*Acta Pharmaceutica Turcica*
*XLIII (3,4) (151-154) 2001*

# POPULATION PHARMACOKINETICS OF AZITHROMYCIN AFTER PERORAL ADMINISTRATION TO HEALTHY VOLUNTEERS

**NASIR M. IDKAIDEK[1*], NAJI M. NAJIB[1, 2]**

[1] College of Pharmacy, University of Science and Technology, Irbid,
[2] International Pharmaceutical Research Center (IPRC) Amman,
Jordan

*The purpose of this study was to determine the population pharmacokinetics of azithromycin following a 500 mg peroral dose. This was achieved by simultaneous data fitting of 46 different individuals using WinNonlin® program. It was shown that azithromycin population plasma profile was characterized by a moderately slow absorption phase, a fast distribution phase into body tissues and a slow elimination phase with a 62 hour elimination half-life. Population absorption profile was obtained using Topfit® program and showed continued and essentially complete absorption of azithromycin in the first 24 hours after peroral dosing. This was consistent with the continued drug excretion, via the bile duct, and thus continued drug absorption. These recycling and slow elimination phenomena offer the advantage of a sustained-release-like action of azithromycin, which allows the once daily dosing regimen.*

**Key words:** *Population; Pharmacokinetics; Azithromycin; WinNonlin®; Topfit®*

## Introduction

Azithromycin is a semi-synthetic antibiotic belonging to the macrolide subgroup of azalides and is similar in structure to erythromycin. Azithromycin has an apparent advantage over erythromycin in that it reaches higher concentrations intracellularly, thus increasing its efficacy and duration of action. Peroral absorption of azithromycin is rapid but is inhibited by food, which also decreases the maximum plasma concentration. Distribution throughout the body is extensive. Azithromycin exhibits significant intracellular penetration and concentrates within fibroblasts and phagocytes. As a result, tissue levels are significantly higher than plasma concentrations. However, CNS penetration is poor. Peak plasma concentrations occur at about 2 hours after peroral administration. The drug is eliminated largely in feces, following excretion into the bile, with less than 10% excreted in the urine. It does not inactivate cytochrome P450 and is unable to modify the pharmacokinetics of other compounds. Azithrotmycin appears to demonstrate a time-dependent versus time-accumulation profile in breast milk. In children, once-daily administration of azithromycin resulted in sustained systemic exposure to the drug. The elimination half-life of azithromycin has been reported to be variable and can reach up to 70 hours, which is partially explained by its extensive tissue uptake and slow tissue release. The disposition of azithromycin from serum is a biphasic process, exhibiting a short tissue distribution phase followed by a longer elimination phase (1 -9).

Detailed data analysis has not been performed on azithromycin on a large scale of acceptable inferences about its population pharmacokinetics up to date. Therefore, the objectives of this work were to determine the population pharmacokinetics of azithromycin by simultaneous data fitting from 46 different individuals using WinNonlin® program, and to characterize its population absorption profile using Topfit® program.

### Materials and Methods

*Drugs and reagents*: Azithromycin 250 mg capsules were purchased from the Jordanian market (Zithromax®, Batch # 71036070). All reagents used were obtained from Sigma Chemical Company, USA.

* Correspondence: E-mail: dekaidek@just.edu.jo

*Subjects*: Fourtysix healthy male subjects submitted written informed consent to participate in the study which was approved by the Institutional Review Board of the study site, Ibn-Annafis Hospital. The subjects were within 15 % of their ideal body weight and were judged to be healthy based on their medical history, physical examination, complete blood count and serum chemistry. In addition, all subjects were medication free, including otc drugs, for 7 days prior to the study.

*Experimental and assay procedure:* Following a ten-hour overnight fast, 500 mg dose of azithromycin capsules were administered perorally followed by 240 ml water. Blood samples were collected at $0_{(predose)}$, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5,6, 8, 10, 12, 18, 24, 48, 72, 96, 120, 144, 168 and 192 hours after dosing. Samples were stored at -20 $^0$C until analysis. A rapid and sensitive HPLC method was developed for the determination of azithromycin in plasma using clarithromycin as the internal standard. The procedure involved basification of azithromycin and clarithromycin from 0.5 ml plasma using *tert*-butyl methyl ether as the extraction solvent. The separation of azithromycin was performed using a stainless steel $C_8$ (4.6 x 100mm) symmetry column with a particle size of 3.5 µm. The mobile phase consisted of 63.5% phosphate buffer and 36.5% acetonitrile. Its pH was adjusted to 7.40 with phosphoric acid. The mobile phase was pumped at a flow rate of 1.2 ml.min$^{-1}$ at a constant oven temperature of 35 $^0$C. The effluent was monitored using an electrochemical detector (ECD). Each analysis required no longer than 15 min. Quantification was achieved by the measurement of peak-area ratio of the drug and the internal standard. The limit of quantification for azithromycin in plasma was 5 ng.ml$^{-1}$. All the samples collected after 192 hours of dosing were below the quantification limit.

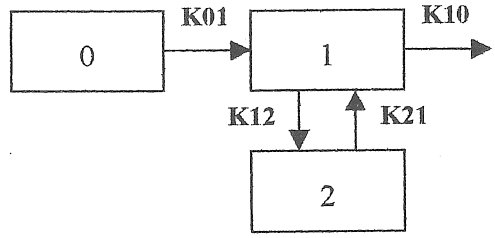
The intra-day and inter-day coefficients of variation (CV%) ranged from 3.95 to 7.61 % at 30, 150 and 300 ng.ml$^{-1}$. Relative recovery ranged from 95.25 to 102.05% while the absolute recovery ranged from 92.68 to 101.21%. Stability tests showed that azithromycin was stable in plasma for at least one month when stored at –20 ± 5 $^0$C.

**Data Analysis**

*1. Model building:* One-, two-, and three-compartment models were evaluated on individual basis using Topfit® Software, Germany (10). First-order absorption with one lag time was used in all models. One-compartment model did not fit the data adequately whereas two-compartment model was much better and fitted the data for all individuals. The fitting did not improve significantly using three-compartment model. The criteria used for our decision involved the following; Examining the fitted curves and the improvement in statistical tests (Akaike test, Schwarz test and Imbimbo test in addition to correlation coefficient of the fitted curves) and examining the improvement in relative residuals vs. data points plots.

*2. Population analysis:* The simultaneous data fitting of the 46 individuals were performed using WinNonlin® program, running on a 233MHz Pentium computer (11). Model 12 (Fig. 1) was used in population data fitting with 6 basic parameters (Volume of distribution, K10, K01, K12, K21 and Lag time) and 11 secondary parameters (Alpha, Beta, K0l half-life, KI0 half-life, Alpha half-life, Beta half-life, AUC, Tmax, Cmax, A-constant and B-constant). Gauss-Newton method (Levenberg and Hartley) was used under uniform weighting. Successful convergence was achieved in approximately 3 minutes and after 10 iterations.

Fig 1. The pharmacokinetic two-compartment model.




## Results and discussion

Fitted population parameter estimates as determined by WinNonlin® are summarized in the table. The population plasma level profile and the residual plots are shown in figs 2 and 3 as determined by WinNonlin®. The population absorption profile was characterized using the Topfit program (Fig. 4)

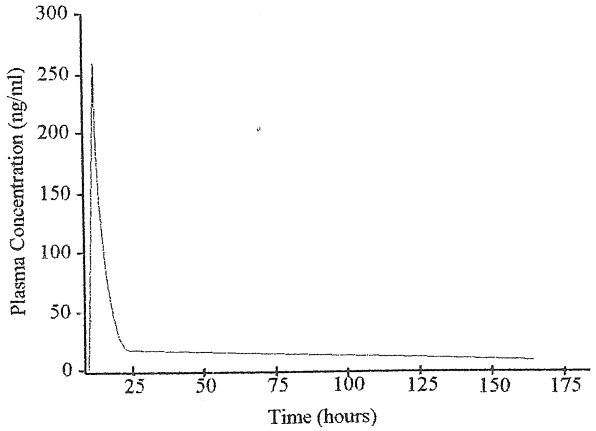



Fig. 2. Population plasma level profile after peroral dose of 500 mg azithromysin.

Data analysis have been performed by simultaneous data fitting from 46 different

individuals to determine the population pharmacokinetics of azithromycin after administration of 500 mg peroral dose. The estimates of all parameters were acceptable and precise due to small standard errors (Table). However, standard errors of Beta and Beta-HL were high suggesting imprecise estimates. Nevertheless, we accepted such results because of their concurrence with the previously reported values (2, 5).

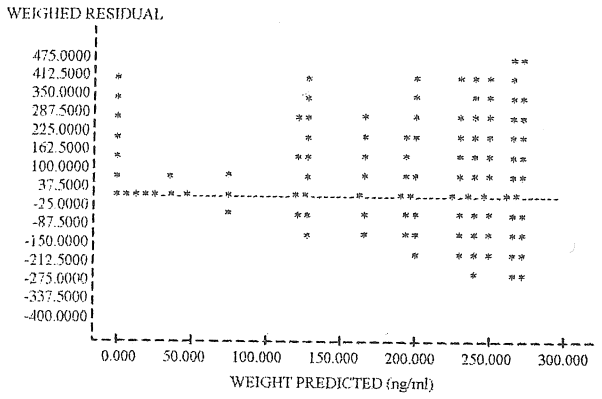



Fig. 3. WinNonlin population plots of weighed residual vs weight predicted.

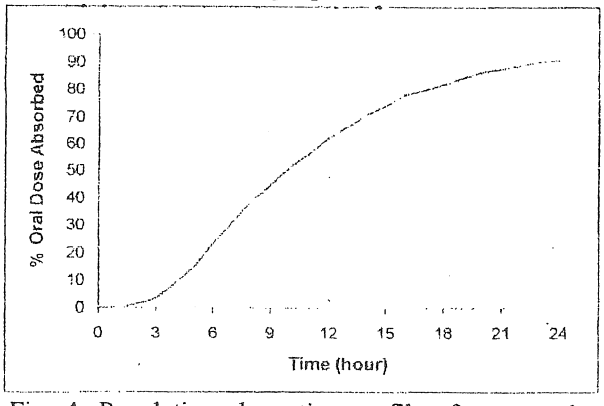



Fig. 4. Population absorption profile after peroral dose of 500 mg azithromysin.

It can be seen from fig. 3 that weighted residuals are essentially of random and homogeneous distribution, indicating acceptable data fitting. However, the positive residuals at the zero prediction point (i.e. from 0.25 to 1.25 hrs) were due to higher individual observations. In fact, the observed data points fluctuated up and down above the limit of quantification during the first 0.25-2.5 hrs within each individual.

We noted continued and essentially completed absorption (>90%) during the first 24 hours (Fig. 4). This was consistent with the continued drug excretion *via* the bile duct and thus continued drug absorption. However, $C_{max}$ occured approximately after 3 hours. This was suggested to be due to the rate of disposition as expressed by K12 and alpha parameters being much higher than the rate of absorption, which was consistent with the high degree of tissue protein binding of azithromycin. These recycling and slow elimination phenomena offer the advantage of a sustained-release-like action of azithromycin, which allows the once daily dosing regimen.

Table. WinNonlin® summary of population pharmacokinetic parameters.

| Parameter | Estimate | SE (±) |
|---|---|---|
| Volume/F(L) | 6800 | 2388 |
| K01 ($hr^{-1}$) | 0.197 | 0.043 |
| K10 ($hr^{-1}$) | 0.810 | 0.411 |
| K12 ($hr^{-1}$) | 1.141 | 0.444 |
| K21 ($hr^{-1}$) | 0.027 | 0.027 |
| T-lag (hr) | 1.267 | 0.066 |
| AUC (ng.ml/hr)* | 3931 | --- |
| K10-HL (hr)** | 0.856 | 0.434 |
| K01-HL (hr) | 3.524 | 0.768 |
| Alpha ($hr^{-1}$) | 1.967 | 0.473 |
| Beta ($hr^{-1}$) | 0.011 | 0.014 |
| Alpha-HL (hr) | 0.352 | 0.085 |
| Beta-HL (hr) | 61.629 | 76.911 |
| A-constant | -8.105 | 0.890 |
| B-constant | 0.641 | 0.519 |
| $T_{max}$ (hr) | 2.611 | 0.125 |
| $C_{max}$ (ng/ml) | 266.091 | 7.321 |

* Computed by trapezoidal rule from 0 to 168 hrs.
** HL: Half-life.

## Acknowledgments

We thank the staff, nurses and technicians in IPRC and Ibn-Annafis Hospital for their help and cooperation. This work was supported by Jordan University of Science and Technology and International Pharmaceutical Research Center.

### References

1. Clinical Pharmacology© Gold Standard Multimedia Inc. USA 1995
2. Wildfeuer, A., Laufen, H., Leiold,M., *et. al.*: J. Antimicrob. Chemother. 31, 51 (1993)
3. Schentag, J.J., Batlow, C.H.: Am. J. Med. 91 (Suppl. 3A) 5S (1999)
4. Peters, D.H., Friedel, H.A.,McTavish, D.: Drugs 44, 750 (1992)
5. Lalak, N.J., Morris, D.L.: Clin. Pharmacokinet. 25, 370 (1993)

6. Periti, P., Mazzei, T., Mini, E., Novelli, A.:*Ibid.* 23, 106 (1992)
7. Kelsey, J.J., Moser, L. R., Jennings, J. C., Munger, M.A.:Am. J. Obstet. Gynecol. 170, 1375 (1994)
8. Glaude, R.P., Snider, M.E.: Antimicrob. Agents Chemother. 34, 1056 (1990)
9. Nahata, M.C., Koranyi, K.I., Gadgil, S.D., Hilligoss, D.M., Fouda, H.G., Gardner, M.J.: *Ibid.* 37, 314 (1993)
10. Heinzel, G., Tanswell, P.: Topfit Manual Version 2.0 Germany 1992
11. WinNonlin Manual Version 1.0 Scientific Consulting Inc. USA 1995

Accepted: 07.11.2000