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Digoxin Population Pharmacokinetics from Routine Clinical Data: Role of Patient Characteristics for Estimating Dosing Regimens

EIJI YUKAWA, HISANORI MINE, SHUN HIGUCHI AND TOSHINOBU AOYAMA

Department of Hospital Pharmacy, Kyushu University Hospital, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812, Japan

Abstract—Routine clinical pharmacokinetic data collected from patients receiving digoxin have been analysed to evaluate the role of patient characteristics for estimating dosing regimens. The data were analysed using NONMEM, a computer program designed for population pharmacokinetic analysis that allows pooling of data. The pharmacokinetic model of digoxin was described using a one-compartment steady-state model. The effect of a variety of developmental and demographic factors on clearance was investigated. NONMEM estimates indicate that digoxin clearance was influenced by the demographic variables of age, total body weight, serum creatinine and sex. The interindividual variability in digoxin clearance was modelled with additive error with an estimated standard deviation of 46·15 L day^{-1} and the intraindividual variability, or residual error was 0·209 ng mL^{-1}. The dosing method based on clearance values obtained by NONMEM analysis allowed the prediction of the steady-state concentration as a function of maintenance dose with acceptable error for therapeutic drug monitoring.

Digoxin is widely prescribed for the treatment of congestive heart failure and atrial fibrillation. However, it is a difficult drug to dose because of a lack of a good relationship between the dose and the desired effect, its narrow therapeutic range, and the variation in the pharmacokinetic characteristics of the drug. Knowledge of the pharmacokinetics of digoxin is essential in optimizing its safety and efficacy. The variability in digoxin clearance creates difficulty for the clinician in choosing the drug dosage. For a given daily dosage, steady-state serum digoxin concentrations vary greatly from patient to patient (Fig. 1). Therefore, the clinician needs methods of predicting digoxin pharmacokinetic values and an appropriate dosage regimen for individual patients. Many attempts (Jelliffe 1968; Jelliffe & Brooker 1974; Jusko et al 1974; Koup et al 1975; Paulson & Welling 1976; Sheiner et al 1977; Keller et al 1980) have been made to improve the ability to predict individual digoxin requirements. The predictive accuracy of the various methods developed for digoxin dosing was evaluated by Hyneck et al (1981) and Jones et al (1982), both of whom reported poor performance of all the methods. The lack of precision was attributed to inaccuracies in digoxin assays, interpatient variability in digoxin pharmacokinetics, undetected patient noncompliance, and the use of small numbers of subjects in developmental studies. Because of the large interpatient variability it may be more useful to determine typical pharmacokinetic behaviour of the drug in this population rather than in an individual patient. This justifies the study of the population pharmacokinetics of digoxin, assuming patient characteristics such as weight, age, sex, renal function and state of health.

In this study, we have examined the population pharmacokinetics of digoxin with the computer program NONMEM, developed by Beal & Sheiner (1980, 1985, 1986). With this approach it is possible to estimate the pharmacokinetic parameters of a population by using sparse data collected during routine clinical care. We can also establish to what degree patient characteristics influence pharmacokinetics of the drug. These variables can then be used to develop equations for predicting drug clearance and steady-state serum drug concentrations in patients.

Correspondence: E. Yukawa, Department of Hospital Pharmacy, Kyushu University Hospital, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812, Japan.

Materials and Methods

Data sources

We selected 184 patients (93 males and 91 females) from Kyushu University Hospital who had stable steady-state serum digoxin measurements. Patients who had their concurrent therapy altered were excluded from the study. All patients had stable renal and hepatic function. All blood samples were drawn before the morning dose. The serum concentration of digoxin was determined by fluorescence polarization immunoassay (FPIA). The coefficient of variation of this assay was less than 10%. The clinical characteristics of the patients studied are given in Table 1.

Population pharmacokinetics of digoxin

Pharmacokinetic model. The data were fitted to the following one-compartment steady-state pharmacokinetic model:

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

where D_{ij} is the dosage of digoxin for the ith Css in the jth patient (μg); Css_{ij} is the steady-state serum concentration (ng mL^{-1}) measured in the jth patient while he received the ith dosage; CL_{ij} is the ith total body clearance (L day^{-1}) for digoxin in the jth patient; and τ_{ij} is the dosing interval (day) for the ith dosage in the jth patient. Bioavailability is not assumed; if it is assumed, CL_{ij} must be regarded as $(CL/F)_{ij}$, where F is the bioavailability of digoxin.

We have also examined the influence of a variety of factors on the population mean values for the total body clearance for the drug. These factors include age, sex, total body

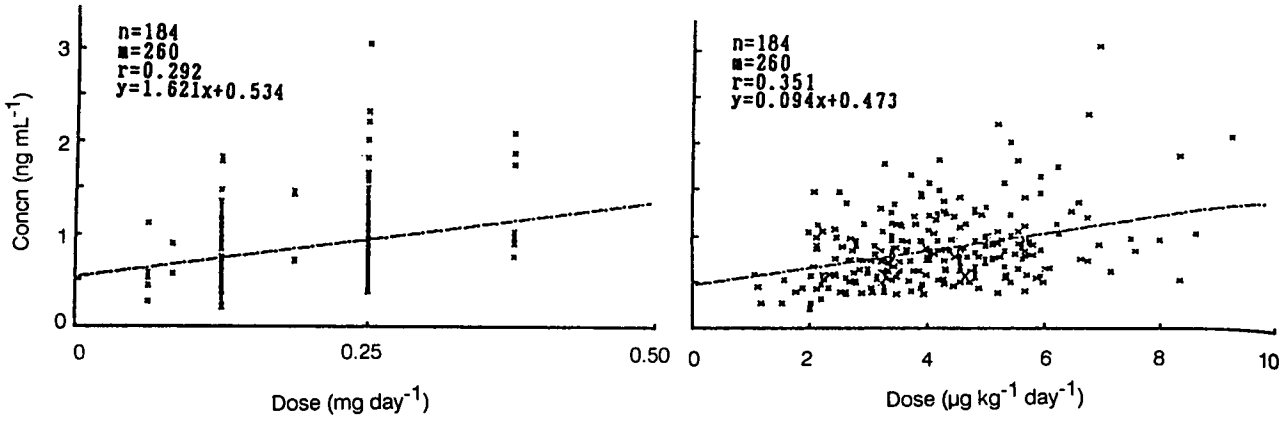

FIG. 1. Relationship between digoxin dose and serum digoxin concentration.

Table 1. Summary of data from patients treated with digoxin.

Characteristic	Population study	Prospective study
Number of patients	184	45
Number of observations	260	52
Proportion of data from males	0·50	0·58
Means ± s.d.		
Age (years)	58·2 ± 12·8	59·2 ± 15·8
Weight (kg)	49·7 ± 10·6	52·1 ± 10·9
Dose ($\mu g\ kg^{-1}\ day^{-1}$)	4·21 ± 1·45	4·11 ± 1·29
Steady-state concentration ($ng\ mL^{-1}$)	0·87 ± 0·39	0·88 ± 0·56

weight, ideal body weight, body surface areas, serum creatinine and creatinine clearance.

Statistical model. The interindividual variability in total body clearance was modelled with additive error according to the following equation:

$$CL_{ij} = \widehat{CL}_{ij} + \eta_j \quad (2)$$

where CL_{ij} is the ith true clearance for the jth individual, $\widehat{CL}_{ij}$ is the ith clearance predicted for the jth individual with the regression model, and η_j are independently distributed random variables with mean zero and variances ω_{CL}^2.

The intraindividual variability, or residual error was also modelled with additive error according to the following equation:

$$Css_{ij} = \widehat{Css}_{ij} + \varepsilon_{ij} \quad (3)$$

where Css_{ij} is the ith measured steady-state serum concentration in the jth patient, $\widehat{Css}_{ij}$ is the corresponding predicted steady-state serum concentration, and ε_{ij} is the difference between these two concentrations. ε_{ij} is the residual intrapatient variability term, representing independent identically distributed statistical error with mean zero and variance σ_E^2.

Data analysis

Data analysis was performed with the NONMEM program (version 2, level 1.4) on the Kyushu University computer (FACOM M-780).

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 model are first estimated iteratively and then restricted to a fixed value. The difference in objective function values obtained by comparing models is asymptotically distributed as chi-square with degree of freedom equal to the difference in the number of parameters between two models.

The first stage in the model-building phase was initiated with a minimum number of parameters that were suspected to influence digoxin clearance. Various statistical models were tested during this phase to determine which model best fitted 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 6·6 (χ^2, $P < 0{\cdot}01$; 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 7·9 (χ^2, $P < 0{\cdot}005$; 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

Scatter plots of total body clearance against patient characteristics such as age, total body weight, ideal body weight,

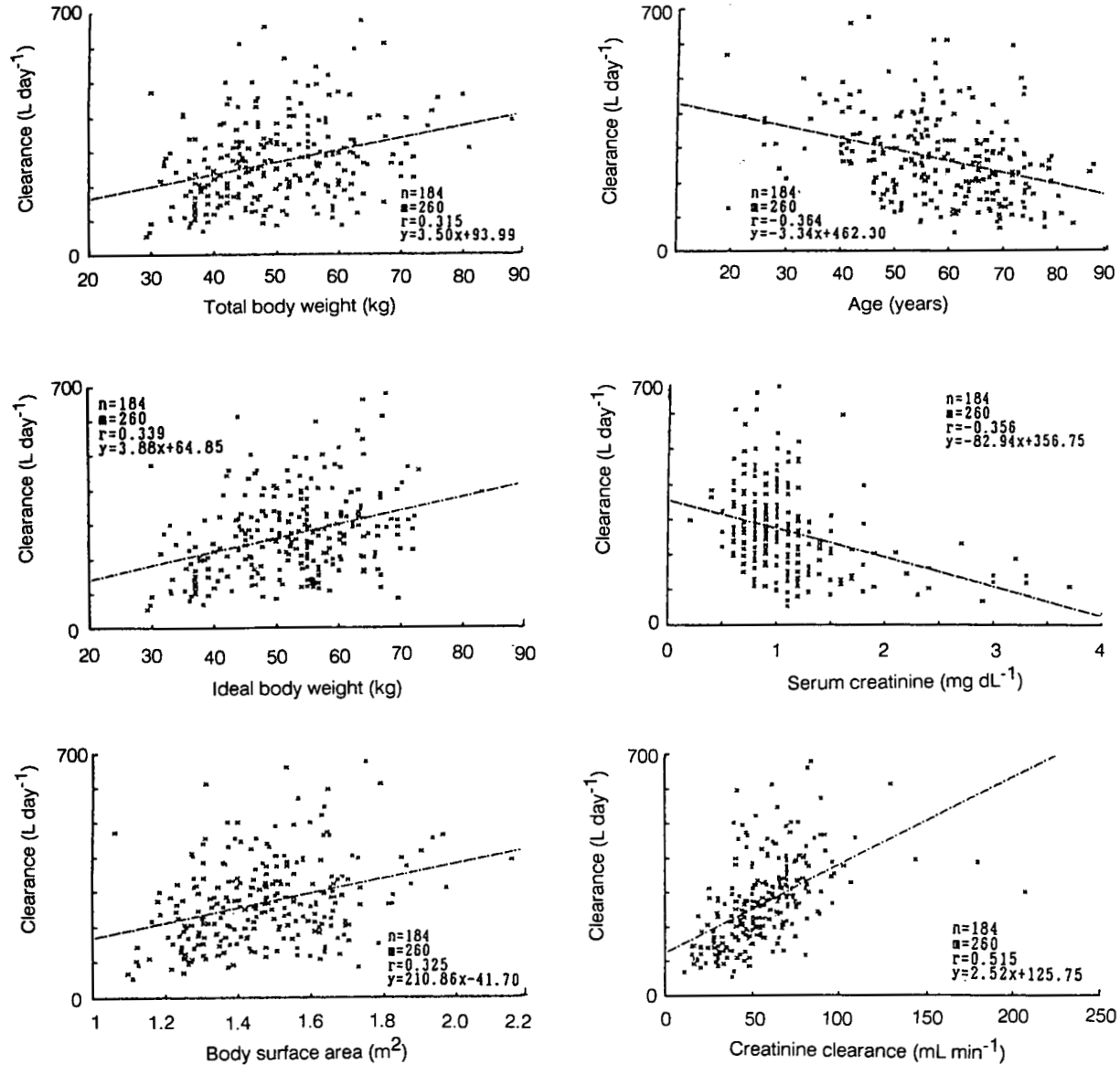

FIG. 2. Relationships between digoxin clearance and patient characteristics.

body surface areas, serum creatinine and creatinine clearance are shown in Fig. 2.

The scatter plot for the individual clearance against patient characteristics showed the wide scatter of digoxin clearance. All the patient characteristics showed poor correlation with digoxin clearance.

NONMEM estimates

In the preliminary analyses, the modelling of clearance with age, sex, body-size and renal function improved the estimate of digoxin clearance. The relation between these factors and clearance could be described by the full versions of the following models:

$$CL_{ij} = \theta_1 \cdot (1 + \theta_2 \cdot AGE_{ij}) \cdot TBW_{ij}^{\theta_3} \cdot Scr_{ij}^{\theta_4} \cdot SEX_j \quad (4)$$

where TBW_{ij} is the ith total body weight of the jth individual in kg; AGE_{ij} is the ith age of the jth individual in years; Scr_{ij} is the ith serum creatinine of jth individual in mg dL^{-1}; and SEX_j is an indicator variable which has a value of unity if the jth patient is male, θ_5 otherwise. The remaining θs represent the fractional increase or decrease in digoxin clearance associated with the presence of patient variables.

The results of the hypothesis testing are summarized in Table 2. When each parameter was eliminated successively from the full regression model, as described above, only the exponential power relationship of total body weight was not found to influence the objective function value significantly.

The parameter estimates of the final regression model are shown in Table 3. The final regression model is presented below:

$$CL_{ij} = 8{\cdot}03 \cdot (1 - 0{\cdot}0058 \cdot AGE_{ij}) \cdot TBW_{ij} \cdot Scr_{ij}^{-0{\cdot}6} \cdot SEX_j \quad (5)$$

Table 2. Hypothesis tested using restricted models of the full model.

Hypothesis	Parameters	Log likelihood Difference	*P* value	Conclusion
Did age influence CL?	$\theta_2=0$	27·6	<0·001	Yes
Did weight influence CL?	$\theta_3=0$	36·5	<0·001	Yes
Did weight influence CL in exponential power relationship?	$\theta_3=1$	3·1	>0·05	No
Did serum creatinine influence CL?	$\theta_4=0$	93·9	<0·001	Yes
Did serum creatinine influence CL in exponential power relationship?	$\theta_4=-1$	32·2	<0·001	Yes
Did gender influence CL?	$\theta_5=1$	10·9	<0·001	Yes

Table 3. Final parameter estimates.

Parameter	NONMEM estimates [mean (95%CI)]
θ_1	8·03 (6·84, 9·22)
θ_2	−0·0059 (−0·0072, −0·0046)
θ_3	1·0
θ_4	−0·6 (−0·714, −0·486)
θ_5	0·881 (0·791, 0·971)
ω_{CL}	46·15 L day^{-1} (23·67, 60·83)
σ_E	0·209 ng mL^{-1} (0·140, 0·261)

95%CI = 95% confidence intervals of the mean.

The estimate of standard deviation for interindividual variability in clearance was 46·15 L day^{-1}, with a 95% confidence interval of 23·67–60·83 L day^{-1}. The standard deviation for intraindividual variability, or residual error was 0·209 ng mL^{-1}, with a 95% confidence interval of 0·140–0·261 ng mL^{-1}.

Evaluation of predicted digoxin concentrations

The final model that was obtained needs to be validated in a separate patient population, and additional studies comparing it with other predictive methods will further elucidate its clinical utility. To assess the utility of these pharmacokinetic values for predicting steady-state digoxin concentration in 45 patients (Table 1), we compared the proposed method with four previously published methods (see Appendix). The precision and bias of each method were evaluated using the mean prediction error (m.e.) and mean absolute prediction error (m.a.e.) according to methods outlined by Sheiner & Beal (1981).

The m.e., m.a.e. and their respective 95% confidence limits for predicted concentration are shown in Table 4. The proposed method was the least biased, with an m.e. of −0·06 ng mL^{-1} of digoxin concentration. The proposed method was superior in precision to the other methods.

Discussion

The large degree of variability in digoxin pharmacokinetics observed makes it difficult to predict the optimal dosing regimen for individual subjects. It would be beneficial to understand the effect of a variety of developmental and demographic factors on pharmacokinetic parameters and the observed patient variables on digoxin disposition.

The final regression model for clearance suggests that the rate of digoxin clearance increases proportionately with increasing weight. Moreover, the further improvement in fit obtained upon the inclusion of serum creatinine in the model for digoxin clearance supports the view that the principal elimination of digoxin takes place via renal excretion. The improvement in fit obtained upon the inclusion of age in the model also indicates that an elderly patient is expected to have a lower rate of clearance than a young patient of equal weight and serum creatinine. The clearance in females is about 12% less than in males. There is a great deal of similarity to the difference between male and female in the prediction formulae of creatinine clearance proposed by Jelliffe (1973) and Cockcroft & Gault (1976), 10 and 15%, respectively.

Nicholson et al (1980) gave the ratio of the serum digoxin concentration at an isolated sampling time to the mean steady-state concentration: in this case, where each sample was taken just before the daily dose, the estimated mean

Table 4. Predicted performance evaluation.

Method	Number of predictions	Bias (m.e., ng mL^{-1})	Precision (m.a.e., ng mL^{-1})
Paulson A (Paulson & Welling 1976)	52	0·09 (0·01,0·16)	0·21 (0·15,0·27)
Paulson B (Paulson & Welling 1976)	52	0·18 (0·09,0·27)	0·26 (0·19,0·33)
Keller (Keller et al 1980)	52	0·67 (0·51,0·83)	0·69 (0·54,0·84)
Sheiner (Sheiner et al 1977)	52	0·16 (0·07,0·24)	0·23 (0·16,0·30)
Proposed method	52	−0·06 (−0·13,0·01)	0·18 (0·13,0·23)

m.e. = mean prediction error; prediction error = predicted value − actual value.
m.a.e. = mean absolute prediction error. Parentheses are the 95% confidence intervals of the mean.

steady-state concentration would be 1·35 times the measured concentration (Dobbs et al 1986). Thus, the clearance estimated would be 1·35 times the true clearance of digoxin.

If the mathematical approach to determining digoxin doses were accurate and practical, the use of calculated doses could reduce the potential for toxicity and decrease the need for repetitious digoxin assays. Unfortunately, some of these methods are impractical and too complex for routine use. Hence, we propose the simple digoxin dosing method. The clinical utility of this predictive set can only be authenticated by a prospective study in individual patients. We tested the equations predicting the minimum digoxin concentration in patients who could be expected to attain a steady-state. The patients were all hospitalized and under the supervision of medical and nursing staff so that resulting compliance was probably complete. Our proposed method was superior in precision to the other methods, followed by Paulson's method A (Paulson & Welling 1976) based on Michaelis–Menten type distribution volume changes.

In the clinical setting, a method that would provide correct predictions about whether a drug concentration is subtherapeutic ($<0{\cdot}5$ ng mL^{-1}), therapeutic, or toxic ($>2{\cdot}0$ ng mL^{-1}) from a given dosage regimen would be valuable. In general, if the clinically acceptable variation of predicted serum values from actual serum concentrations ranges from ± 10 to $\pm 20\%$, the resultant acceptable range of predicted serum digoxin concentration would be from $\pm 0{\cdot}05$ to $\pm 0{\cdot}2$ ng mL^{-1} and from $\pm 0{\cdot}1$ to $\pm 0{\cdot}4$ ng mL^{-1} for the therapeutic range of 0·5–2·0 ng mL^{-1}, respectively. With this range in mind, in this population, the precision of the proposed method (m.a.e. $= 0{\cdot}18$ ng mL^{-1}) may be acceptable.

Appendix

Prediction formula of minimum steady-state digoxin concentration.

Paulson A
(Paulson & Welling 1976)

$$C_{ss}^{min} = F \cdot D\,[e^{-k_e \cdot \tau}]/Vd\,[1 - e^{-k_e \cdot \tau}]$$

$F = 0{\cdot}7$

$k_e(day^{-1}) = 0{\cdot}158 + 0{\cdot}00276 \cdot CL_{cr}$ $\quad CL_{cr}(mL\ min^{-1}/1{\cdot}73\ m^2)$

$$Vd(L) = \left[\frac{298[CL_{cr}]}{29{\cdot}1 + CL_{cr}} + 226\right]\frac{BSA(m^2)}{1{\cdot}73}$$

Paulson B
(Paulson & Welling 1976)

$$C_{ss}^{min} = F \cdot D\,[e^{-k_e \cdot \tau}]/Vd\,[1 - e^{-k_e \cdot \tau}]$$

$F = 0{\cdot}7$

$k_e(day^{-1}) = 0{\cdot}158 + 0{\cdot}00276 \cdot CL_{cr}$ $\quad CL_{cr}(mL\ min^{-1}/1{\cdot}73\ m^{-2})$

$Vd(L) = [4{\cdot}5 + 0{\cdot}028 \cdot CL_{cr}]IBW(kg)$

Keller
(Keller et al 1980)

$$C_{ss}^{min} = F \cdot D \cdot CF\,[e^{-k_e \cdot \tau}]/Vd\,[1 - e^{-k_e \cdot \tau}]$$

$F = 0{\cdot}6$

$k_e(day^{-1}) = 0{\cdot}106 + 0{\cdot}00326 \cdot CL_{cr}$ $\quad CL_{cr}(mL\ min^{-1})$

$Vd(L) = 145 + 118 \cdot k_e$

CF = BW/65 in case of obvious obesity, BW is [height(cm) − 100]

Sheiner
(Sheiner et al 1977)

$$C_{ss}^{min} = F \cdot D\,[e^{-k_e \cdot \tau}]/Vd\,[1 - e^{-k_e \cdot \tau}]$$

$F = 0{\cdot}6$

$Vd(L) = 3{\cdot}12 \cdot CL_{cr} + 3{\cdot}84 \cdot TBW$ $\quad CL_{cr}(mL\ min^{-1})$

$CL(L\ h^{-1}) = 0{\cdot}06 \cdot CLcr + 0{\cdot}02 \cdot TBW$

$k_e = CL/Vd$

Proposed method

$C_{ss}^{min} = [D/\tau]/[8{\cdot}03 \cdot TBW[1 - 0{\cdot}0059 \cdot AGE]Scr^{-0{\cdot}6}$ for male

$C_{ss}^{min} = [D/\tau]/[7{\cdot}07 \cdot TBW[1 - 0{\cdot}0059 \cdot AGE]Scr^{-0{\cdot}6}$ for female

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