Eur J Clin Pharmacol (2001) 57: 19–24
DOI 10.1007/s002280100274

PHARMACOKINETICS AND DISPOSITION

**Fumihiro Suematsu · Eiji Yukawa · Miho Yukawa
Masao Minemoto · Shigehiro Ohdo
Shun Higuchi · Yoshinobu Goto**

Population-based investigation of relative clearance of digoxin in Japanese neonates and infants by multiple-trough screen analysis

Received: 25 September 2000 / Accepted in revised form: 18 December 2000 / Published online: 28 March 2001

Abstract *Objective*: The steady-state concentrations of digoxin at trough levels were studied to establish the role of patient characteristics in estimating doses for digoxin using routine therapeutic drug monitoring data.
Method: The data ($n = 448$) showing steady state after repetitive oral administration in 172 hospitalized neonates and infants were analyzed using Nonlinear Mixed Effect Model (NONMEM), a computer program designed to analyze pharmacokinetics in study populations by allowing pooling of data. Analysis of the pharmacokinetics of digoxin was accomplished using a simple steady-state pharmacokinetic model. The effects of a variety of developmental and demographic factors on the clearance of digoxin were investigated.
Results: Estimates generated using NONMEM indicated that clearance of digoxin ($l \cdot h^{-1}$) was influenced by the demographic variables of age, total body weight, serum creatinine, the coadministration of spironolactone, and the presence or absence of congestive heart failure. The interindividual variability in digoxin clearance was modeled with proportional errors with an estimated coefficient of variation of 32.1%, and the residual variability was 28.9%. In the validation set of 66 patients, the performance (bias, precision) of the final population model was good (mean prediction error –0.04 $ng \cdot ml^{-1}$; mean absolute prediction error 0.20 $ng \cdot ml^{-1}$).

F. Suematsu (✉) · M. Minemoto
Department of Hospital Pharmacy,
Kyushu Kosei-Nenkin Hospital, 2-1-1 Kishinoura,
Yahatanishi-Ku, Kitakyushu 806-8501, Japan
E-mail: suematsu@ca.mbn.or.jp
Tel.: +81-93-6415111
Fax: +81-93-6415139

E. Yukawa · S. Ohdo · S. Higuchi
Laboratory of Clinical Pharmacokinetics,
Graduate School of Pharmaceutical Sciences,
Kyushu University, 3-1-1 Maidashi,
Higashi-Ku, Fukuoka 812-8582, Japan

M. Yukawa · Y. Goto
Faculty of Pharmaceutical Sciences, Fukuoka University,
Nanakuma, Jonan-Ku, Fukuoka 814-0180, Japan

Key words Digoxin · Neonates · Infants

Introduction

Digoxin is a cardiac glycoside that is widely prescribed for the treatment of congestive heart failure and atrial fibrillation. It is a difficult drug to administer because of the lack of a good relationship between the dose and the desired effect, the narrow therapeutic range (0.5–2.0 $ng \cdot ml^{-1}$ in adults), and the variation in the pharmacokinetic characteristics of the drug [1]. Despite widespread use of digoxin in neonates and infants with cardiac disease, there are few studies on its pharmacokinetics for this age group. Gorodischer [2] and Soyka [3] both recommended that serum digoxin concentrations below 2.0 $ng \cdot ml^{-1}$ can be considered as the "therapeutic (nontoxic) range", with 2.0–3.0 $ng \cdot ml^{-1}$ as the "borderline", and levels greater than 3.0 $ng \cdot ml^{-1}$ as the "toxic range" in infants.

Previous studies [4, 5, 6] reported that infants require higher digoxin doses than adult cardiac patients (mg kg^{-1} body weight basis) to obtain the same serum concentrations. For a dose given daily, steady-state serum concentrations of digoxin vary greatly from patient to patient [7]. Because of this large interpatient variability, the clinician needs an appropriate dosage regimen for individual neonates and infants. It may be more useful to determine the typical pharmacokinetic behavior of the drug in a population rather than in an individual pediatric patient. Previously, the population pharmacokinetics of digoxin were examined using the computer program NONMEM [8, 9], which was developed by Beal and Sheiner [10]. However, at that time only adult patients were targeted. No attempt was made to improve the ability to predict individual digoxin requirements in neonates and infants. Therefore, we aimed at estimating the digoxin clearance values of Japanese neonates and infants, and so collected digoxin therapeutic drug monitoring (TDM) data and organized them.

We examined the population clearance of digoxin with the computer program NONMEM using the multiple-trough screen approach [11]. With this approach, it is possible to estimate the pharmacokinetic parameters of a population using sparse data collected during routine clinical care. We can also establish to what degree neonate and infant characteristics influence the clearance of the drug.

Materials and methods

Data sources

Routine clinical pharmacokinetic data (448 observations) were retrospectively collected from 172 patients, among them 8 premature patients (birth before the 37th gestational week) in Kyushu Kosei-Nenkin Hospital between 1994 and 1997, who were twice daily administered a powder preparation of digoxin (Digosin, Chugai Pharmaceutical Co., Ltd., Tokyo Japan), which was diluted with water. The patients were all hospitalized and under the supervision of medical and nursing staff so that resulting compliance and administration of treatments were standardized. The clinical characteristics of patients in this study are given in Table 1.

The data collected were the patient's age, gestational week, gender, total body weight, serum creatinine, concomitant medications, dosage regimen of digoxin, drug administration data, serum concentration of digoxin with the date and time of each measurement, and signs and symptoms of congestive heart failure. We reconfirmed, from medical charts, basic information on the patients and pathologies from blood samples. At least 8 days in neonates and 2 weeks in infants were allowed for the steady-state condition to be reached. We analyzed 90% of the serum digoxin concentration data that were collected in routine drug monitoring. Patients taking additional drugs (other than spironolactone) known to exhibit interactions with digoxin (e.g. verapamil, quinidine, amiodarone, phenytoin) were excluded from the population (10% of those screened).

All blood samples for assay were drawn by venipuncture before the morning dose (12 h after the previous dose). Sixty patients had one trough value, 44 patients had two trough values on separate occasions, 25 patients had three, 21 patients had four, 9 patients had five, 2 patients had six, 6 patients had seven, 3 patient had eight, and 2 patients had nine.

Digoxin concentration measurement reagent CEDIA digoxin plus (Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan) and those based on a cloned enzyme donor immunoassay were used, and the measurements were carried out using COBAS-FARA (Hoffmann-La Roche, Inc., Nutley, N.J.). The minimum detectable concentration for digoxin was 0.2 $ng \cdot ml^{-1}$ and the coefficients of variation of both intra- and interassay precision were less than 10%. The measurements made using this method were free from the effects of a digoxin-like immunoreactive substance (DLIS) [12]. The cross-reactivity to spironolactone, if 10 $\mu g \cdot ml^{-1}$ was added, was less than 0.02% (based on the manufacturer's Food and Drug Administration information).

Pharmacokinetic model

The main purpose of analyzing the pharmacokinetics of digoxin in a cohort of the patient population was to identify sources of pharmacokinetic variability among the patients screened. In particular, the major concern was variability in the relationship between dose and steady-state digoxin concentrations.

Since all serum concentrations of digoxin were at steady state, the pharmacokinetics were described using the following simple pharmacokinetic model:

$$Css_{ij} = D_{ij} / (CL_{ij} \cdot \tau_{ij}) \quad (1)$$

where Css_{ij} is the steady-state serum digoxin concentration ($ng \cdot ml^{-1}$) measured in the jth patient while he or she received the ith dosage; D_{ij} is the dosage of digoxin ($\mu g \cdot kg^{-1}$) for the Css in the jth patient; CL_{ij} is the ith total body clearance ($l \cdot h^{-1}$) for digoxin in the jth patient; and τ_{ij} is the dosing interval (h) for the ith dosage in the jth patient. A bioavailability (F) of unity is assumed for this model, if not, CL_{ij} must be regarded as $(CL \cdot F^{-1})_{ij}$.

In this case, where the sample for assay was taken just before the morning dose (12 h after the previous dose), the Css measured is at minimum concentration (C_{min}), causing the estimated relative clearance of digoxin to overestimate the mean clearance [13].

We have also examined the influence of a variety of factors on the population mean values for digoxin relative clearance. These factors included total body weight (kg), age (days), gender, serum creatinine ($mg \cdot dl^{-1}$), daily digoxin dose ($\mu g \cdot kg^{-1} \cdot day^{-1}$), the coadministration of spironolactone, and the presence or absence of congestive heart failure.

Statistical model

The interindividual variability in the clearance of digoxin was modeled with proportional errors according to the following equation:

$$CL_{ij} = \tilde{C}L_{ij}(1 + \eta_j) \quad (2)$$

where CL_{ij} is the ith true clearance for the jth individual; $\tilde{C}L_{ij}$ is the ith clearance predicted for the jth individual with the regression model and η_j is an independently distributed random variable with a mean of zero and variances ω^2_{CL}. The residual variability was also

Table 1 Summary of patient data. Values in parentheses indicate males. *SPI (+)* with coadministration of spironolactone, *CHF (+)* with congestive heart failure, *Premature* birth before the 37th gestational week

Characteristic	Modeling	Validation
Number of patients	172 (96)	66 (35)
Premature	8 (6)	0
Number of observations	448 (261)	81 (43)
SPI (+)	378 (216)	67 (32)
CHF (+)	265 (146)	62 (34)
Premature	9 (6)	0
Age (days, mean ± SD)	86.4 ± 79.0	92.1 ± 88.9
Range	8∼362	12∼362
Total body weight (kg, mean ± SD)	3.66 ± 1.31	3.99 ± 1.45
Range	1.49∼9.65	2.10∼8.21
Dose ($\mu g \cdot kg^{-1} \cdot day^{-1}$, mean ± SD)	9.40 ± 1.92	9.69 ± 1.81
Range	3.82∼15.72	4.76∼13.30
Steady-state concentrations ($ng \cdot ml^{-1}$, mean ± SD)	0.84 ± 0.39	0.85 ± 0.35
Range	0.24∼2.10	0.29∼1.83

modeled with proportional error according to the following equation:

$$Css_{ij} = \tilde{C}ss_{ij}(1 + \varepsilon_{ij}) \quad (3)$$

where Css_{ij} is the jth measured steady-state serum concentration in the jth patient. $\tilde{C}ss_{ij}$ is the corresponding predicted steady-state serum concentration and ε_{ij} is the residual intrapatient variability term, representing independent, identically distributed statistical error with a mean of zero and variance σ_E^2.

Data analysis

Data analysis was performed using the NONMEM program (Version IV, level 1.1) on a Hewlett Packard computer (HP Apollo 9000 model 712/60; Palo Alto, Calif.). Minimizing the objective function provided by each NONMEM fitting routine is equivalent to maximizing the likelihood of data. Hypothesis testing can be performed by monitoring changes in the objective function when one or more parameters in the regression model are first estimated iteratively and then restricted to a fixed value. The difference in objective function values obtained by comparing each regression model is asymptotically distributed as chi-square with a degree of freedom equal to the difference in the number of parameters between the two regression models.

The first stage in the model-building phase was initiated with a minimum number of parameters that were suspected to influence clearance. Alternate statistical models were tested during this phase to determine which model would afford the best fit of the data. Additional parameters were incorporated into the initial regression model in a stepwise fashion to develop the full regression model. Any fixed effect that reduced the objective function by more than 3.841 (χ^2, $P < 0.05$, 1 degree of freedom) was considered to be significant and added to the model.

After all statistically significant parameters were added to the full regression model, each parameter was eliminated from the model one at a time to identify those factors that were contributing unique information. If the objective function did not increase by more than 3.841(χ^2, $P < 0.05$, 1 degree of freedom), the parameter was excluded from the final model. The final regression model included all parameters that could not be eliminated from the full regression model during this restriction process.

Results

Individual data treatment

Figure 1 shows the serum concentration of digoxin as a function of the daily digoxin dose. Serum digoxin concentrations varied between 0.24 $ng \cdot ml^{-1}$ and 2.10 $ng \cdot ml^{-1}$ for oral doses from 3.82 $\mu g \cdot kg^{-1} \cdot day^{-1}$ to 15.72 $\mu g \cdot kg^{-1} \cdot day^{-1}$. The wide scattering of serum concentrations at each digoxin dose implies that it is difficult to predict serum concentrations on the basis of the daily digoxin dose ($\mu g \cdot kg^{-1} \cdot day^{-1}$) alone (Fig. 1). Our first intention was to calculate individual digoxin relative clearance from each digoxin dose and serum concentration pair using Eq. 1 (not using the Bayesian algorithm in NONMEM). Scatter plots of the relative clearance against patient characteristics such as total body weight and age are shown in Fig. 2. The scatter plot for the individual clearance against patient characteristics displayed a wide scatter of digoxin clearance.

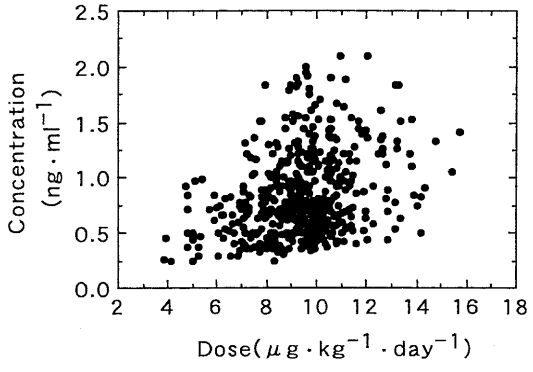

Fig. 1 Serum concentration of digoxin as a function of the daily digoxin dose

NONMEM estimates

In the preliminary analyses, the modeling of clearance with total body weight, age, serum creatinine, gender, congestive heart failure, and spironolactone improved the estimates for clearance (Table 2). The relationship between these factors and clearance could be described using the full version of the following models:

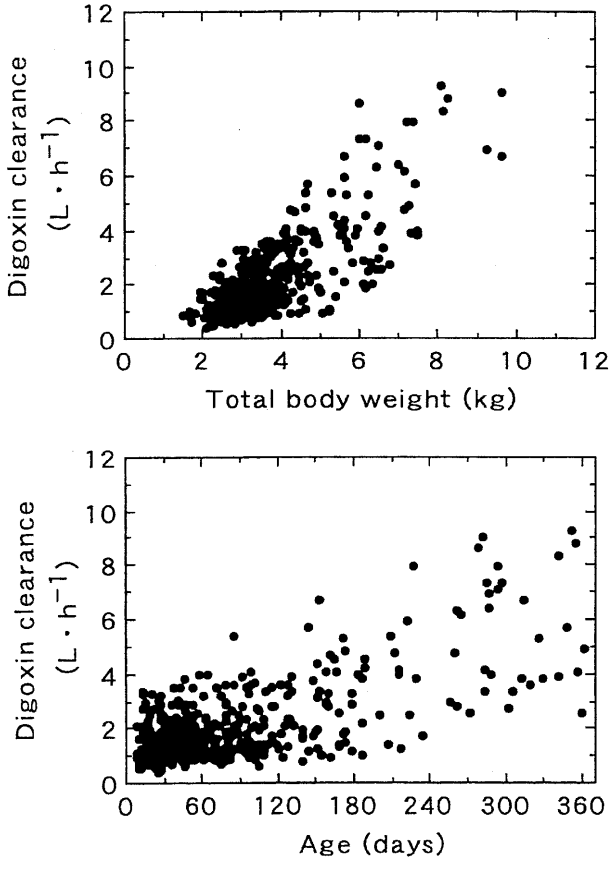

Fig. 2 Scatter plots of the relative clearance against patient characteristics

Table 2 Population mean parameter values and their variances obtained using NONMEM analysis. *OBJ* the minimum value of objective function (–2 log likelihood) in each NONMEM run, *LLD* –2 log likelihood difference, *CL* clearance, *TBW* total body weight, *Scr* serum creatinine, *GEN* gender, *SPI* Spironolactone, *CHF* congestive heart failure, σ_E identically distributed statistical error with a mean of zero and variance

Hypothesis	Equation	OBJ	LLD	*P* value	Conclusion
Basic model	$CL = \theta_1$ $\theta_1 = 1.53$ $\omega_{CL} = 40.1\%$ $\sigma_E = 38.7\%$	–317.721			
Did total body weight influence CL?	$CL = \theta_1 \cdot TBW^{\theta_2}$ $\theta_1 = 0.336$ $\theta_2 = 1.25$ $\omega_{CL} = 35.5\%$ $\sigma_E = 28.2\%$	–563.349	245.628	< 0.001	Yes
Did age influence CL?	$CL = \theta_1 \cdot AGE^{\theta_2}$ $\theta_1 = 0.378$ $\theta_2 = 0.354$ $\omega_{CL} = 39.2\%$ $\sigma_E = 31.3\%$	–502.044	184.323	< 0.001	Yes
Did serum creatinine influence CL?	$CL = \theta_1 \cdot Scr^{\theta_2}$ $\theta_1 = 1.04$, $\theta_2 = -0.287$ $\omega_{CL} = 40.5\%$ $\sigma_E = 36.6\%$	–357.780	40.059	< 0.001	Yes
Did daily dose influence CL?	$CL = \theta_1 \cdot DOSE^{\theta_2}$ $\theta_1 = 1.53$ $\theta_2 = 1.76\times10^{-5}$ $\omega_{CL} = 40.1\%$ $\sigma_E = 38.7\%$	–317.721	0	–	No
Did gender influence CL?	$CL = \theta_1 \cdot \theta_2^{GEN}$ $\theta_1 = 1.46$ $\theta_2 = 1.12$ $\omega_{CL} = 42.9\%$ $\sigma_E = 32.9\%$	–322.811	5.09	< 0.05	Yes
Did spironolactone influence CL?	$CL = \theta_1 \cdot \theta_2^{SPI}$ $\theta_1 = 1.81$ $\theta_2 = 0.821$ $\omega_{CL} = 39.1\%$ $\sigma_E = 38.5\%$	–330.142	12.421	< 0.001	Yes
Did congestive heart failure influence CL?	$CL = \theta_1 \cdot \theta_2^{CHF}$ $\theta_1 = 1.86$ $\theta_2 = 0.743$ $\omega_{CL} = 39.2\%$ $\sigma_E = 37.9\%$	–353.001	35.280	< 0.001	Yes

$$CL_{ij}\left(l \cdot h^{-1}\right) = \theta_1 \cdot TBW_{ij}^{\theta_2} \cdot AGE_{ij}^{\theta_3} \cdot Scr_{ij}^{\theta_4} \cdot \theta_5^{GEN_j} \cdot \theta_6^{CHF_j} \cdot \theta_7^{SPI_j} \quad (4)$$

where TBW_{ij} is the ith total body weight of the jth individual in kilograms; AGE_{ij} is the ith age of the jth individual in days; Scr_{ij} is the ith serum creatinine of the jth individual in milligrams deciliter^{-1}; GEN_j is an indicator variable that has a value of unity if the patient is female, zero otherwise; CHF_j is an indicator variable that has a value of unity if the patient has congestive heart failure, zero otherwise; and SPI_j is an indicator variable that has a value of unity if the patient is receiving spironolactone, zero otherwise. The remaining θ's represent the fractional increase or decrease in clearance associated with the patient's variables.

The results of the hypothesis testing are summarized in Table 3. Gender and exponential power relationship of total body weight did not significantly improve the estimate of clearance. When each factor was eliminated successively from the full regression model, the final regression model is presented below:

$$CL(l \cdot h^{-1} \cdot kg^{-1}) = 0.298 \cdot AGE^{0.099} \cdot Scr^{-0.153} \cdot 0.882^{CHF} \cdot 0.897^{SPI}$$

The parameter estimates of the final model are shown in Table 4. Concentration predictions using both basic and final models are shown in Fig. 3, where deviation among pairs of predicted and observed digoxin concentrations was small in the case of the final model.

Validation

If the mathematical approach to determining digoxin doses was accurate and practical, the use of calculated

Table 3 Hypothesis tested using restricted models of the full model. *LLD* –2 log likelihood difference; *CL* clearance; *TBW* total body weight; *Scr* serum creatinine; *GEN* gender; *SPI* Spironolactone

Hypothesis	Reduced model	LLD	*P* value	Conclusion
Did total body weight influence CL?	$TBW^{\theta} = 0$	86.954	< 0.001	Yes
Did total body weight influence CL in exponential power relationship?	$TBW^{\theta} = 1$	2.131	> 0.5	No
Did age influence CL?	$AGE^{\theta} = 0$	15.981	< 0.001	Yes
Did serum creatinine influence CL?	$Scr^{\theta} = 0$	9.988	< 0.005	Yes
Did gender influence CL?	$\theta^{GEN} = 0$	0.169	> 0.5	No
Did spironolactone influence CL?	$\theta^{SPI} = 0$	53.409	< 0.001	Yes
Did congestive heart failure influence CL?	$\theta^{CHF} = 0$	8.819	< 0.005	Yes

Table 4 Final estimates of clearance. *95% CI* 95% confidence interval

Parameter	Estimate	95% CI
θ_1	0.298	0.192, 0.405
θ_2	0.099	0.031, 0.167
θ_3	–0.153	–0.276, –0.03
θ_4	0.882	0.772, 0.992
θ_5	0.897	0.782, 1.012
ω_{CL}	32.1%	26.9, 36.6%
σ_E	28.9%	25.6, 31.9%

$CL\left(L \cdot h^{-1} \cdot kg^{-1}\right) = \theta_1 \cdot AGE^{\theta_2} \cdot Scr^{\theta_3} \cdot \theta_4^{CHF} \cdot \theta_5^{SPI}$
CHF = 0 for without congestive heart failure
CHF = 1 for with congestive heart failure
SPI = 0 for without coadministration of spironolactone
SPI = 1 for with coadministration of spironolactone

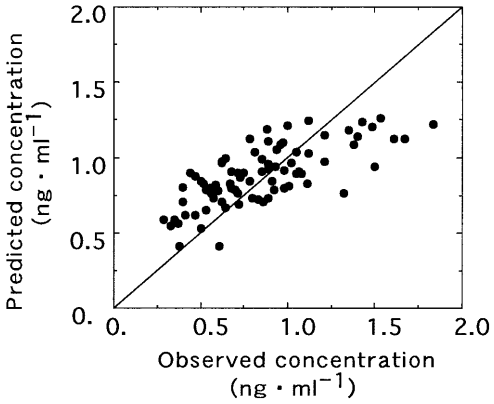

Fig. 4 Concentrations predicted using the final model plotted versus observed concentrations

doses could reduce the potential for toxicity and decrease the need for repetitious digoxin assays. In the validation group of 66 patients, predictions of the digoxin serum concentrations were made with the final regression model using the dosing history and demographic characteristics. The demographic and biological data concerning patients included in the validation group were not statistically different from those included in the population group (Mann-Whitney U-test). The predictive performance of the final regression model was evaluated using the mean prediction error (ME) and mean absolute prediction error (MAE) according to methods outlined by Sheiner and Beal [14]. The ME for predicted concentration was –0.04 ng·ml^{-1} (95% confidence interval –0.09, 0.02). The MAE for predicted concentration was 0.20 ng·ml^{-1} (95% confidence interval 0.17, 0.24). The concentrations predicted using the final model are plotted versus the observed concentrations in Fig. 4.

Discussion

Interindividual variability in drug disposition and response is commonly observed in therapeutics, and thus evaluation and management of such variability form the basis for individualized pharmacotherapy. The large degree of variability observed in the pharmacokinetics of digoxin makes it difficult to predict a priori the optimal dosing regimen for an individual patient. It would be useful to understand the effect of a variety of developmental and demographic factors on pharmacokinetic parameters and the observed patient variables on the disposition of digoxin.

The final regression model for clearance suggests that the clearance increases nonlinearly with increasing age. The relative clearance values increased by up to 28% with varying patient age from 30 days to 360 days.

The clearance of digoxin decreased 10.3% with administration of spironolactone in infants ($P < 0.001$), an effect that is comparable with that of the decreased digoxin renal clearance previously demonstrated, 10%, 24%, 18%, 13%, and 12.2% respectively [9, 15, 16, 17, 18]. This effect of spironolactone may reflect a decrease in digoxin renal clearance caused by inhibition of the digoxin-transporting role of P-glycoprotein [19], because spironolactone does not affect the determination of digoxin using the CEDIA digoxin plus kit.

Several studies reported that congestive heart failure was an important factor in estimating clearance of digoxin [20, 21]. Sheiner et al. [20] reported that the digoxin clearance was significantly lower in patients with congestive heart failure than in those without congestive heart failure [clearance $(l \cdot h^{-1}) = 0.06 \cdot$ creatinine clearance$(ml \cdot min^{-1}) + 0.05 \cdot$ body weight (kg) for those

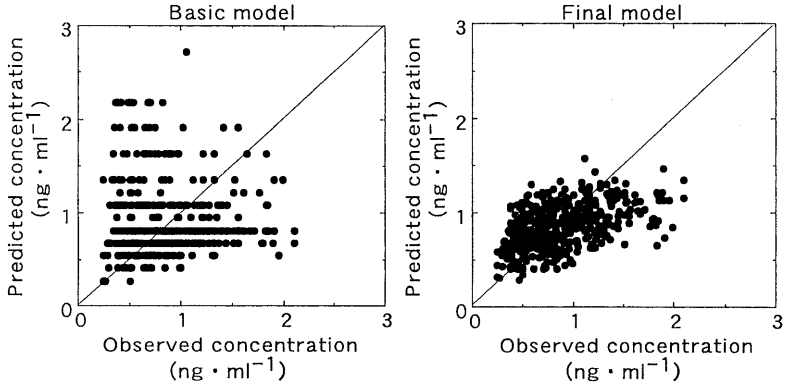

Fig. 3 Concentration predictions using both basic and final models

without congestive heart failure; clearance($l \cdot h^{-1}$) = 0.053 · creatinine clearance($ml \cdot min^{-1}$) + 0.02 · body weight (kg) for those with congestive heart failure]. Naafs et al. [21] found that the clearance of digoxin was significantly lower in patients with congestive heart failure than in patients with atrial fibrillation (2.88 $l \cdot h^{-1}$ versus 4.26 $l \cdot h^{-1}$), and Yukawa et al. [9] reported that the clearance of digoxin decreased about 19% with congestive heart failure using NONMEM analysis in adults. In the present study, the digoxin clearance was also decreased 11.8% with congestive heart failure in infants ($P < 0.005$).

The interindividual variability of clearance was determined to be 32.1%, as a coefficient of variation, which increased to 40.1% if the patient's characteristics were not incorporated into the regression model. The residual variability was determined to be 28.9%, which increased to 38.7% if the patient's characteristics were not incorporated. This large residual variability may result from measurement errors, pharmacokinetic model misspecification, and changes in an individual's pharmacokinetics with time. Furthermore, the digoxin measurements made via CEDIA digoxin plus are free from the influence of DLIS, but it may be that the influence of DLIS [22, 23] cannot be absolutely guaranteed.

In the validation set of 66 patients, the performance (bias, precision) of the final population model was good. Clinical application of the findings in the present study to patient care may permit selection of an appropriate initial maintenance dose, thus enabling the clinician to achieve a desired therapeutic effect. Thus, an a priori method of predicting the minimum Css of digoxin based on clearance values obtained using NONMEM analysis has been developed to assist in the determination of rational dosage regimens and to avoid multiple blood level determinations as follows:

$$C_{ss}^{min} = \mathrm{Dose}\left(\mu g \cdot kg^{-1} \cdot day^{-1}\right) / \left[0.298 \cdot \mathrm{AGE}^{0.099} \cdot \mathrm{Scr}^{-0.153} \cdot 0.882^{\mathrm{CHF}} \cdot 0.897^{\mathrm{SPI}} \cdot 24\left(1 \cdot kg^{-1} \cdot day^{-1}\right)\right] \quad (5)$$

However, the digoxin dosage regimen should be set based on appraisal of the individual patient's clinical need for the drug.

References

1. Wagner JG (1974) Appraisal of digoxin bioavailability and pharmacokinetics in relation to cardiac therapy. Am Heart J 88:133–138
2. Gorodischer R (1980) Pediatric pharmacology. Therapeutic principles in practice. In: Yaffe SJ (ed) Cardiac drugs. Grune and Stratton, New York, pp 281–304
3. Soyka LF (1972) Clinical pharmacology of digoxin. Pediatr Clin N Am19:241–256
4. Wettel G (1977) Distribution and elimination of digoxin in infants. Eur J Clin Pharmacol 11:329–335
5. Wettrel G, Anderson KE (1975) Absorption of digoxin in infants. Eur J Clin Pharmacol 9:49–55
6. Halkin H, Radomsky M, Millman P, Almog S, Bleiden L, Boichis H (1978) Steady state serum concentrations and renal clearance of digoxin in neonates, infants and children. Eur J Clin Pharmacol 13:113–117
7. Suematsu F, Minemoto M, Yukawa E, Higuchi S (1999) Population analysis for the optimization of digoxin treatment in Japanese paediatric patients. J Clin Pharm Ther 24:203–208
8. Yukawa E, Mine H, Higuchi S, Aoyama T (1992) Digoxin population pharmacokinetics from routine clinical data: role of patient characteristics for estimating dosing regimens. J Pharm Pharmacol 44:761–765
9. Yukawa E, Honda T, Ohdo S, Higuchi S, Aoyama T (1997) Population-based investigation of relative clearance of digoxin in Japanese patients by multiple trough screen analysis: an update. J Clin Pharmacol 37:92–100
10. Beal SL, Sheiner LB (1992) (eds) NONMEM user's guides. NONMEM Project Group, University of California at San Francisco, San Francisco
11. Sheiner LB, Benet LZ (1985) Premarketing observational studies of population pharmacokinetics of new drugs. Clin Pharmacol Ther 38:481–487
12. Ishii T, Ohisa N, Karino A, Ishii K, Minakata Y, Sasaki A (1996) Fundamental study of CEDIA digoxin plus assay and CEDIA theophylline assay on the Hitachi-7070 analyzer. J Clin Lab Instr Reag 19:171–177
13. Dobbs RJ, O'Neill CJA, Deshmukh AA, Nicholson PW, Dobbs SM (1991) Serum concentration monitoring of cardiac glycosides: how helpful is it for adjusting dosage regimens? Clin Pharmacokinet 20:175–193
14. Sheiner LB, Beal SL (1981) Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 9:503–512
15. Waldorff S, Andersen JD, Heeboll-Nielsen N, Nielsen OG, Moltke E, Sorensen U, Steiness E (1978) Spironolactone-induced changes in digoxin kinetics. Clin Pharmacol Ther 24:162–167
16. Fenster PE, Hager WD, Goodman MM (1984) Digoxin-quinidine-spironolactone interaction. Clin Pharmacol Ther 36:70–73
17. Hori R, Miyazaki K, Mizugaki M, Ogata H, Goto M, Ichimura F, Yasuhara M, Tanigawara Y, Hashimoto Y, Koue T, Mimaki T, Tanaka K, Okumura K, Gomita H, Higuchi S (1994) Estimation of population pharmacokinetc parameters in the Japanese. I. Digoxin (in Japanese). Jpn J Ther Drug Monit 11:7–17
18. Hedman A, Angelin B, Arvidsson A, Dahlqvist R (1992) Digoxin-interactions in man: spironolactone reduces renal but not biliary digoxin clearance. Eur J Clin Pharmacol 42:481–485
19. Tanigawara Y, Okumura N, Hirai M, Yasuhara M, Ueda K, Kioka N, Komano T, Hori R (1992) Transport of digoxin by human P-glycoprotein expressed in a porcine kidney epithelial cell line (LLC-PK_1). J Pharmacol Exp Ther 263:840–845
20. Sheiner LB, Rosenberg B, Marathe W (1977) Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm 5:445–479
21. Naafs MAB, van der Hoek C, van Duin S, Koorevaar G, Schopman W, Silberbusch J (1985) Decreased renal clearance of digoxin in chronic congestive heart failure. Eur J Clin Pharmacol 29:249–252
22. Valdes Jr R, Graves SW, Brown BA, Landt M (1983) Endogenous substance in newborn infants causing false positive digoxin measurements. J Pediatr 102:947–950
23. Morris RP, David WS, Bery EJ, Michael FW (1983) Seven different immunoassay kits substance in serum from premature and full-term infants. Clin Chem 29:1972–1974