al.: Biokinetics of clarithromycin

Introduction
Human body is composed of complex structure performing different functions. It is differentiated into anatomically, physiologically and biochemically. The biochemical characteristics depend upon the composition of different body fluid which ultimately important either acidic, basic and neutral peculiarities. These characters are important for disposition of endogenous or exogenous organic molecules. In such molecules, drugs are mostly used in human and veterinary medicine (Baggot, 1977). Environmental influences on genetics, manifested through biochemical and physiological parameters, affecting fate of drugs in population are explained by term genetics (Nawaz et al., 1989). The genetic influences for blood urine, pH biochemistry, drug metabolism and kidney function have been reported by Nawaz (1984).

Clarithromycin is a member of macrolide group of antibiotics. It is a broad spectrum antibiotic used in the treatment of skin, respiratory tract, and Mycobacterium avium (MAC) infections. Investigation have shown that the biodisposition kinetics, renal clearance and urinary excretion of investigated drugs were different under indigenous conditions, as compared to literature. The study was planned to evaluate the biodisposition kinetics of clarithromycin in male volunteers under local conditions to measure the effects of genetics.

Materials and Methods
The research was conducted on 15 male volunteers in the Department of Physiology and Pharmacology, University of Agriculture, Faisalabad. The body weight, height, age and blood pressure for each volunteer were recorded. A clarithromycin tablet of 250mg dosage, manufactured by Abbott Laboratories Pvt. Ltd. was given orally to the volunteers after overnight fasting. Blank samples of blood were taken. Then the blood sample of each volunteer after drug administration were collected with predetermined time intervals 0.5, 1.5, 2.5, 3.4, 5, 6, 8 and 12 h in heparinized centrifuge tubes. Plasma was separated by centrifugation at 4000 rpm for 15 min and stored at 20°C until analysis.

Analysis: Clarithromycin concentration in plasma samples was determined by microbiological assay, by disc agar diffusion technique using Streptococcus faecalis as a test organism (Arret et al., 1971). The pH of the medium was kept at 7.9 and temperature 30-32°C (British Pharmacopoeia, 1993). In each sample, clarithromycin concentration versus time data were analyzed and disposition kinetic parameters were calculated following two compartment open model by a computer program MW/PHARM version 3.02 by Rombov (1987).

Results and Discussion
Mean ± SE (Standard error) values of clarithromycin plasma concentration at different intervals following oral dose of 250mg in 15 male volunteers are given in Fig.1, while mean ± SE results of biodisposition kinetic parameters are shown in Table 1. The elimination half life t1/2 β (1.36 h) of volunteers were shorter than reported values; 3.3 hours in adults (Fraschini et al., 1993) after 500 mg dose and 19 hours of roxithromycin followed by clarithromycin (Nelson, 1996). As the glomerular filtration is major excretory mechanism and filtration rate of volunteers were higher because of winter conditions. The other factors which counts, for difference from reported values age and drug interactions.

Apparent volume of distribution (Vd) relates drug concentration in plasma to the total amount of drug in the body after distribution equilibrium has been attained. The vD (39.91 ± 1.46 ml/kg) is higher than the value of 2.6 ± 0.51 l/kg reported by Fraschini et al. (1993). It indicated that an excellent penetration of clarithromycin in tissues. Earlier investigation have also shown lower Vd in summer than in winter (Nawaz, 1983).

The difference in values may also be attributed to species variations. Butt (1986) reported Vd of spiramycin is 167.17 ± 21.44 ml/kg under local condition which is higher than the values reported by Fraschini et al. (1993). Total body clearance of clarithromycin calculated is 20.43 ± 2.06 ml/kg which is higher than the reported value 7.35 ± 0.8 ml/kg of clarithromycin in adults (Fraschini et al., 1993). Area under curve (AUC) represent the total area under plasma concentration curve from t1 to t∞. The mean value of the area under curve is 12.37 ± 1.43 h·mg/l, which is lower than 46.18 ± 4.05 h·mg/l of spiramycin after 500mg dose as reported by Butt (1986) under local conditions. The variation in values under local conditions may be attributed to the dose difference. The peak plasma concentration Cmax, 3.10 ± 0.69 μg/ml is lower than 4.10 ± 0.44 μg/ml reported by Iwai et al. (1989). However Cmax, in experiments conducted on dog 3.0 ± 0.6 μg/ml was lower and is attributed to high clearance, environmental condition difference and may be due to species differences. So it infers that drug evaluation should be based upon the disposition study determined in the species and environment in which a drug to be employed clinically.

Table 1: Mean ± SE value for the disposition kinetic parameters of the clarithromycin following a single oral dose of 250 mg in 15 volunteers

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>Unit</th>
<th>Mean ± SE</th>
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<tbody>
<tr>
<td>Absorption rate constant (Kε)</td>
<td>h⁴</td>
<td>0.51 ± 0.05</td>
</tr>
<tr>
<td>Half life (absorption) (t1/2)</td>
<td>h</td>
<td>1.35 ± 0.16</td>
</tr>
<tr>
<td>Area under curve (AUC)</td>
<td>mg/l</td>
<td>12.36 ± 1.43</td>
</tr>
<tr>
<td>Peak time (Tmax)</td>
<td>h</td>
<td>2.21 ± 0.2</td>
</tr>
<tr>
<td>Peak concentration (Cmax)</td>
<td>μg/ml</td>
<td>3.10 ± 0.69</td>
</tr>
<tr>
<td>Half life elimination (t1/2)</td>
<td>h</td>
<td>136 ± 0.14</td>
</tr>
<tr>
<td>Volume of distribution (Vd)</td>
<td>ml/kg</td>
<td>39.91 ± 1.46</td>
</tr>
<tr>
<td>Mean resident time (MRT)</td>
<td>h</td>
<td>4.17 ± 0.43</td>
</tr>
<tr>
<td>Lagtime</td>
<td>h</td>
<td>28.00 ± 0.7</td>
</tr>
<tr>
<td>Clearance (Cl)</td>
<td>l/kg</td>
<td>20.43 ± 2.05</td>
</tr>
</tbody>
</table>

Fig. 1: Mean plasma concentration (μg/ml) versus time after oral administration of 250 mg clarithromycin tablet

References
Ahmad et al.: Biokinetics of clarithromycin


Nilson, O.G., 1996. Pharmacokinetics of macrolides. Comparison of plasma tissues and free concentration with special reference to roxithromycin (G08); 23 Suppl 1S 5-9.