International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2018.981.991

Research Article
Unique Pharmacokinetic Parameters with Prolonged Elimination Half-life of Oral Azithromycin and Analysis of Pharmacokinetic Phenotype in Young Taiwanese Population

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Abstract

Background and Objective: Transporter proteins have been well investigated and are known to play significant roles in drug absorption, distribution and excretion. According to previous research, variations in the ATP-binding cassette B1(ABCB1) gene likely contributed to inter-individual variability azithromycin pharmacokinetics. This study aimed to investigate the phenotypes of azithromycin pharmacokinetics (PK) in Taiwanese population following oral administration. **Materials and Methods:** One hundred and seventeen individuals were orally administered 500 mg Zithromax® (an azithromycin immediate-release capsule). Bio samples were taken at appropriate times. Azithromycin concentration was quantitated by liquid chromatography tandem mass spectrometry. Non-compartmental models were utilized to illustrate azithromycin PK. **Results:** Using data from the clinical study involving 117 healthy male volunteers, a normal distribution modeling approach was applied. A comprehensive model considering the PK of azithromycin was newly built. Following oral administration of azithromycin, the maximum observed concentration, time to peak concentration, area under the concentration-time curve from time 0 h to last time point (AUC_{0-t}) and area under the concentration-time curve from time 0 h to time infinity ($AUC_{0-\infty}$) were found to be 498±196 ng mL^{-1}, 2.5 h, 4042±1344 h×ng mL^{-1} and 4401±1468 h×ng mL^{-1}, respectively. The elimination half-life ($t_{1/2}$) of azithromycin was 84.2±25.8 h. The Kolmogorov-Smirnov's test and quantile plots revealed that the frequency distributions of area under the concentration-time curve (AUC), Peak concentration (C_{max}) and $t_{1/2}$ were mono-modal. **Conclusion:** The present finding that azithromycin PK parameters exhibited a normal distribution in the Taiwanese population was inconsistent with previous research of ABCB1 gene polymorphism on PK as no polymorphism-linked effect was observed. Also, population analysis indicated lack of phenotype differences of azithromycin PK in young Taiwanese. The present data revealed a prolonged $t_{1/2}$ on the basis of normal distribution of azithromycin PK, implicating a potential increased risk of antimicrobial resistance. This research demonstrate the unique PK parameters of oral azithromycin, indicating the representative PK phenotype in young Taiwanese that can be helpful to choice of antibiotics clinically.

Key words: Azithromycin, pharmacokinetics, ABCB1 gene, phenotype, polymorphism

Received: February 09, 2018 Accepted: June 23, 2018 Published: September 15, 2018

Citation: Wen-Kuei Chang, Chao-Hsien Chen, Yen-An Chen, Mei-Chuan Tang, Sy-Yeuan Ju, Szu-Wei Huang and Kun- Ming Wu, 2018. Unique pharmacokinetic parameters with prolonged elimination half-life of oral azithromycin and analysis of pharmacokinetic phenotype in young Taiwanese population. Int. J. Pharmacol., 14: 981-991.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Azithromycin is an azalide antibiotic categorized as a subclass of the macrolide antibiotic family which can bind to the 50S ribosomal subunit of susceptible organisms, thereby interfering with protein synthesis. After oral administration of azithromycin, blood concentrations decline in two or three phases with a terminal elimination half-life of over 60 h (h)[1]. It is approved worldwide for treatment of patient with pneumonia, acute sinusitis, uncomplicated skin infection and genital ulcer disease as both intravenous and oral formulations. Due to increasing resistance, azithromycin is more recommended only as a treatment option for pneumonia caused by atypical bacteria or a second-line treatment in cases of life-threatening beta-lactam allergy. One of the possible cause of growing resistance of azithromycin is the long $t_{1/2}$[2-5].

Previously, azithromycin pharmacokinetic studies were conducted in Japanese subjects and a population pharmacokinetic-pharmacodynamic (PK-PD) analysis approach was implemented to bridge data from Western populations with the Japanese data in accordance with the guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use[2]. The results demonstrated that azithromycin exposure was similar between Japanese and Western subjects and that the exposure-efficacy relationship of azithromycin could be characterized by area under the concentration-time curvedivided by the minimum inhibitory concentration(AUC/MIC). For the relationship between the systemic exposure and safety, the incidence of treatment-related diarrhea was positively associated with azithromycin exposure, indicating that adverse drug reaction incidents were linked with higher azithromycin exposure.

However, the great variations of azithromycin pharmacokinetics, including C_{max} and $t_{1/2}$, were observed from clinical trials in other ethnicities[6-12], raising concerns about clinical application universally.

Therefore, the objective of this study was to investigate azithromycin PK in healthy young Taiwanese subjects as well as the variation in azithromycin PK in these subjects.

MATERIALS AND METHODS

Subjects: These studies were conducted in Mackay Memorial Hospital, a medical center in Taiwan, during May 27, 2012 to October 10, 2014. The study protocol was approved by the Institutional Review Board of Mackay Memorial Hospital. All subjects signed the informed consent. One hundred and seventeen healthy volunteers were enrolled for this study. The clinical characteristics of the volunteers were demonstrated as Mean±Standard Deviation (Mean±SD): Age, 23.5±2.9 years, height, 172.5±6.2 cm and body weight, 65.9±6.3 kg. The volunteers were free from diseases and routine examinations were within reference values.

Drug administration and blood collection: The study subjects were fasted overnight and orally administered a single 500 mg azithromycin dose with 240 mL water. Zithromax® was used as the investigation drug. Blood samples (10 mL) were drawn in heparinized tubes prior to dosing (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 168 (Day 8) and 216 (Day 10) h post administration. After centrifugation, plasma was transferred to pre-labeled tubes and stored at a temperature of -20°C until further experimentation. The time between blood collection and freezer storage was not greater than 1.5 h.

Chemicals and reagents: USP azithromycin was purchased from Rockville (MA, USA). Oxybutynin, which was used as an internal standard (IS), was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Acetonitrile (ACN) and methanol (MeOH) were of ChromAR® grade (Avantor™ Performance Materials, Inc., NJ, USA). Diethyl ether was purchased from J.T. Baker (NJ, USA). Ammonium acetate was purchased from Sigma-Aldrich Chemie GmbH (Seelze, Germany). Formic acid (FA) was of analytic grade from Merck KGaA (Darmstadt, Germany).

Chromatographic conditions: The High performance liquid chromatography(HPLC) system (Agilent-1260 infinity series, Wilmington, DE, USA) contained a Binary pump, an autosampler and an Phenomenex®, Synergi 4u, Polar-RP 80A column (75×4.6 mm, 4 µm). Chromatography was performed at 30°C. The compound was chromatographed on a Phenomenex®, Synergi, Polar-RP analytical column with a mobile phase composed of 85% mobile phase A and 15% mobile phase B. Mobile phase A was ACN:FA = 100:0.2, mobile phase B was MeOH:H_2O:FA = 10:90:0.2, flow rate was 1.0 mL min^{-1}. The tandem mass spectrometry detection system was assayed using an API 4000™ model. Ion transition mass divided by charge number(m/z) values for azithromycin and oxybutynin were 749.8-591.7 and 358.5-141.9, respectively.

Sample preparation: A 200 µL aliquot of human plasma was spiked with 500 µL of acetonitrile with 100 ng mL^{-1} IS and was vortexed for 1 min. The mixture was centrifuged at 3,000 rpm for 10 min and the solvent layer was transferred to a clean tube. Then, 50 µL of 1 M CH_3COONH_4 and 3 mL of diethyl ether were added and vortexed. Centrifugation was performed at 3,000 rpm for 5 min. The organic layer was transferred to a fresh tube and evaporated under a stream of nitrogen. The residues were resolved into 2 mL of mobile phase A and a 10 µL aliquot was injected into the HPLC and subjected to analysis.

Method validation: The retention times for azithromycin and oxybutynin were 1.82 and 1.44 min (Fig. 1 and 2), respectively. No significant interfering peak was detected as shown in Fig. 3. Azithromycin calibration curves showed a linear relationship over a concentration range of 1-1000 ng mL^{-1}. The regression equation for azithromycin was y = 0.0385x-0.00691 and the correlation coefficient (r^2) was 0.9974. The mean relative error ranged from -9.0-7.0% and the coefficients of variance were all less than 5.6%.

The within and between-run analysis precision (%coefficient of variation [%CV]) and accuracy (%relative error[%RE]) were determined at azithromycin concentrations of 1, 3, 30, 800 ng mL^{-1}. The result of precision and accuracy of within-run analysis test and between-run analysis test for azithromycin quality control samples were shown as below (Table 1 and 2). The result indicated that the liquid chromatography tandem mass spectrometry (LC/MS/MS) method is excellent for the quantitative analysis of azithromycin in plasma.

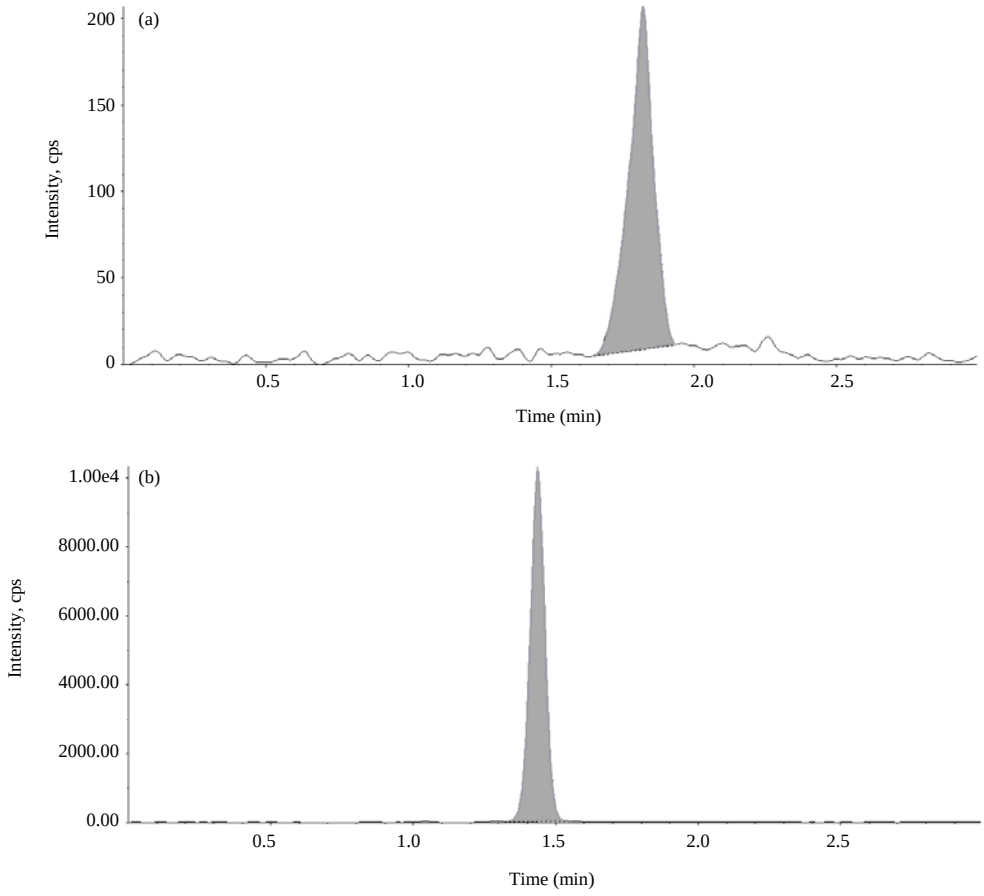

Fig. 1(a-b): Representative chromatogram of a plasma sample spiked with a concentration of 1 ng mL^{-1} of azithromycin, (a) LLOQ: Azithromycin (standard) 749.800/591.700 Da-sample 3 of 16 from 15.wiff, Area: 1.254e+003 counts Height: 1.993e+002 cps RT: 1.82 min and (b) LLOQ: Oxybutynin (IS) (standard) 358.500/141.900 Da-sample 3 of 16 from 15.wiff, Area: 3.929e+004 counts Height: 1.034e+004 cps RT: 1.82 min

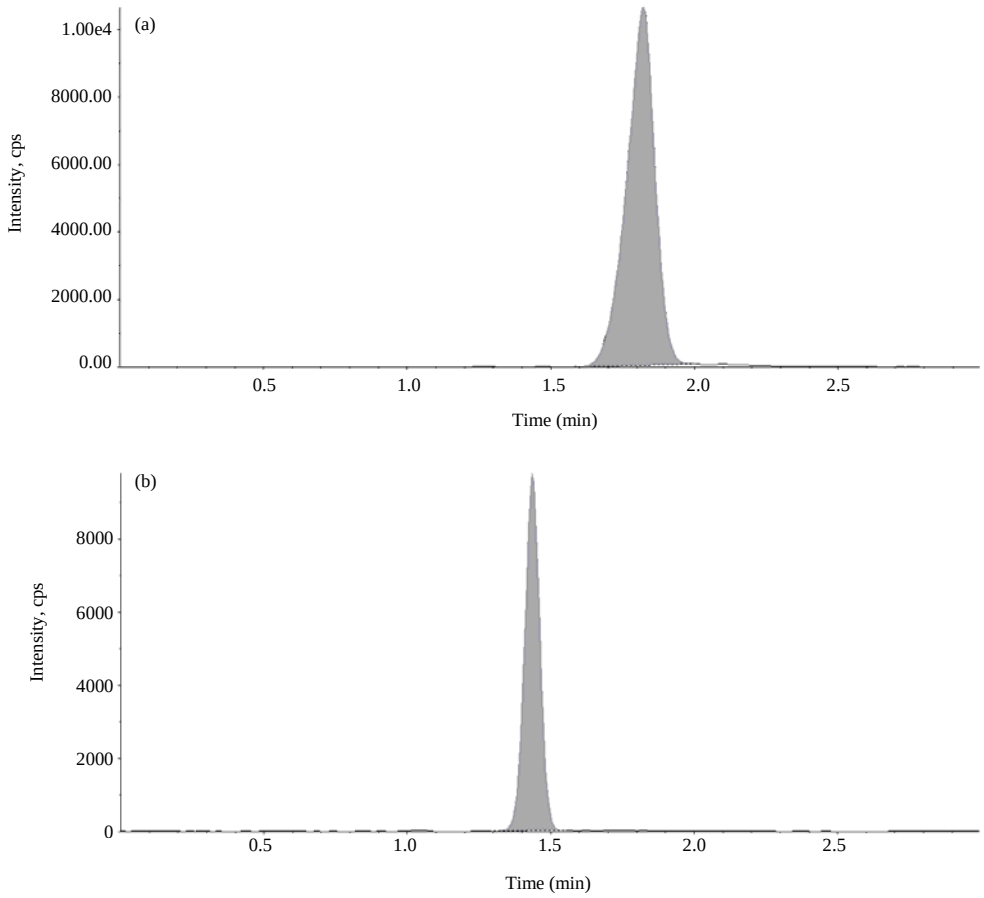

Fig. 2(a-b): Representative chromatogram of a plasma sample spiked with a concentration of 50 ng mL^{-1} of azithromycin, (a) STD4: Azithromycin (standard) 749.800/591.700 Da-sample 7 of 16 from 15.wiff, Area: 7.472e+004 counts Height: 1.063e+004 cps RT: 1.82 min and (b) STD4: Oxybutynin (IS) (standard) 358.500/141.900 Da-sample 7 of 16 from 15.wiff, Area: 3.744e+004 counts Height: 9.792e+003 cps RT: 1.44 min

Table 1: Precision and accuracy of within-run analysis test for Azithromycin quality control samples

		Nominal concentration (ng mL^{-1})			
Items	Sample number	1	3	30	800
Within-run	1	1.06	2.92	29.7	786
	2	1.03	2.79	30.8	776
	3	1.08	3.16	31.5	767
	4	1.12	2.95	30.2	857
	5	0.964	2.94	32.0	800
	6	1.05	3.15	29.2	777
	n	6.00	6.00	6.0	6.0
	Mean	1.05	2.99	30.6	794.0
	SD	0.05	0.14	1.1	33.0
	%CV	4.80	4.70	3.6	4.2
	%RE	5.00	-0.30	2.0	-0.8

Data analysis: Non-compartmental model was applied to describe the pharmacokinetic properties of azithromycin in the present study and the results were found to correspond with those reported previously[9-14]. Individual azithromycin plasma concentration data were analyzed by the WinNonlin® (Pharsight, Cary, NC) program. The PK parameters including

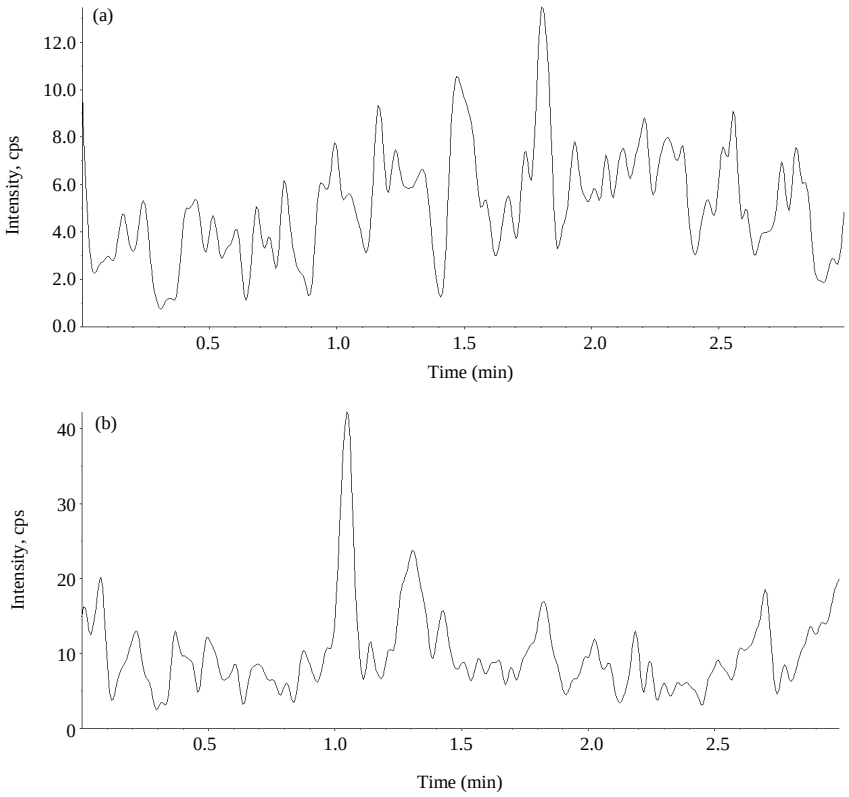

Fig. 3(a-b): Representative extracted ion chromatogram (EIC) of a drug-free plasma sample (double blank), (a) Signals for azithromycin and (b) Oxybutamin (IS) were monitored by mass spectrometry with the same detection parameters as in Fig. 1. Wherein x-axis is retention time and y-axis is intensity in cps (counts per second). The scale of y-axis is enlarged to show that no significant interfering peak was existed

Table 2: Precision and accuracy of between-run analysis test calibration for Azithromycin quality control samples

	Nominal concentration (ng mL^{-1})							
Run numbers	1	RE (%)	3	RE (%)	30	RE (%)	800	RE (%)
Between-run 1	1.12	12.0	3.37	12.3	28.6	-4.7	846	5.8
Between-run 2	0.991	-0.9	2.98	-0.7	33.1	10.3	836	4.5
Between-run 3	1.08	8.0	3.00	0.0	28.0	-6.7	788	-1.5
Between-run 4	1.04	4.0	3.06	2.0	30.3	1.0	732	-8.5
Between-run 5	0.960	-4.0	2.62	-12.7	29.5	-1.7	771	-3.6
n	5.00		5.00		5.0		5.0	
Mean	1.04		3.01		29.9		795.0	
SD	0.06		0.27		2.0		47.0	
CV (%)	5.80		9.00		6.7		5.9	
RE (%)	4.00		0.30		-0.3		-0.6	

C_{max}, $t_{1/2}$, AUC and CL/F were expressed as Mean±SD. The time to achieve peak concentration (T_{max}) was expressed as median (range). Quantile analysis was used to explore the variation of C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $Dose_{po}/AUC_{po}$ (CL/F) and were described through normal quantile-quantile plots (Q-Q plots) (Fig. 4-7). The two-sample t-test was used to compare the difference between data of this research and that of other ethnicities. The statistical analysis was to be performed using SAS® Version 9.2 (SAS-Institute, Cary NC, USA).

RESULTS

Representative plasma concentration against time profiles for azithromycin is shown in Fig. 8. Azithromycin concentrations were determined in all samples. In previous studies, the methods used to quantify azithromycin concentrations were of limited value because of their poor sensitivity. However, the results indicated that the method developed in this study was suitable for pharmacokinetic studies. The T_{max}, C_{max}, CL/F and $t_{1/2}$ were 2.5 1.00-6.00 h,

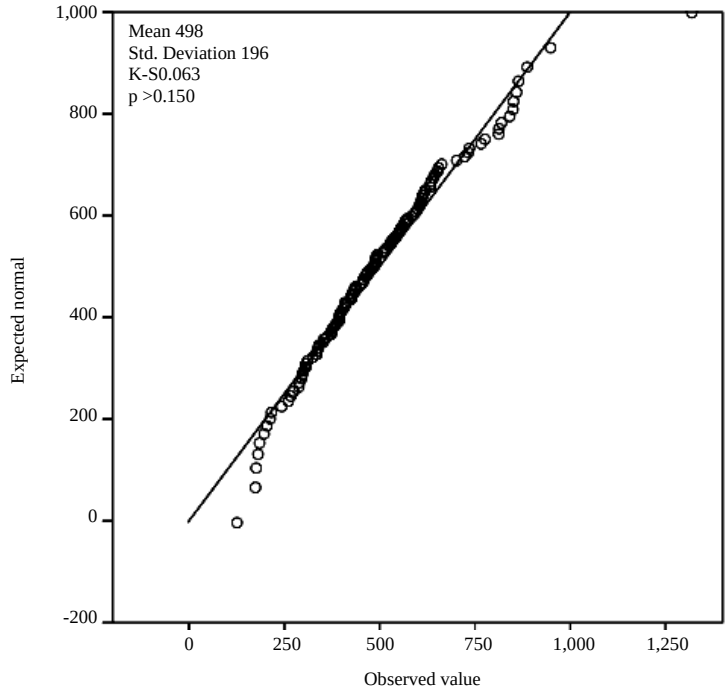

Fig. 4: Normal quantile-quantile plot for Cmax of Azithromycin in a young Taiwanese (n = 117)

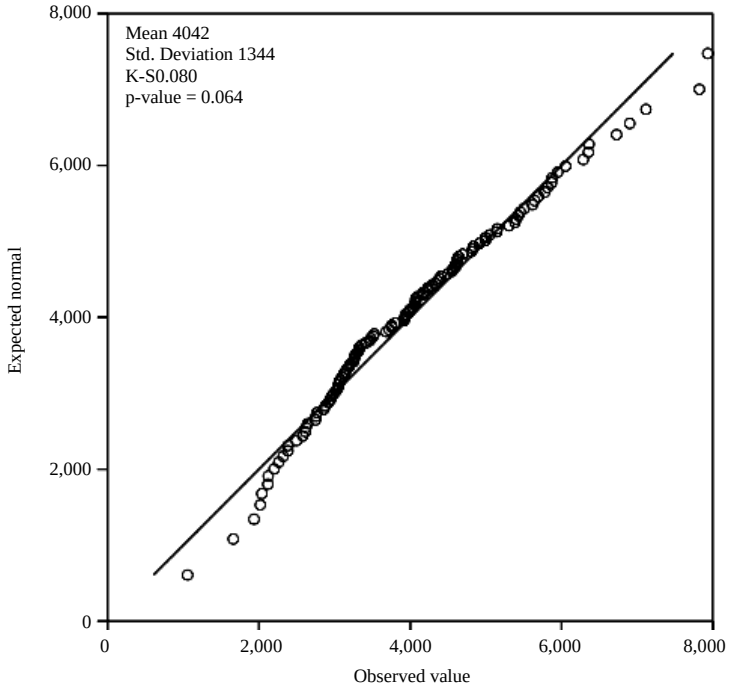

Fig. 5: Normal quantile-quantile plot for AUC0-t of Azithromycin in a young Taiwanese (n = 117)

498±196 ng mL^{-1}, 46.0±17.6 L h^{-1} and 84.2±25.7 h, respectively (n = 117). After azithromycin administration, the AUC_{0-t} and $AUC_{0-\infty}$ were 4042±1344 h×ng mL^{-1} and 4401±1468 h×ng mL^{-1}, respectively. The mean ratio of AUC_{0-t} to $AUC_{0-\infty}$ was over 80%, which represented a suitable sampling schedule. The extent of variation in oral azithromycin pharmacokinetics in young Taiwanese, it is revealed a prolonged half-life on the basis of normal distribution of

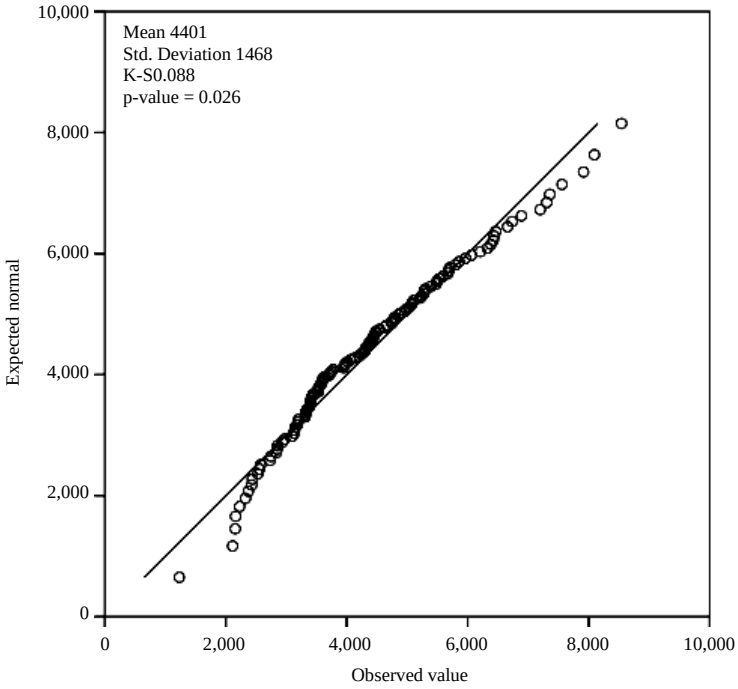

Fig. 6: Normal quantile-quantile plot for AUC0-8 of Azithromycin in a young Taiwanese (n = 117)

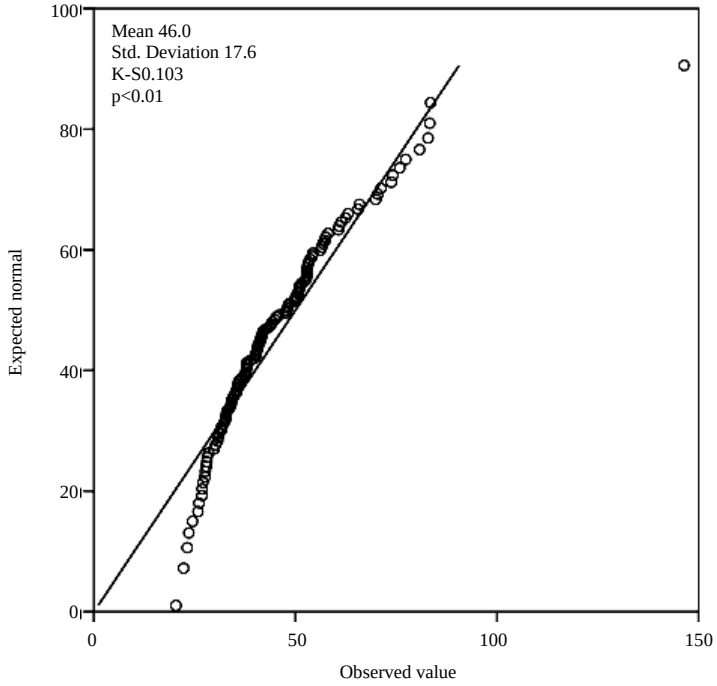

Fig. 7: Normal quantile-quantile plot for CL/F of Azithromycin in a young Taiwanese (n = 117)

azithromycin pharmacokinetics. Normality tests, agglomerative hierarchical clustering and non-hierarchical K-means clustering were performed using AUC_{0-t} data. No distinct phenotypes were identified, which was an unexpected result. Figure 4-7 show normal Q-Q plots with the results of the K-S tests for azithromycin C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and CL/F, respectively. Briefly, theresults could not identify any polymorphism on azithromycin PK characteristics.

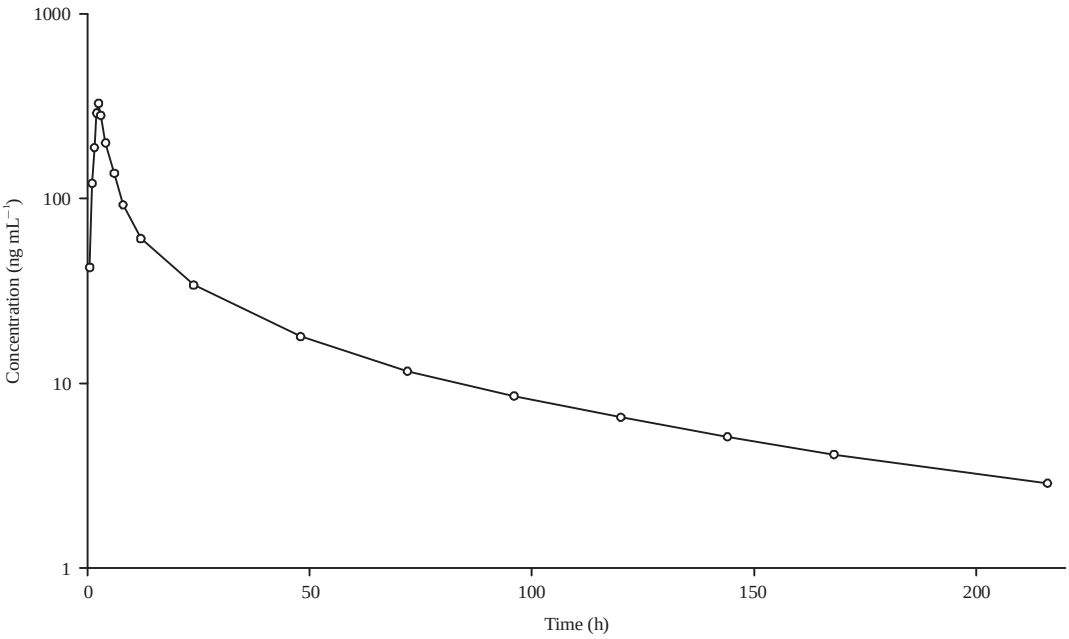

Fig. 8: Representative plasma concentration-time curves for azithromycin

DISCUSSION

In present study, azithromycin pharmacokinetic parameters exhibited a normal distribution and ABCB1 genetic polymorphism influence on azithromycin pharmacokinetics was not observed in young Taiwanese. This observation was unexpected. Previous research indicated that azithromycin pharmacokinetic parameters exhibited great variability between individuals with ABCB1 genotypes[15]. A number of single nucleotide polymorphisms (SNPs) have been identified for the ABCB1 gene. Three SNPs, 1236C>T, 2677G>T and 3435C>T, were discovered and demonstrated to affect P-glycoprotein (P-gp) expression levels and function. The frequencies at which these polymorphisms exist within a population have been shown to be linked to ethnicity[16]. Clinical studies have been conducted to investigate the association between such polymorphisms and the expression and function of P-gp as well as the pharmacokinetics of its substrates[15]. These SNPs may be the underlying cause of the aforementioned variation in azithromycin pharmacokinetics.

It had been reported that drug transporter geneticpolymorphisms affect pharmacokinetics as well as drug pharmacological and toxicologicaleffects. Previous reports showed that azithromycin pharmacokinetics may be influenced by particular polymorphisms of the *ABCB1* gene. In the Chinese population, the SNP at 3435C>T played a significant role in the *ABCB1* gene and pharmacokinetic parameters also exhibited great variability between the 2677GG/3435CC, 2677GT/3435CT and 2677TT/3435TT groups[15]. Haplotype and genotype analysis from these data may be used as a basis for future studies on the relationship between ABCB1 genotypes and drug efficacy, drug toxicity, disease susceptibility or other phenotypes.

The highest frequencies of the three aforementioned SNPs of the ABCB1 gene were exhibited in Asian and Caucasian populations, with the lowest in African populations[17]. Pharmacokinetic parameters such as T_{max}, $t_{1/2}$ and $AUC_{0-\infty}$ have all been highly variable among published studies. The Taiwanese population was also shown to possess ABCB1 SNPs (C3435T, G2677T and C1236T)[18,19] but the impact of ABCB1 polymorphisms on azithromycin has not been investigated.

Azithromycin is also a substrate for numerous transporter systems. Co-administration with a transporter inhibitor or inducer resulted in altered azithromycin pharmacokinetic parameters, including C_{max} and AUC. The results of previous animal studies demonstrated that azithromycin administration with organic anion transporting polypeptide (OATP) inhibitors significantly decreased the C_{max} and AUC of azithromycin[20]. Although most nucleotide variants are located within the coding regions of the OATP gene, no SNPs were discovered in the young Taiwanese[21]. Thus, variations in the promoter region may account for inter-individual differences in OATP expression, enzymatic activity as well as placental and hepatic mRNA levels. Further studies taking into

Table 3: Comparison of azithromycin pharmacokinetic parameters in healthy volunteers from different ethnicities

	Parameters						
Population (n)	Dosage (mg)	T_{max} (h)	C_{max} (ng mL^{-1})	AUC_{0-t} (h×ng mL^{-1})	$AUC_{0-\infty}$ (h×ng mL^{-1})	$t_{1/2}$ (h)	References
Thai (14)	500	1.5±0.4	425±198	4027±1839	4027±1839	28.1±13.1	Boonleang *et al.*[9]
Chinese (24)	500	2.1±0.5	448±102	4308±1236	4986±1553	42.3±12.6	Chen *et al.*[7]
Chinese (18)	500	1.9±0.6	566±208	4536±1019	5243±1257	50.0±5.0	Chen *et al.*[6]
Germany (24)	500	3.0±0.9	304±344	4365±1936			Beringer *et al.*[10]
Indonesian (18)	500	2.0	420	4276	5578	51.0	Setiawati *et al.*[11]
Indian (24)	500	4.8±1.0	392±190	6293±9670	7023±9610	41.2±6.4	Ahmed *et al.*[12]
Pakistani (12)	500	2.91	380±400	2850±4800		8.8±1.0	Samiullah *et al.*[8]
Taiwanese (117) (present study)	500	2.5	498±196	4042±1344	4401±1468	84.2±25.7	

consideration of such factors are required for a full understanding of azithromycinpharmacokinetic activity.

Transporter proteins have been well investigated and are known to play significant roles in drug absorption, distribution and excretion[22]. Azithromycin is a substrate for P-gp, the product of the ABCB1 gene. P-gp was initially identified owing to its over expression in human tumor cells[23]. It was subsequently found in various non-neoplastic human tissues, including the small and large intestinal epithelium, adrenal gland, placenta, kidney, liver, pancreas and capillary endothelial cells in the brain and testes. Moreover, P-gp is located on the apical or luminal surface of the epithelial cells of the aforementioned tissues or organs[24-27].

Previous studies have reported the PK characteristics of azithromycin to be dose dependent. However, the variability in azithromycin PK characteristics has not been exhaustively discussed. In this study, azithromycin was rapidly absorbed and reached T_{max} at 2.5 h after administration. The C_{max} was 498±196 ng mL^{-1} and AUC_{0-t} was 4042±1344 h×ng mL^{-1}. These results were similar to previous results obtained in Chinese and Thai populations (Table 3).

The $t_{1/2}$ of azithromycin was 84.2±25.7 h in the present study. However, the $t_{1/2}$ of azithromycin ranged from 8.8 to 51 h in previous studies. The factors affecting the plasma half-life of azithromycin could be complex. The sensitivity of the analytical methods, duration of blood sampling and individual variation might also alter pharmacokinetic results. After azithromycin administration, plasma concentrations at 72 h were under 10 ng mL^{-1}. Bioanalytical methods with lower limit of quantification (LLOQ) values of 1-50 ng mL^{-1} varied, some of them were not sensitive enough to detect the drug in the elimination phase. The sampling duration of single oral doses of azithromycin ranging from 48-120 h was investigated but is was unable to estimate the terminal $t_{1/2}$ because of a short duration of blood sampling.

Chen *et al.* developed a specific assay for azithromycin with a LLOQ of 1 ng mL^{-1}, which was a significant improvement over previous methods and this validated bioanalytical method has also been applied in pharmacokinetic studies[6,7,28]. A similar result was obtained and it is similar to the reported pharmacokinetic parameters with the same dosage form and dosage with a longer half-life, indicating that these improvements in assay sensitivity resulted in similar results to those obtained by Gandhi *et al.*[29,30]. Analytical methods with significant improvements in sensitivity also enabled longer plasma concentration-time profiles for azithromycin. Sufficient duration of blood sampling is required for the adequate calculation of the terminal elimination rate to compute profiles[29,30]. Samiullah *et al.*[8] reported azithromycin pharmacokinetics in Pakistani volunteers at 48 h after drug administration and found a $t_{1/2}$ of 8.8 h, which was shorter than that reported previously. Taken together, these data indicate that blood sampling should be continued for at least 120 h during azithromycin pharmacokinetic studies in order to capture the complete plasma-concentration profile and the true elimination half-life. Unfortunately, the prolonged $t_{1/2}$ could be also the risk of higher resistant rate in terms of clinical practice as it could result in the emergence of resistant strains due to the subinhibitory concentrations at tissue sites over an extended period of time[4,5].

This study has several limitations. Since the pharmacodynamics characteristics was not analyzed, including AUC/MIC, the details of antimicrobial effect of azithromycin was not evaluated in this study. More data should be collected, even be combined with clinical practice and research on patients, to explore the benefit of clinical application of azithromycin.

CONCLUSION

According to previous research, variations in the ATP-binding cassette B1 gene likely contributed to inter-individual variability azithromycin PK. The finding that

azithromycin PK parameters exhibited a normal distribution in the Taiwanese population was therefore inconsistent with previous research of ABCB1 gene polymorphism on PK as no polymorphism-linked effect was observed. Also, population analysis indicated lack of phenotype differences of azithromycin PK in young Taiwanese. The present data revealed a prolonged $t_{1/2}$ on the basis of normal distribution of azithromycin PK, implicating a potential increased risk of antimicrobial resistance. This research demonstrate the unique PK parameters of oral azithromycin, indicating the representative PK phenotype in young Taiwanese that can be helpful to choice of antibiotics clinically.

SIGNIFICANCE STATEMENT

This research discovered that there are no significant differences between phenotypes of azithromycin pharmacokinetics in young Taiwanese population. A longer half-life of azithromycin was observed and it indicated that a potential increased risk of antimicrobial resistance in clinical practices.

ACKNOWLEDGMENT

This manuscript was revised by Dr. Yu-Jen Chen.

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