Acta Pharmacologica Sinica (2010) 31: 753–758
 1671-4083/10 $32.00
www.nature.com/aps

Original Article

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

Xiao-dan ZHOU[1, 2], Yan GAO[1], Zheng GUAN[3], Zhong-dong LI[1, *], Jun LI[2, *]

[1]*Department of Pharmacy, General Hospital of Air Force, PLA, Beijing 100142, China;* [2]*School of Pharmacy, Anhui Medical University, Hefei 230032, China;* [3]*School 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}); V_d/F=550 (L). The population estimates for Cl/F and V_d/F were 5.9 L/h and 550 L, respectively. The interindividual variabilities (CV) were 49.0% for Cl/F and 94.3% for V_d/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

Acta Pharmacologica Sinica advance (2010) 31: 753–758; doi: 10.1038/aps.2010.51

Introduction

Digoxin is widely prescribed for the treatment of congestive heart failure in clinical practice. Because of its low therapeutic index, narrow safety range and strong side effects, toxicity may also be caused by routine dosage[1–4]. Elderly patients with heart failure are more susceptible to toxicity because their impaired renal function may cause the clearance of digoxin to decrease. Therefore, individualized medication of digoxin is of great significance.

Approved by the US FDA in 1999, NONMEM[1–8] is the best model for clinical individualized medication. It was built on the basis of a combination of the classical pharmacokinetic model, the fixed-effect model and the statistical model. The principle of the extended non-linear least squares was applied to estimate the population pharmacokinetic parameters using the patients' sparse plasma concentration data, pathological factors, physiological factors and coadministration.

This paper aimed: 1) to build a population pharmacokinetic basic model of digoxin in 119 older Chinese patients; 2) to analyze the effects of fixed-effect factors such as weight, age, gender, hepatic and renal function, and concomitant medications on this model; 3) to establish the full regression model and the final model; and 4) to determine whether the final model is stable and reliable by intra-validation and clinical applications.

* To whom correspondence should be addressed.
E-mail zhdl009@126.com (Zhong-dong LI);
lijun@ahmu.edu.cn (Jun LI)
Received 2009-08-10 Accepted 2010-03-30

Materials and methods

Data sources

Routine clinical data were retrospectively collected from 119 older patients in the General Hospital of the Air Force, PLA.

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.

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: [a]Mean and [b]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 (*eg*, a one-, two-, or three-compartment model)[5] 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:

$$Cl/F=\theta_1\times ExP(ETA(1))$$
$$V_d/F=\theta_2\times ExP(ETA(2))$$
$$Ka=\theta_3\times ExP(ETA(3))$$
$$Y=Y_{PRED}+Y_{PRED}\times ERR(1)+ERR(2)$$

where Cl, V_d, and Ka represents clearance rate (L/h), apparent volume of distribution (L), and absorption rate constant (h^{-1}), 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 θ_1, θ_2, and θ_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 independently distributed random variables with mean zero and variance ω^2. Y, and Y_{PRED} represent observed concentrations and the corresponding predicted values, respectively. ERR(1) and ERR(2) are inter-individual random effect factors, representing independent, identically distributed statistical error with mean zero and variance σ^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 (*ie*, 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[5, 8] (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 V_d/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.

Table 2. Parameter estimates of digoxin basic model.

OFV=22.738 Parameter	Estimate	RSE (%)	95% CI	Inter-Indv (%)
Cl/F (L/h)	4.88	5.92	4.31–5.45	61.2
V/F (L)	514	16.4	349–679	63.1
Ka (h^{-1})	1.63 (fixed)			
Residual error				
Proportional, CV (%)	0.0461			
Addictive, 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 V_d/F was markedly affected by SPI, ALB, WT, Cr (Table 3). However, when these factors were stacked, Cl/F or V_d/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 V_d/F and 1.63 h^{-1} for Ka (Table 5).

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

Model	OFV	ΔOFV	P<0.05
Basic model	22.738	–	–
SPI-Cl	4.070	18.668	Yes
ALB-Cl	6.495	16.243	Yes
WT-Cl	12.924	9.814	Yes
Cr-Cl	13.767	8.971	Yes
Gender-Cl	16.293	6.445	Yes
SPI-V_d	6.698	16.04	Yes
ALB-V_d	12.104	10.634	Yes
Cr-V_d	16.220	6.518	Yes
WT-V_d	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
(SPI-Cl)	4.070	–	–
(SPI-Cl) & (WT-Cl)	-2.676	6.746	Yes
(SPI-Cl) & (WT-Cl) & (Cr-Cl)	-11.354	8.678	Yes
(SPI-Cl) & (WT-Cl) & (Cr-Cl) & (SPI-V_d)	-15.552	4.198	Yes
(SPI-Cl) & (WT-Cl) & (Cr-Cl) & (SPI-V_d) & (WT-V_d)	-21.658	6.106	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 V_d/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 V_d/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}); V_d/F: 550 (L). The figure of the final model is presented in Figure 1.

Table 5. Parameter estimates of digoxin full regression model by NONMEM.

OFV=-21.658 Parameter	Estimate	RSE (%)	95% CI	Inter-Indv (%)
Cl/F (L/h)	5.63	9.31	4.60–6.66	49.1
V/F (L)	707	25.7	350–1060	63.1
Ka (h^{-1})	1.63 (fixed)			
θ_{SPI-Cl}	0.332	26.5	0.160–0.504	
θ_{WT-Cl}	0.0130	17.7	0.00849–0.0175	
θ_{Cr-Cl}	0.00114	51.3	0–0.00229	
θ_{SPI-Vd}	0.547	17.1	0.364–0.730	
θ_{WT-Vd}	0.0158	0.596	0.0156–0.0160	
Residual Error				
Proportional, CV (%)	–			
Addictive, SD (μg /L)	0.371			

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

Table 6. Backward elimination process of full regression model.

OFV=-21.658 Model	OFV	ΔOFV	*P*<0.01
– (SPI-Cl)	-11.450	10.208	Yes
– (WT-Cl)	-14.143	7.515	Yes
– (Cr-Cl)	-14.082	7.576	Yes
– (SPI-V_d)	-16.335	5.323	No
– (WT-V_d)	-15.552	6.106	No

Note: The OFV of the full regression model is -21.658; "–", eliminate one factor from the full regression model at a time; ΔOFV, difference between each OFV and -21.658.

Table 7. Parameter estimates of digoxin final model by NONMEM.

OFV=-11.354 Parameter	Estimate	RSE (%)	95% CI	Inter-Indv (%)
Cl/F (L/h)	5.90	6.97	5.09–6.71	49.0
V/F (L)	550	19.6	338–762	94.3
Ka (h^{-1})	1.63 (fixed)			
θ_{SPI-Cl}	0.412	26.5	0.198–0.626	
θ_{WT-Cl}	0.0101	120	-0.0136–0.0338	
θ_{Cr-Cl}	0.00120	45.8	0.000122–0.00228	
Residual Error				
Proportional, CV (%)	–			
Addictive, SD (μg/L)	0.365			

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

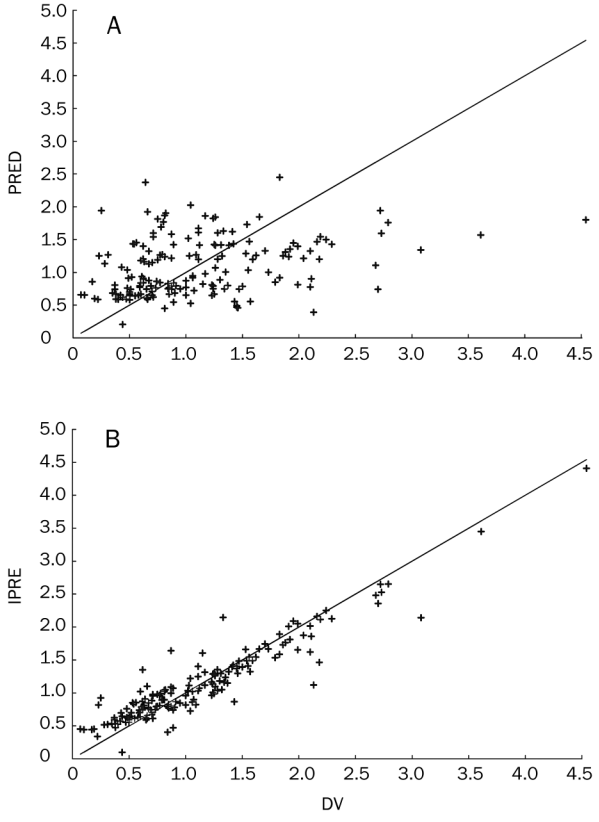

Figure 1. The distribution of data points were more concentrated and uniform in the lower graph (B) than those in the upper graph (A). Predicted values, individual predicted values *vs* observed concentrations. Predicted values (PRED); Individual predicted values (IPRE); Observed concentrations (DV).

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, β_2-receptor antagonists, organic nitrates, and diuretics (furosemide, spironolactone). The

Table 8. Individual predicted values *vs* observed concentrations.

ID	WT (kg)	Dose (mg)	Cr (μmol/L)	SPI	IPRE (μg/L)	Obs (μg/L)	Percentage (%)
1	58	0.125	250	0	1.03	1.37	24.8
2	70	0.125	87	1	0.99	0.93	-6.5
3	63	0.125	80	0	1.11	1.36	18.4
4	58	0.125	171	1	1.93	1.99	3.02
5	67.5	0.125	74	0	0.59	0.51	-15.7
6	86.5	0.125	65	1	2.28	2.56	10.9
7	55	0.125	57	1	1.20	1.15	-4.3
8	65	0.125	115	0	1.28	1.58	18.99

Note: 1 for combination with SPI, 0 for otherwise; Individual predicted value (IPRE); Observed value (Obs).

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[4], 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[9] and 5.2–6.3 L/h[10] 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)[12] (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)[14] (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 quinidine) [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 aldosterone 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[22].

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 (y=1.35x+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[5, 6]. 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. Popula-

tion pharmacokinetic investigation of digoxin in Japanese neonates. J Clin Pharm Ther 2007; 32: 381–6.
2 Martín-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, Yukawa E, Yukawa 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 2001; 57: 19–24.
4 Yukawa E, Suematu F, Yukawa 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 2003; 55: 544–51.
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, Ludwing 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 Yukawa 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 Williams PJ, Lane J, Murray W, Mergener MA, Kamigaki M. Pharmacokinetics of the digoxin-quinidine interaction via mixed-effect modelling. Clin Pharmacokinet 1992; 22: 66–74.
15 Verschraagen M, Koks CH, Schellens JH, Beijnen JH. P-glycoprotein system as a determinant of drug interactions: the case of digoxin-verapamil. Pharmacol Res 1999; 40: 301–6.
16 Koren G, Woodland C, Ito S. Toxic digoxin-drug interactions: the major role of renal P-glycoprotein. Vet Hum Toxicol 1998; 40: 45–6.
17 Kim RB, Leake BF, Choo EF, Dresser GK, Kubba SV, Schwarz UI, *et al*. Identification of functionally variant MDR1 alleles among European Americans and African Americans. Clin Pharm Ther 2001; 70: 189–99.
18 Hunter J, Hirst BH. Intestinal secretion of drugs. The role of P-glycoprotein and related drug efflux systems in limiting oral drug absorption. Adv Drug Deliv Rev 1997; 25: 129–57.
19 Li YH, Wang YH, Li Y, Yang L. MDR1 gene polymorphisms and clinical relevance. Acta Genet Sin 2006; 33: 93–104.
20 Hoffmeyer S, Burk O, von Richter O, Arnold HP, Brockmöller J, Johne A, *et al*. Functional polymorphism of the human multidrug resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acd Sci USA 2000; 97: 3473–78.
21 Sakaeda T, Nakamura T, Horinouchi M, Kakumoto M, Ohmoto N, Sakai T, *et al*. MDR1 genotype-related pharmacokinetics of digoxin after single oral administration in healthy Japanese subjects. Pharm Res 2001; 18: 1400–4.
22 Hanratty CG, McGlinchey P, Johnston GD, Passmore AP. Differential pharmacokinetics of digoxin in elderly patients. Drugs Aging 2000; 17: 353–62.
23 Schwartz JB, Migliore PJ. Effect of nifedipine on serum digoxin concentration and renal digoxin clearance. Clin Pharmacol Ther 1984; 36: 19–24.
24 Ferrara S, Pazzucconi 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 elderlies. Pharm Res 2004; 50: 105–8.
25 Suematsu F, Minemoto M, Yukawa E, Higuchi S. Population analysis for the optimization of digoxin treatment in Japanese paediatric patients. J Clin Pharm Ther 1999; 24: 203–8.