Population pharmacokinetic model of digoxin in older Chinese patients and its application in clinical practice

Xiao-dan ZHOU1, 2, Yan GAO1, Zheng GUAN3, Zhong-dong LI1, *, Jun LI2, *

1Department of Pharmacy, General Hospital of Air Force, PLA, Beijing 100142, China; 2School of Pharmacy, Anhui Medical University, Hefei 230032, China; 3School of Pharmacy, Beijing University, Beijing 100191, China

Aim: To establish a population pharmacokinetic (PPK) model of digoxin in older Chinese patients to provide a reference for individual medication in clinical practice.

Methods: Serum concentrations of digoxin and clinically related data including gender, age, weight (WT), serum creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), albumin (ALB), and co-administration were retrospectively collected from 119 older patients taking digoxin orally for more than 7 d. NONMEM software was used to get PPK parameter values, to set up a final model, and to assess the models in clinical practice.

Results: Spironolactone (SPI), WT, and Cr markedly affected the clearance rate of digoxin. The final model formula is Cl/F=5.9×[1–0.412×SPI]×[1–0.0101×(WT–62.9 )]×[1–0.0012×(Cr–126.8 )] (L/h); Ka=1.63 (h⁻¹); Vd/F=550 (L). The population estimates for Cl/F and Vd/F were 5.9 L/h and 550 L, respectively. The interindividual variabilities (CV) were 49.0% for Cl/F and 94.3% for Vd/F. The residual variability (SD) between observed and predicted concentrations was 0.365 μg/L. The difference between the objective function value and the primitive function value was less than 3.84 (P>0.05) by intra-validation. Clinical applications indicated that the percent of difference between the predicted concentrations estimated by the PPK final model and the observed concentrations were -4.3%−+25%. Correlation analysis displayed that there was a linear correlation between observated and predicted values (y=1.35x+0.39, r=0.9639, P<0.0001).

Conclusion: The PPK final model of digoxin in older Chinese patients can be established using the NONMEM software, which can be applied in clinical practice.

Keywords: digoxin; population pharmacokinetics; aging; retrospective studies; NONMEM
113 of the 119 patients (95%) were suffering from varying degrees of congestive heart failure (CHF). The data collected were the patient’s age, gender, weight (WT), dosage regimen of digoxin, serum concentration (173 observations), hepatic and renal function including alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (Cr), and albumin (ALB), as well as concomitant medications including spironolactone (SPI), calcium channel blocker (CCB), nitrate, and propofenone. Patient information is given in Table 1.

### Table 1. Summary of patient’s information.

| Parameter                        | Value         |
|----------------------------------|---------------|
| Number of patients               | 119           |
| Number of patients with CHF      | 113           |
| Gender (M:F)                     | 69:50         |
| Age (Y)                          | 71.0 a (60–88) b |
| WT (kg)                          | 62.9 a (34–91) b |
| ALT (U/L)                        | 29.3 a (3–383) b |
| AST (U/L)                        | 33.9 a (8–402) b |
| BUN (mmol/L)                     | 9.0 a (2.5–28.9) b |
| Cr (μmol/L)                      | 126.8 a (36–686) b |
| ALB (g/L)                        | 63.3 a (31–89) b |
| Observations                     | 173           |
| Digoxin serum concentration (μg/L) | 1.11 a (0.07–4.45) b |
| Interval of last medication and phlebotomizing (h) | 22.9 a (6–192) b |

Combination medications:
- SPI: 32
- CCB: nifedipine 53, diltiazem 1
- Nitrate 86
- Propofenone 27

Note: *Mean and a range. Weight (WT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (Cr), albumin (ALB), spironolactone (SPI), calcium channel blocker (CCB).

### Drug
Digoxin, 0.25 mg/pellet, was from Sine Pharmaceutical Co, Ltd, Shanghai, China.

### Inclusion and exclusion criteria

#### Inclusion criteria
Older patients (over 60 years old) taking digoxin orally for more than 7 d were included in the study.

#### Exclusion criteria
Patients with serious hepatic and renal dysfunction and digoxin serum concentrations higher than the maximum detection limit or lower than the minimum detection limit were excluded from the study.

### Instruments and software
The measurement of digoxin in serum was carried out by fluorescence polarization immunoassay (FPIA) using the TDx-FLx system (Abbott, USA). The minimum detectable concentration for digoxin was 0.2 μg/L[4, 7]. The population pharmacokinetics analysis of digoxin was performed using NONMEM software (Version V, Level 1.0, Globomax, USA).

### Structural pharmacokinetic model
The structural pharmacokinetic model (e.g., a one-, two-, or three-compartment model)[9] was considered first. Previous studies[1, 2, 7] reported that a one-compartment model and the first-order kinetics process could describe the time course of digoxin steady state concentrations in plasma. In this paper, a one-compartment open model was selected as a population structural PK model.

#### Equations of digoxin PPK basic model
Equations of the digoxin PPK basic model were as follows:
\[
\begin{align*}
Y_{\text{Pred}} &= \frac{\theta_1}{\theta_2} \times \exp(\theta_3) \\
Y &= Y_{\text{Pred}} + Y_{\text{Pred}} \times \text{ERR}(1) + \text{ERR}(2)
\end{align*}
\]
where Cl, \( V_d \), and Ka represents clearance rate (L/h), apparent volume of distribution (L), and absorption rate constant (h), respectively. Since all doses in the present study were given orally and it was impossible to assess the absolute bioavailability (F), the parameters Cl and \( V_d \) were interpreted as Cl/F and \( V_d/F \), respectively. The typical population value for Cl/F, \( V_d/F \), and Ka is \( \theta_1, \theta_2 \), and \( \theta_3 \) respectively. The inter-individual random effect for Cl/F, \( V_d/F \), and Ka is \( \eta_1, \eta_2 \), and \( \eta_3 \), respectively. They are independent and identically distributed random variables with mean zero and variance \( \omega_1^2 \), \( \omega_2^2 \), and \( \omega_3^2 \), respectively. \( Y \) and \( Y_{\text{Pred}} \) represent observed concentrations and the corresponding predicted values, respectively. \( \text{ERR}(1) \) and \( \text{ERR}(2) \) are inter-individual random effect factors, representing independent, identically distributed statistical error with mean zero and variance \( \omega^2 \) for serum concentrations. The former is the proportional error and the latter is the additive error.

### Framework of the full regression model
Before establishing a full regression model, we selected some initial parameters of Ka, \( V_d/F \), and Cl/F in accordance with the relevant literature to estimate parameters of the basic model (i.e., no covariates). Each candidate covariate such as gender, age, WT, ALT, AST, BUN, Cr, ALB, and coadministration was added, in turn, to the base model and the difference in the objective function values was noted. The difference of the objective function value (ΔOFV) obtained by comparing each model was analyzed by chi-square test (test level was set to 0.05). Any single covariate that made ΔOFV exceed 3.84 was considered significant (\( P<0.05 \), 1 degree of freedom) and added to the model; otherwise it was excluded. According to the ΔOFV, meaningful covariates were lined up in descending order; then the effect of covariates on the model was further investigated by stacking covariates stepwise according to the above order to screen the significant covariates. The full regression model was to be established by the covariates.
Establishing the final model
To check the role of each covariate in the full regression model, backward elimination was used (test level was set to 0.01). A change of OFV was observed once one covariate was eliminated from the model. If the OFV increased by more than 6.63 (P<0.01, 1 degree of freedom), it indicated that the factor was significant and may be reserved in the final model.

Model validation
Intra-validation
The bootstrap method was used to verify the stability of this model in this research. All data were randomly divided into ten groups, one of which contained 10% of the raw data. The control file of the final model was used to calculate the OFV of each of 10 groups. The final model would be proved stable if the difference of OFV between each group and the final model was less than 3.84 (P>0.05).

Application in clinical practice or extra-validation
After fixing each θ value estimated by the final model, clinical information data of another 8 patients were input into the NONMEM program to estimate the individually predicted values of the digoxin steady-state serum concentration and compared them with the observed values. The percent difference between the predicted and observed concentrations was calculated using the formula [(observed value – individual predicted value)/observed value]×100%. The linear relation was also analyzed between the predicted and observed concentrations.

Results
Basic model
The collected data were analyzed by the subroutines ADVAN2 of the NONMEM software according to a one-compartment model. We got parameter estimates of 4.88 L/h for Cl/F, 514 L for Vd/F, and 1.63 h⁻¹ for Ka (Table 2). Because the absorption phase in the data had been completed, Ka and inter-individual variation were fixed to 1.63 h⁻¹ and 0, respectively, in the next calculation to avoid the effect of Ka fluctuation on the stability of model.

| Parameter | Estimate | RSE (%) | 95% CI | Inter-Indv (%) |
|-----------|----------|---------|--------|---------------|
| Cl/F (L/h) | 4.88 | 5.92 | 4.31–5.45 | 61.2 |
| Vd/F (L) | 514 | 16.4 | 349–679 | 63.1 |
| Ka (h⁻¹) | 1.63 (fixed) |
| Residual error | | | |
| Proportional, CV (%) | 0.0461 |
| Additive, SD (µg/L) | 0.329 |

Note: Objective function value (OFV); Relative standard error (RSE); 95% Confidence interval (CI); Inter-individual variability (Inter-Indv); Standard deviation (SD).

Full regression model
The basic model of Cl/F was markedly affected by SPI, ALB, WT, Cr, and gender and the basic model of Vd/F was markedly affected by SPI, ALB, WT, Cr (Table 3). However, when these factors were stacked, Cl/F or Vd/F was significantly affected by the combination of SPI, WT, and Cr or the combination of SPI and WT (Table 4). We got parameter estimates of 5.63 L/h for Cl/F, 707 L for Vd/F and 1.63 h⁻¹ for Ka (Table 5).

Table 2. Parameter estimates of digoxin basic model.

Table 3. Fixed effect factors of significance when they existed individually.

| Model | OFV | ΔOFV | P<0.05 |
|-------|-----|------|--------|
| Basic model | 22.738 | – | – |
| ALB-Cl | 4.070 | 18.668 | Yes |
| WT-Cl | 6.495 | 16.243 | Yes |
| Cr-Cl | 12.924 | 9.814 | Yes |
| Gender-Cl | 13.767 | 8.971 | Yes |
| SPI-Vd | 16.293 | 6.445 | Yes |
| ALB-Vd | 6.698 | 16.04 | Yes |
| Cr-Vd | 12.104 | 10.634 | Yes |
| WT-Vd | 16.220 | 6.518 | Yes |
| WT-Vd | 17.327 | 5.411 | Yes |

Note: OFV, the minimum value of objective function in each NONMEM run; 22.738 is the OFV of the basic model; ΔOFV, difference between each OFV and 22.738.

Table 4. Modeling process of full model of digoxin population pharmacokinetics.

| Model | OFV | ΔOFV | P<0.05 |
|-------|-----|------|--------|
| Model 1 | 22.738 | – | – |
| (SPI-Cl) | 4.070 | – | – |
| (SPI-Cl)&(WT-Cl) | 6.495 | 18.668 | Yes |
| (SPI-Cl)&(WT-Cl)&(Cr-Cl) | 12.924 | 9.814 | Yes |
| (SPI-Cl)&(WT-Cl)&(Cr-Cl)&(SPI-Vd) | 13.767 | 8.971 | Yes |
| (SPI-Cl)&(WT-Cl)&(Cr-Cl)&(SPI-Vd)&(WT-Vd) | 16.293 | 6.445 | Yes |
| (SPI-Cl)&(WT-Cl)&(Cr-Cl)&(SPI-Vd)&(WT-Vd) | 6.698 | 16.04 | Yes |
| (SPI-Cl)&(WT-Cl)&(Cr-Cl)&(SPI-Vd)&(WT-Vd) | 12.104 | 10.634 | Yes |
| (SPI-Cl)&(WT-Cl)&(Cr-Cl)&(SPI-Vd)&(WT-Vd) | 16.220 | 6.518 | Yes |
| (SPI-Cl)&(WT-Cl)&(Cr-Cl)&(SPI-Vd)&(WT-Vd) | 17.327 | 5.411 | Yes |

Note: ΔOFV, difference between the latter model and the former.

Final model
The combination of SPI, WT, and Cr significantly affected Cl/F using backward elimination (ΔOFV>6.63, P<0.01) (Table 6). All parameters of the final model are given in Table 7. The population estimates for Cl/F and Vd/F were 5.9 L/h and 550 L, respectively. The inter-individual variability (CV) was 49.0% for Cl/F and 94.3% for Vd/F. The residual variability (SD) between the observed and predicted concentrations was 0.365 µg/L. The final regression model formula is Cl/F=5.9×[1−0.412×SPI]×[1−0.0101×(WT−62.9)]×[1−0.0012×(Cr−126.8)] (L/h); Ka: 1.63 (h⁻¹); Vd/F: 550 (L). The figure of the final model is presented in Figure 1.
Model validation

We used the control file of the final model to calculate OFV of each of the 10 groups. The difference between OFV and the primitive function value was less than 3.84 (P>0.05), which showed that the model was stable.

Clinical information of another 8 elderly patients with heart failure taking digoxin orally for a long time was collected. The individual values of digoxin steady-state serum concentration from these 8 patients had been predicted by the established final model (Table 8). The results displayed that the percent difference between the predicted and the observed concentration was -4.3%–+25%. Correlation analysis showed that there was a linear correlation between observations and predicted values (y = 1.35x + 0.39, r = 0.9639, P<0.0001), indicating that the model can be used in clinical practice to predict digoxin serum concentration.

Discussion

The treatment of heart failure in the elderly often involves many kinds of medicines such as cardiac glycosides (digoxin, cedilanid D), ACEI, CCB, β2-receptor antagonists, organic nitrates, and diuretics (furosemide, spironolactone). The
serum concentration of digoxin may be affected by various covariates such as gender, WT, Cr, or other medicines. This study showed that covariates such as SPI, WT, and Cr markedly affected the total clearance of digoxin (Cl/F). The total clearance of digoxin was modeled as the sum of renal and non-renal clearance. According to the view reported by Yukawa[16], the non-renal clearance of digoxin in our study was related to body weight, and the renal clearance was related to serum creatinine level. When the covariates were not considered, the population estimate for clearance was 4.88 L/h with a coefficient of variation (CV) of 61.2%. After Cr, WT and SPI were considered as covariates of Cl/F, the population estimate of Cl/F was 5.9 L/h with a CV of 49%, which fell within 4.4–7.7 L/h[19] and 5.2–6.3 L/h[19] in American patients (reported by Cheng et al and Bauer et al, respectively). However, Cl/F (5.9 L/h) was slightly higher than that in Korean patients (4.38 L/h)[11] (Nagaraja et al) and American patients (4.87 L/h)[11] (Sheiner et al) and lower than that in Japanese patients (10.3 L/h)[13] (Yukawa et al) and American patients (8.25 L/h)[11] (Williams et al). These differences may be related to case characteristics, different populations, population size, the length of disease course, the extent of myocardial damage and peripheral vascular tension, and/or the method of population analysis. In addition, P-glycoprotein (P-gp), the expression product of the human multidrug resistance 1 (MDR1) gene, is an important factor in the disposition of many drugs (such as digoxin, amiodarone, and quindine)[15–18]. There are 50 SNPs (single nucleotide polymorphism) in the MDR1 gene[19] and exon 26 C3435T SNP is associated with a change in digoxin’s oral absorption[20, 21]. The distribution of C3435T polymorphism is significantly influenced by ethnicity[19]. The interindividual variation in Chinese patients compared with American patients in our study may also be related to the different expression amounts of P-gp. A silent mutation in exon 26 of human MDR1 is associated with the impaired oral bioavailability of digoxin in humans; however, the causative molecular genetic mechanism of this observation is unknown[20]. In short, the exact causes of the above Cl/F differences remain to be further explored.

Spironolactone, a mineralocorticoid receptor antagonist, or a diuretic, which could reserve potassium, is usually combined with digoxin to treat CHF. The main reason that SPI increases the serum concentration of digoxin is its inhibition of digoxin renal tubular excretion[21].

Some literatures[4, 22] have shown that when digoxin is taken orally with CCBs, such as verapamil and diltiazem, serum concentration of digoxin is raised, potentially resulting in an increased risk of digitalis poisoning. Among the 119 patients in our study, 53 patients took nifedipine with digoxin and only one person took diltiazem. Our research revealed that nifedipine, one of the CCBs, had no effect on the final model, a finding similar to the results reported by Schwartz JB et al[23].

In the validation group of 8 patients, predictions of the digoxin serum concentrations were made with the final regression model. The performance was interpreted as good because there was a good linear correlation between observations and the predicted values (r=1.35×+0.39, r=0.9639, P<0.0001). However, the use of this model in routine monitoring requires that certain conditions be met that are consistent with the conditions of the sub-population in the present study (for details see Table 1).

NONMEM can make full use of the sparse data of serum drug concentration to estimate PPK, and this might decrease sampling times. Therefore, it will be easily accepted by patients, especially older people[22, 24] and neonates[1–3, 7, 25], and is suitable for clinical individual administration of special populations[6, 4]. Although NONMEM demands few sampling times, it requires more cases from various phases — for example, the absorption phase, distribution phase, and elimination phase. The accuracy of the sampling time and the determination of the results should also be stressed to reduce the error. In short, the NONMEM method may be widely applied today and in the future in the study of population pharmacokinetics and individualized medication.

In conclusion, a population pharmacokinetic model for digoxin in a population of older Chinese patients was developed by NONMEM. The final PPK model that described digoxin clearance in a population of older Chinese patients is as follows: Cl/F=5.9×[1–0.412×SPI]×[1–0.0101×(WT–62.9)]×[1–0.0012×(Cr–126.8)] (L/h). This model can be used to predict digoxin serum concentration in clinical practice.

Acknowledgements

This work was supported by the Natural Science Foundation of PLA, China (No 06MA024). The authors are grateful to Prof Wei LU for his instruction.

Author contribution

Zhong-dong LI and Jun LI designed the research; Yan GAO collected clinical information; Xiao-dan ZHOU performed the research; Xiao-dan ZHOU and Zheng GUAN analyzed data; Xiao-dan ZHOU and Zhong-dong LI wrote the paper.

References

1. Yukawa E, Akiyama K, Suematsu F, Yukawa M, Minemoto M. Population...
tion pharmacokinetic investigation of digoxin in Japanese neonates. J Clin Pharm Ther 2007; 32: 381–6.

2 Martin-Suárez A, Falcao AC, Outeda M, Hernandez FJ, Gonzalez MC, Quero M, et al. Population pharmacokinetics of digoxin in pediatric patients. Ther Drug Monit 2002; 24: 742–5.

3 Suematsu F, Yokawa E, Yokawa M, Minemoto M, Ohdo S, Higuchi S, et al. Population-based investigation of relative clearance of digoxin in Japanese neonates and infants by multiple-trough screen analysis. Eur J Clin Pharmacol 2003; 57: 19–24.

4 Yokawa E, Suematsu F, Yokawa M, Minemoto M, Ohdo S, Higuchi S, et al. Population pharmacokinetics of digoxin in Japanese patients. Clin Pharmacokinet 2001; 40: 773–81.

5 Jonsson EN, Antila S, McFadyen L, Lehtonen L, Karlsson MO. Population pharmacokinetics of levosimendan in patients with congestive heart failure. J Clin Pharmacol 2000; 40: 157–66.

6 Hornestam B, Jerling M, Karlsson MO, Held P. Intravenously administered digoxin in patients with acute atrial fibrillation: a population pharmacokinetic/pharmacodynamic analysis based on the Digitalis in Acute Atrial Fibrillation trial. Eur J Clin Pharmacol 2003; 58: 747–55.

7 EL Desoky ES, Nagaraja NV, Derendorf H. Population pharmacokinetics of digoxin in Egyptian pediatric patients: Impact of one data point utilization. Am J Ther 2002; 9: 492–8.

8 Phillips L, Grasela TH, Agnew JR, Ludwig EA, Thompson GA. A population pharmacokinetic-pharmacodynamic analysis and model validation of azimilide. Clin Pharmacol Ther 2001; 70: 370–83.

9 Cheng JWM, Charland SL, Shaw LM, Kobrin S, Goldfarb S, Stanek EJ, et al. Is the volume of distribution of digoxin reduced in patients with renal dysfunction? Determining digoxin pharmacokinetics by fluorescence polarization immunoassay. Pharmacotherapy 1997; 17: 584–90.

10 Bauer LA, Horn JR, Pettit H. Mixed-effect modeling for detection and evaluation of drug interactions: digoxin-quinidine and digoxin-verapamil combinations. Ther Drug Monit 1996; 18: 46–52.

11 Nagaraja NV, Park YJ, Jeon S, Sands CD, Derendorf H. Population pharmacokinetics of digoxin in Korean patients. Int J Clin Pharmacol Ther 2000; 38: 291–7.

12 Sheiner LB, Rosenberg B, Marathe W. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm 1977; 5: 445–79.

13 Yokawa E, Honda T, Ohdo S, Higuchi S, Aoyama T. Population-based investigation of relative clearance of digoxin in Japanese patients by multiple trough screen analysis: an update. J Clin Pharmacol 1997; 37: 92–100.

14 Schwartz JB, Migliore PJ. Effect of nifedipine on serum digoxin concentration and renal digoxin clearance. Clin Pharmacol Ther 1984; 36: 19–24.

15 Ferrara S, Pazzuconi F, Bondioli A, Mombelli G, Agrati A, Ferraro G, et al. Development of a model based on body composition to predict drug kinetics II. Application of the model to the use of digoxin in elderly patients. Pharm Res 2004; 50: 105–8.

16 Suematsu F, Minemoto M, Yokawa E, Higuchi S. Population analysis for the optimization of digoxin treatment in Japanese paediatric patients. J Clin Pharm Ther 1999; 24: 203–8.