Population Pharmacokinetics of Digoxin in Thai Pediatric Patients

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Objective: *To determine the digoxin population pharmacokinetic parameters and influence of various factors on pharmacokinetic parameters in Thai pediatric patients with heart disease*
Material and Method: *The present study was an analytical cross-sectional study design and population pharmacokinetic modeling study. The data of 130 patients and 264 samples with an age range of 0.1-15.7 years old were collected during routine care. Blood samples were drawn at various times after administration. All patients received digoxin administration with a dose ranged of 1.7-13.6 μg/kg/day at Queen Sirikit Heart Center, Khon Kaen University, Thailand. Population pharmacokinetic modeling was developed from digoxin data by using NONMEM program (Version V) according to one-compartment of subroutine ADVAN2 TRANS2 model.*
Results: *Weight, age, height and the presence of congestive heart failure (CHF) were significant covariates on CL. Weight and the presence of CHF were significant covariates on Vd. The final population model of CL and Vd in pediatric patients were as follows: CL/F (L/h) for infant (0-1 year) = 0.322 * WT (kg); CL/F (L/h) for children (> 1 year) = (0.138 * WT (kg) + 0.0319 * HT (cm) * 0.765^{CHF}; and Vd/F (L) for all ages = 9.27 * WT (kg) * 1.75^{CHF}. The interindividual variability of CL/F, Vd/F and intraindividual variability with proportional error model were 31.48, 35.56, and 41.7%, respectively. In the validation data set (57 samples), predictive performance in terms of bias (ME) and precision (RMSE) were -0.049 ng/mL (95% CI: -0.118-0.020) and 0.269 ng/mL (95% CI: 0.216-0.312), respectively.*
Conclusion: *This simple final population model of Vd and CL can be used in clinical practice for estimating appropriate dosage regimen of loading dose and maintenance dose, respectively. Current weight, height, and presence of CHF should be taken into account when designing dosage regimen for individualized pediatric patients.*

Keywords: *Digoxin, Heart failure, Pediatrics, Pharmacokinetics, Population*

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Problem of digoxin use is narrow therapeutic range and serious toxic effect may occur even if the drug is used in a recommended dose. Furthermore, the large interpatient variability in its pharmacokinetic was altered by the patient specific factor such as age, weight, disease state and renal function. Especially of special populations such as the pediatric group, advanced age and physiologic change of aging are primarily responsible for the altered pharmacokinetic parameters[1,2]. In pediatrics, the incidence of congenital heart disease (CHD) is approximately 0.8%[3]. Digoxin is the most commonly used cardiac glycoside in the treatment of heart failure and cardiac rhythm disturbance in neonate, infant, and children[4]. Pharmacokinetic parameters on the basis of their demographic data and clinical factors are appropriate

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to propose individualized dosage regimen. Recently, population pharmacokinetic approach is appropriate for pharmacokinetic study in pediatric patients with heart disease because of several advantages; can utilize data collected during clinical routine work, can analyze 'sparse' data, needs a few samples from each individual, can identify important covariates, and explaining interindividual and intraindividual variability[5]. However, there are few studies of digoxin population pharmacokinetics in this population. Therefore, the present study was developed to determine the digoxin population pharmacokinetics and influence of various factors on pharmacokinetic parameters in Thai pediatric patients with heart disease.

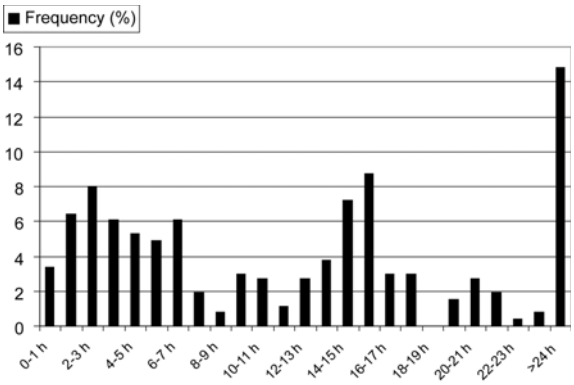

Fig. 1 Histogram of sampling time after dosing in modeling group

Material and Method

Data sources

The present study was an analytical cross-sectional study design. Data sources were carried out in 130 pediatric patients and 264 samples during routine care at Queen Sirikit Heart Center, Khon Kaen University between November, 2004 and June, 2006. Number of patients more than 100 was adequate for population pharmacokinetic analysis. Most of the patients (98.15%) received orally digoxin administration of various dosage regimens (Lanoxin Elixir®, Lanoxin PG®, Lanoxin® tablet by GlaxoSmithKline and Glaxo Wellcome), others received by intravenous route (1.85%). The digoxin doses administration ranged between 1.7 and 13.6 μg/kg/day with the mean ± SD of 6.6 ± 2.6 μg/kg/day (median 6.9 μg/kg/day) and serum digoxin concentration (SDC) ranged between < 0.2 and 3.11 ng/mL with the mean ± SD of 0.71 ± 0.5 ng/mL (median 0.58 ng/mL). The collected data were (1) demographic data; age, gender, total body weight and height, (2) clinical data; sign and symptom of congestive heart failure (CHF) and laboratory data during routine care, (3) medication history; dosage regimen of digoxin, concomitant medications, date and time of administration and miss dose were detected by a pharmacist. All blood samples were drawn at various times after administration. Serum digoxin concentrations (SDCs), date and time of each measurement were recorded. All the blood samplings were randomly allocated into 2 groups, 264 samples for a modeling study (modeling group) and 57 samples for a predictive performance study (validation group). The demographic data of the patients in the modeling group and validation group are presented in Table 1. For the modeling group, the histogram of sampling times at which blood was sampled after dosing is present in Fig. 1. The present study was approved by the Ethic Committee of Human Research, Faculty of Medicine, Khon Kaen University. Informed consent was obtained from their parent(s) or caregiver(s) to participate in the present study.

Digoxin assay

SDCs were determined by the fluorescence polarization immunoassay (FPIA) technology, using TDx analyzer from Abbot Laboratories (TDx digoxin-II), Abbot Park, IL, U.S.A. located at Academic Research Tool, Faculty of Pharmaceutical Sciences, Khon Kaen University. Sensitivity is defined as the lowest measurable level which can be distinguished from zero with 95% confidence; it is determined to be 0.2 mg/L. The typical yield coefficient of variation (CV) was less than 8%.

Population pharmacokinetic model

Population pharmacokinetic modeling was performed by using NONMEM program (Version V) developed by Sheiner and Beal. Total of 264 SDCs from 130 patients (range 1-7 samples) were used to develop the population modeling (modeling group) and 57 patients with 57 SDCs were used for validation data set (validation group). Pharmacokinetic model was tested on 1- and 2- compartment model. After testing found that 1-compartment model was appropriate to describe the digoxin disposition in this study population. One compartment model with using the subroutines ADVAN2 and TRANS2 were performed. Data was parameterized in terms of clearance (CL), volume of distribution (Vd), and absorption rate constant (Ka). However, the interindividual variability

Table 1. Demographic data of the patients in modeling and predictive performance group

Characteristics	Modeling group	Predictive group	p-value[a]
Number of patients	130	57	
Number of samples	264	57	
Infants (0-1 year)	27	10	
Children (> 1-15 years)	237	47	
Sample per patient	2.03	1.00	
Gender (n (%))			0.429
Boy	117 (44.3)	22 (38.6)	
Girl	147 (55.7)	35 (61.4)	
Age (years, mean ± SD)			
Total	6.7 ± 4.7, 5.7 (8.4)[b]	6.9 ± 4.8, 6.7 (9.6)[b]	0.824
Infants (0-1 year)	0.6 ± 0.2, 0.6 (0.3) [b]	0.6 ± 0.3, 0.8 (0.5) [b]	0.645
Children (1-15 years)	7.3 ± 4.5, 6.6 (8.1)	8.2 ± 4.2, 8.3 (8.5)	0.171
Weight (kg, mean ± SD)	19.5 ± 12.5, 16 (16.6)[b]	19.4 ± 12.2, 16.5 (17.1)[b]	0.981
Height (cm, mean ± SD)	107.3 (29.8)	104.3 (32.2)	0.464
	105.5 (51.1)	101.3 (61.1)	
Digoxin dose (μg/kg/day, mean ± SD)	6.60 ± 2.60, 6.90 (4.70)[b]	6.56 ± 2.66, 6.94 (4.60)[b]	0.870
Serum digoxin concentration (ng/mL)	0.71 ± 0.50, 0.58 (0.53)[b]	0.60 ± 0.35, 0.55 (0.48)[b]	0.486
Indications (n (%))			1.000
CHF	257 (97.3)	56 (98.2)	
Arrhythmia	7 (2.7)	1 (1.8)	
Serum creatinine[c] (mg/dL, mean ± SD)	0.55 ± 0.17, 0.50 (0.20)[b]	0.57 ± 0.17,0.50 (0.25)[b]	0.477
Creatinine clearance[c] (mL/min, mean ± SD)	38.87 ± 31.53, 24.11 (42.80)[b]	41.28 ± 26.40, 36.41 (40.96)[b]	0.450
Serum potassium[d] (mEq/L, mean ± SD)	4.3 ± 0.6, 4.3 (0.8)[b]	4.30 ± 0.8, 4.3 (0.9)[b]	0.668
Concomitant drugs (n (%))			
Spironolactone	13 (4.9)	0 (0)	0.137
Thiazides diuretics	135 (51.1)	26 (45.6)	0.450
Loop diuretics	50 (18.9)	15 (26.3)	0.209
ACEIs	101 (38.3)	22 (38.6)	0.962
Macrolides	6 (2.3)	2 (3.3)	0.644
Antacid	8 (3)	1 (1.7)	1.000

[a] Nonparametric test by Mann-Whitney U test for continuous data and Chi-Square test or Fisher's Exact test for categorized data

[b] Median value (IQR)

[c] Calculated from 52 and 21 samples in modeling and predictive performance group, respectively

[d] Calculated from 111 and 30 samples in modeling and predictive performance group, respectively

of Ka was a high unacceptable value. It may be due to the insufficient data in the absorption phase (1 hour after dosing)[6]. The model was simplified by fixing Ka to 5.6 h^{-1} from the model gave minimized objective function. Because most of the doses (98.15%) were given orally of Lanoxin®, it was rarely possible to estimate the absolute bioavailabilitly (F). The parameters CL, Vd were interpreted as CL/F, Vd/F, respectively, where F is the bioavailability of digoxin (80-90% for liquid form[7]).

The interindividual variability in the CL/F and Vd/F were best explained by proportional error model according to the following equations:

$$CL_{ij} = TVCL/F * (1 + \eta_{iCL/F})$$
$$Vd_{ij} = TVVd/F * (1 + \eta_{iVd/F})$$

where CL_{ij} are the *j*th true CL for *i*th individual, Vd_{ij} are the *j*th true Vd for *i*th individual, TVCL are typical value of CL, TVVd are typical value of Vd predicted by a regression model, F is the bioavailability of digoxin (80-90% for liquid form[7]), and $\eta_{iCL/F}$ and $\eta_{iVd/F}$ are random variable distributed with zero means and respective variance of $\omega^2_{CL/F}$ and $\omega^2_{Vd/F}$, respectively**.** The residual (error) variability was also best explained by proportional error model and can be expressed as follows:

$$C_{ij} = C_{pred,ij} * (1 + \varepsilon_{ij})$$

Table 2. NONMEM output of base model

Base models	Error model (Interindividual/ intraindividual variability)	OF	θ_1 (Ka, CV%)	θ_2 (CL, CV%)	θ_3 (Vd, CV%)	ω^2_1 (Ka, CV%)	ω^2_2 (CL, CV%)	ω^2_3 (Vd, CV%)	σ^2 (CV%)
$TVKa = \theta_1$ (fixed 5.6) $TVCL = \theta_2$ $TVVd = \theta_3$	$CL = TVCL/F * (1+\eta_{CL/F})$ $Vd = TVVd/F * (1+\eta_{Vd/F})$ $C_{obs} = C_{pred} * (1+\varepsilon)$	8.813	5.6	4.5 (7.2)[a]	205 (12.34)[a]	0	0.266 (51.57)[b]	1.07 (103.4)[b]	0.358 (59.8)[b]

[a] Coefficient of variation associated with parameter estimation (CV% = s.e./value*100)
[b] For proportional error model CV% = $(\omega^2)^{\square}$ * 100

CL = total clearance (L/h); Vd = volume of distribution (L); F = bioavailability (elixir = 0.85, tablet = 0.7, intravenous = 1); TVCL = typical population value for CL; TVVd = typical population value of Vd; CV (%) = coefficient of variation; C_{obs} = observed concentration; C_{pred} = predicted concentration

where C_{ij} is the *j*th observed concentration for the *i*th individual, $C_{pred,ij}$ is the digoxin concentration predicted by the pharmacokinetic model, and ε_{ij} is a difference value between C_{ij} and $C_{pred,ij}$ and randomly distributed term of zero mean and variance σ^2 which represented the residual intraindividual variability[8]. Table 2 presents the NONMEM output of base model.

Data analysis

In the first step, the data from the modeling group were used to develop the basic regression model (without covariate) for fixed effect model. Then each covariate was added into the basic model and the change in objective function (OF) was considered for candidate covariate (Preliminary screening phase). Next step, the candidate covariate was added at one time to the basic regression model and the apparent influence of covariate on digoxin disposition was observed by the changing of the OF (Forward Stepwise Fashion). The difference between OF values for a model containing n covariates and that containing n-1 covariates by more than 6.63 (χ^2, $p < 0.01$; 1 degree of freedom) was considered to be significant and added to the model. The other factors were added cumulatively to the model in order of the contribution of each factor to the reduction in OF from the preliminary screening phase until there was no further reduction in the OF. Finally, back elimination was carried out to eliminate any unnecessary covariates (confounding factors) from the full regression model. Each parameter was eliminated from the full regression model in descending order of their contribution to the reduction in OF. If the objective function did not increase by more than 6.63, the parameter was excluded from the final model. The final regression model included all parameters that can not be eliminated from the full regression model[9-11].

Predictive performance

The predictive performance was determined in terms of bias and precision. The objective was to examine whether the model is a good description of the data in validate group. The mean prediction error (ME) defined as:

$$ME = \frac{1}{N}\sum_{i=1}^{N} pe_i$$

where pe_i is the difference between the *i*th measured and predicted plasma concentration, N is a number of pairs of measured and predicted concentrations.

The mean squared prediction error (MSE) or the root mean squared prediction error (RMSE) is a measure of precision and estimates scatter or variability. These quantities are defined as follows:

$$MSE = \frac{1}{N}\sum_{i=1}^{N} pe_i^2$$

$$RMSE = \sqrt{MSE}$$

The smaller of ME and MSE are the less bias and more precise the prediction[12].

Results

There was no significant difference in demographic data between the modeling group and

validation group ($p > 0.05$). According to a previous report it was revealed that when infants and children were appropriately divided into age group, there was less variability in pharmacokinetic factors[13]. Generally of renal functions, predominate route of digoxin elimination, have the various fully development to reach adult values during 6-12 months[14]. Therefore, the samples were divided into 2 groups by age; 0-1 year or infant group (27 samples, 10.2%) and > 1 year or children group (237 samples, 89.8%). Moreover, in the first step, the modeling of CL with weight, height, age group, the presence of congestive heart failure (CHF) and the modeling of Vd with weight, age group, and the presence of CHF reduced OF from basic model more than 6.63 (χ^2, $p < 0.01$, 1 degree of freedom) (Table 3). In the forward stepwise, the cumulative inclusion of weight, height, age group, and the presence of CHF in > 1 year group on CL and weight and the presence of CHF on Vd reduced the objective function by more than 6.63 at each addition (Table 4). The relationship between these covariates with CL and Vd are described by the full regression of the following model:

$TVKa(h^{-1}): \theta_1$ (5.6 fixed)

$TVCL/F(L/h)_{\text{for infant}}: \theta_2 * WT(kg) + \theta_3 * HT(cm)$

$TVCL/F(L/h)_{\text{for children:}} (\theta_4 * WT(kg) + \theta_5 * HT(cm)) * \theta_6^{CHF}$

$TVVd/F\ (L)_{\text{for ages}}: \theta_7 * WT(kg) * \theta_8^{CHF}$

where TVKa is a typical value of Ka, TVCL is a typical value of CL, TVVd is a typical value of Vd, F is oral bioavailability (80-90% for liquid form[7]), WT is weight in kilograms, HT is height in centimeters, CHF is indicator variable with a value of 1 if the patient has congestive heart failure (otherwise it is zero).

Final step, back elimination phase, when removed height from the full regression model of CL of the infant group, OF did not increase more than 6.63. Thus, height was excluded from the full model. The final regression model included covariates of weight, age group, height and the presence of CHF in > 1 year

Table 3. Preliminary screening of covariates by ADVAN2 TRANS2 and fixed Ka model

Hypothesis	Equation	OF	LLD	p-value	Conclusion
Base model (ADVAN2 TRANS2)	$Ka = \theta_1$(fixed 5.6) $CL = \theta_2$ $Vd = \theta_3$	8.813			
CL (clearance)					
Did weight influence CL?	θ_2*WT	-242.154	-250.967	<0.01	Yes
Did height influence CL?	θ_2*HT	-186.914	-195.727	<0.01	Yes
Did age group influence CL?	If 0-1y = θ_2 Else θ_4	-101.468	-110.281	<0.01	Yes
Did CHF influence CL?	$\theta_2*\theta_4^{CHF}$	-36.316	-45.129	<0.01	Yes
Did diuretics influence CL?	$\theta_2*\theta_3^{DIUR}$	6.810	-2.003	>0.01	No
Did gender influence CL?	$\theta_2*\theta_3^{SEX}$	7.214	-1.599	>0.01	No
Did ACEIs influence CL?	$\theta_2*\theta_3^{ACEI}$	9.141	0.328	>0.01	No
Did serum creatinine influence CL?	θ_2*Scr^{-1}	37.310	28.497	>0.01	No
Did creatinine clearance influence CL?	θ_2*CLcr	707.447	698.634	>0.01	No
Vd (volume of distribution)					
Did weight influence Vd?	θ_3*WT	-149.484	-158.297	<0.01	Yes
Did age group influence Vd?	If 0-1y = θ_2 Else θ_4	-40.365	-49.178	<0.01	Yes
Did CHF influence Vd?	$\theta_3*\theta_4^{CHF}$	-18.075	-26.888	<0.01	Yes
Did ACEIs influence Vd?	$\theta_3*\theta_4^{ACEI}$	3.994	-4.819	>0.01	No
Did gender influence Vd?	$\theta_3*\theta_3^{SEX}$	5.445	-3.368	>0.01	No
Did diuretics influence Vd?	$\theta_2*\theta_4^{DIUR}$	8.792	-0.021	>0.01	No
Did creatinine clearance influence Vd?	θ_3*CLcr	11.789	2.976	>0.01	No
Did height influence Vd?	θ_3*HT	25.577	16.764	>0.01	No
Did serum creatinine influence Vd?	θ_3*Scr^{-1}	37.369	28.556	>0.01	No
Did potassium influence Vd?	θ_3*K	48.347	39.534	>0.01	No

CL = total body clearance; Ka = absorption rate constant; LLD = -2 log likelihood difference from the base model; OF = objective function; Vd = volume of distribution

Table 4. Forward stepwise fashion analysis: effect on objective function changing of addition of significant covariates in the basic model

Hypothesis	Model	OF	LLD	Conclusion
Base model	Ka = θ_1 (fixed 5.6) CL = θ_2, Vd = θ_3	8.813		
Did weight influence CL?	CL = f (WT) Vd = θ_3	-243.192	-252.005	Yes
Did height influence CL?	CL = f (WT, HT) Vd = θ_3	-268.634	-25.442	Yes
Did weight influence Vd?	CL = f (WT, HT) Vd = f (WT)	-275.984	-7.35	Yes
Did age group influence CL?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, HT) Vd = f (WT)	-285.622	-9.638	Yes
Did age group influence Vd?	CL (0-1 year) = f (WT, HT) Vd (0-1 year) = f (WT) CL (> 1 year) = f (WT, HT) Vd (> 1 year) = f (WT)	-291.133	-5.511	No
Did CHF influence CL in age >1 year group?	CL (0-1 year) = f (WT, HT, CHF) CL (> 1 year) = f (WT, HT) Vd = f (WT)	-285.652	-0.03	No
Did CHF influence CL in age >1 year group?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, HT,CHF) Vd = f (WT)	-303.276	-17.654	Yes
Did CHF influence Vd?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, HT,CHF) Vd = f (WT,CHF)	-311.670	-8.394	Yes

CL = total body clearance; Ka = absorption rate constant; LLD = -2 log likelihood difference from the base model; OF = objective function; Vd = volume of distribution

group for CL; weight and the presence of CHF for Vd. Steps of back elimination are presented in Table 5. The final regression model for CL and Vd are presented as follows:

$CL/F\ (L/h)_{\text{for infant}}$ (0-1year): 0.322 * WT(kg)

$CL/F(L/h)_{\text{for children}}$ (>1year): (0.138 * WT(kg) + 0.0319 * HT(cm)) * 0.765^{CHF}

$Vd/F\ (L)_{\text{for all ages}}$: 9.27 * WT(kg) * 1.75^{CHF}

Scatterplot between pairs of measured concentration and predicted concentration obtained from base model (without covariate) was compared with final model (Fig. 2). The scatterplot of the final model confirmed that the final model is an improvement: the group of points far from identity line had disappeared. Scatterplot of weighted residual versus predicted concentration obtained from the base model was compared with the final model (Fig. 3). The scatterplot of the final model indicated an improvement in that the large positive residuals were clear.

The imprecision (uncertainty) in parameter estimation of the model was calculated by dividing the standard error of each by its value and expressed as a percentage of coefficient of variation (CV%). The amount of uncertainty (CV%) associated with estimation of the coefficient of the structural model: $\theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_7$ were 10.87%, 48.90%, 34.17%, 12.78%, 15.30%, 17.90%, respectively and for interindividual variability of CL/F and Vd/F were 41.37% and 107.20%, respectively. The interindividual variability (CV%) in CL/F, Vd/F and intraindividual variability were calculated by taking the square root of the omega value ($\omega^2_{CL/F}$ and $\omega^2_{Vd/F}$) and error variance (σ^2), respectively, obtained by NONMEM in the final model. These values were expressed as a percentage. Interindividual variability in CL/F, Vd/F and intra-individual variability were 31.48%, 35.56%, and 41.70%, respectively. Summary results of the final structural, statistical models and variability are presented in Table 4.

Table 5. Backward elimination analysis: effect on objective function changing of significant covariates deleted from full regression model

Hypothesis	Model	OF	LLD	Conclusion
Full model	Ka = fixed 5.6 CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, HT, CHF) Vd = f (WT, CHF)	-311.670		
Did weight influence CL in age 0-1 year group?	CL (0-1 year) = f (HT) CL (> 1 year) = f (WT, HT, CHF) Vd = f (WT, CHF)	-300.183	11.487	Yes
Did weight influence CL in age >1 year group?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (HT, CHF) Vd = f (WT, CHF)	-291.831	19.839	Yes
Did height influence CL in age 0-1 year group?	CL (0-1 year) = f (WT) CL(> 1 year) = f (WT, HT, CHF) Vd = f (WT, CHF)	-311.670	0	No
Did height influence CL in age >1 year group?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, CHF) Vd = f (WT, CHF)	-277.052	34.618	Yes
Did weight influence Vd?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, HT, CHF) Vd = f (CHF)	-297.919	13.751	Yes
Did age group influence CL?	CL = f (WT, HT, CHF) Vd = f (WT, CHF)	-289.845	22.060	Yes
Did CHF influence CL in age >1 year group?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, HT) Vd = f (WT, CHF)	-302.174	9.732	Yes
Did CHF influence Vd?	CL (0-1 year) = f (WT, HT) CL (> 1 year) = f (WT, HT, CHF) Vd = f (WT)	-303.276	8.394	Yes

CHF = congestive heart failure; CL = clearance; HT = height (cm.); Ka = absorption rate constant; LLD = -2 log likelihood difference from the base model; OF = objective function; Vd = volume of distribution; WT = body weight (kg)

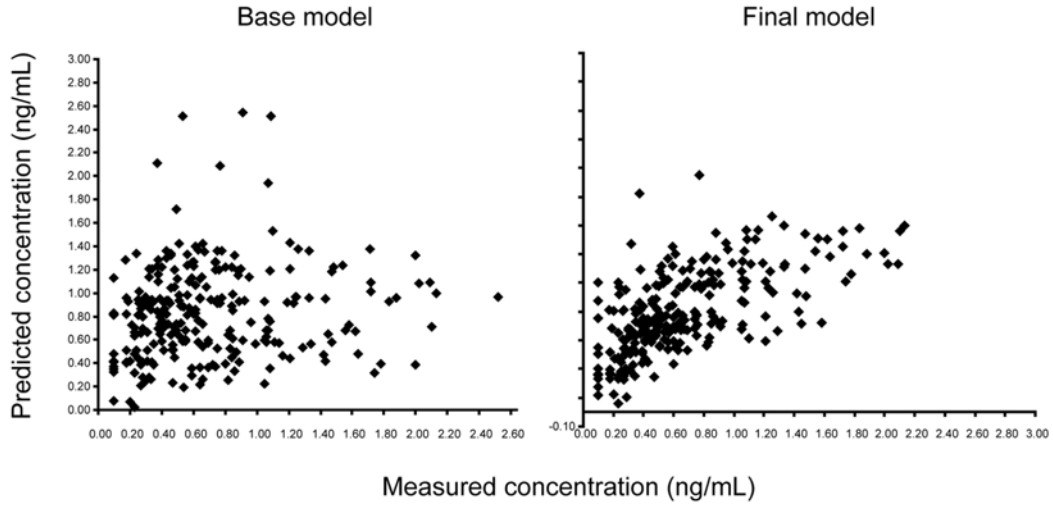

Fig. 2 Comparison of scatterplot of measured concentration versus predicted concentration obtained from base model and final model

Table 6. Final model of pediatric population pharmacokinetic parameters for digoxin

Parameters	Meaning	Estimated value	Variability estimation	
			Standard error (SE)	CV[a] (%)
θ_1	Absorption rate constant	Fixed 5.6	-	-
θ_2	Coefficient of weight in CL of infant group	0.3220	0.0350	10.87
θ_3	Coefficient of weight in CL of children group	0.1380	0.0676	48.90
θ_4	Coefficient of height in CL of children group	0.0319	0.0110	34.17
θ_5	Coefficient of CHF in CL of children group	0.7650	0.0978	12.78
θ_6	Coefficient of weight in Vd	9.2700	1.4200	15.30
θ_7	Coefficient of CHF in Vd	1.7500	0.3140	17.90
$\omega^2_{CL/F}$	Interindividual variability (CV%)[b] in CL/F	0.0991 (31.48)	0.0410	41.37
$\omega^2_{Vd/F}$	Interindividual variability (CV%)[b] in Vd/F	0.1250 (35.36)	0.1340	107.20
σ^2	Intraindividual variability (CV%)[b]	0.1740 (41.7)	0.0224	12.87

[a] Coefficient of variation associated with parameter estimation (CV% = s.e./value * 100)

[b] For proportional error model CV% = $(\omega^2)^{\square}$ * 100

Structural model: TVKa (h^{-1}): θ_1 (5.6 fixed)

TVCL/F (L/h) for infant group: θ_2 * WT(kg)

TVCL/F (L/h) for children group: (θ_3 * WT(kg) + θ_4 * HT(cm)) * θ_5^{CHF}

TVVd/F (L) for all groups: θ_6 * WT(kg) * θ_7^{CHF}

Random-effects models: $CL = TVCL/F * (1 + \eta_{CL/F})$

$Vd = TVVd/F * (1 + \eta_{Vd/F})$

$C_{obs} = C_{pred,} * (1 + \varepsilon)$

where, CL = total clearance (L/h); Vd = volume of distribution; F = bioavailability (liquid form = 0.8-0.9, intravenous = 1); TVCL = typical population value for CL; TVVd = typical population value of Vd; CV (%) = coefficient of variation; CHF = congestive heart failure; WT = body weight (kg); HT = height (cm); C_{obs} = observed concentration; C_{pred} = predicted concentration

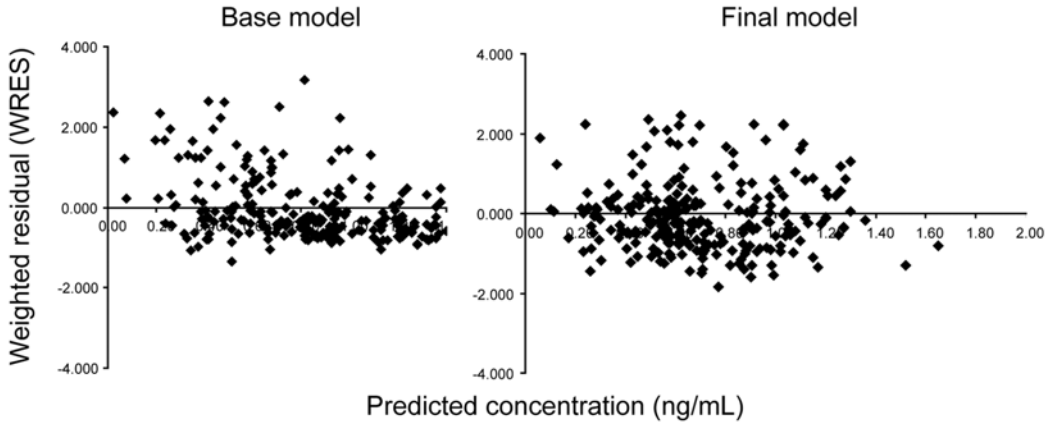

Fig. 3 Comparison of scatterplot of weight residuals versus predicted concentration obtained from base model and final model

Fifty-seven prediction concentrations of 57 patients in the validation group were calculated from parameters obtained from the modeling group and compared with the measured concentrations to determine the predictive performance. The predictive performance of the population models are presented in Table 7. The mean prediction error (ME) was -0.049 ng/mL with 95% confidence interval (95% CI) of -0.118-0.020. The mean

Table 7. Predictive performance of digoxin population pharmacokinetic models

Parameter	Value (ng/mL)	SE (ng/mL)	95% CI (ng/mL)
Precision			
RMSE	0.269	0.013	0.216-0.312
Bias			
ME	-0.049	0.035	-0.118-0.020

squared prediction error (MSE) and root mean squared prediction error (RMSE) were 0.072 ng/mL (95% CI: 0.047-0.098) and 0.269 ng/mL (95% CI: 0.216-0.312), respectively. A scatterplot between pairs of predicted and measured concentrations is shown in Fig. 4. A scatterplot of weighted residuals (predicted minus measured concentration and weighted by the standard deviation) versus predicted concentration was confirmed that the residuals were normally distributed around the zero ordinate (Fig. 5).

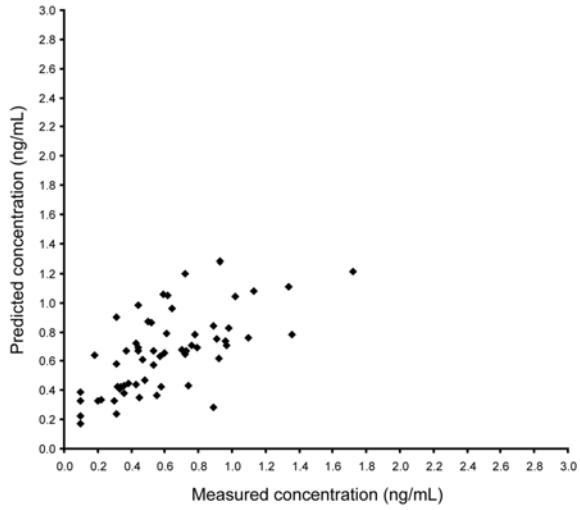

Fig. 4 Scatterplot of measured concentrations versus predicted concentrations of validation group

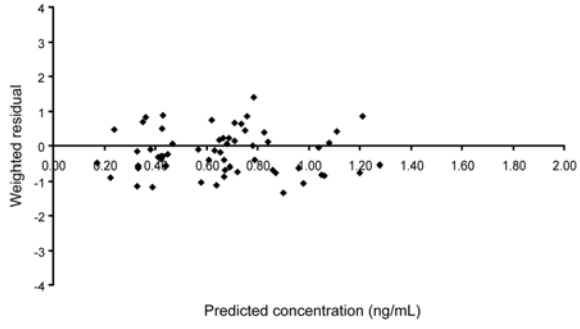

Fig. 5 Scatterplot of weighted residuals versus predicted concentrations of validation group

Discussion

Use of digoxin in adults and children, appropriate dosage regimen should be individualized. Developmental changes in children lead to changes of digoxin pharmacokinetics in comparison to adults. The demographic factors would be useful to effect on pharmacokinetic parameters. According to the objectives, population pharmacokinetics of digoxin in Thai pediatric patients was established as the first time. Pharmacokinetic parameter of CL and Vd although the previous report indicated that the disposition curve of serum digoxin can be described by use of a 2-compartment model, a 1-compartment model best described the digoxin profile of this pediatric population. Two-compartment modeling generated the unrealistic values of parameters and the errors of the sufficient condition appeared not to be satisfactory. Furthermore, 1-compartment model was easy application for therapeutic drug monitoring service in the clinical practice. The final regression model of the present study suggested that CL of digoxin was influenced by age group, and weight. Similar to a previous report, age and total body weight of children were most closely correlated with digoxin CL[16]. In early reports, clearance of digoxin in infants was a wide range of 0.162-0.6 L/h/kg[2,4,17,18]. NONMEM analysis demonstrated that digoxin clearance in infants was 0.32 L/h/kg (CL/F (L/h) = 0.32 * WT (kg)) which was within the range of early reports but had more specific value. This typical value was similar to the results obtained from two population pharmacokinetic studies. Suematsu et al and Martin-Suarez et al reported mean digoxin clearance in infants were 0.38 L/h/kg and 0.29 L/h/kg, respectively[11,19]. However, the final regression model of Japanese infants demonstrated that serum creatinine (Scr), CHF, and spironolactone (SPI) administration significantly related to digoxin clearance as follows: CL (L/h/kg) = $0.298 * \text{AGE (days)}^{0.099} * \text{Scr}^{-0.153} * 0.882^{\text{CHF}} * 0.897^{\text{SPI}}$[11]. In the children's group, weight, height, and CHF were significant covariates of digoxin clearance and final population model for CL is presented as follows: CL/F (L/h): $(0.138 * \text{WT(kg)} + 0.0319 * \text{HT(cm)}) * 0.765^{\text{CHF}}$. The study in Egyptian pediatric patients. Found that the final model of digoxin CL were CL (L/h/kg) = 0.388–[0.78* (Scr–0.6)][20]. Several studies of adult and

children, serum creatinine was a significant covariate for clearance and support the point that predominate of digoxin elimination is renal excretion[10-11,20-23]. This final model could not detect the influence of serum creatinine to digoxin clearance. This did not negate the potential influence of serum creatinine on digoxin clearance. The reason may have been that the serum creatinine values from 52 samples were within the narrow range (0.4 to 1.1 mg/dL) which may not vary enough to present as significant covariate in this population. Digoxin clearance of patients with CHF was 23.5% lower than patients without CHF. Several of early studies supported that CHF is an important factor to digoxin clearance estimation. In adults, Sheiner et al. found that digoxin clearance in patients with CHF was significantly lower than patients without CHF[24]. In a further study, Yukawa et al and Suematsu et al reported that the digoxin clearance was decreased 19% and 11.8% in adults and infants with CHF, respectively[11,21]. CHF decreases the CL of digoxin by reducing the perfusion to the absorption and elimination site but the observed difference might be due to the difference of disease severity between population analyses. Otherwise, the present study could not present the effect of CHF in infants which might be due to most of the infant patients presenting CHF (77.8%). The clearance of digoxin decreased 10-24% with administration of spironolactone in previous reports[11,21,25]. Only 4.9% of SDC collected from patients administered digoxin with spironolactone, therefore, could not investigate the influence of spironolactone in digoxin clearance. Some studies reported that the addition of ACEIs, captopril, to the heart failure treatment increased 20-30% in the mean digoxin concentration[26,27]. On the other hand, some studies reported that no interactive effect of once-daily doses of 20 mg of enalapril given for digoxin treatment with CHF[28,29]. In this present study did not find the effect of ACEIs, enalapril, to digoxin pharmacokinetic in pediatric patients.

Final population model of Vd was consistent with the pediatric Egyptian population reported earlier, Vd/F = 9.27 L/kg and Vd = 9.8 L/kg, respectively[20]. These values were in the range of that previously reported (8-16.3 L/kg for infants and 8.6-12.8 L/kg for children)[2,4,17,18]. However, Vd of patient with CHF was 75% higher than patients without CHF because the patients developed signs of edema are likely to encounter and increase in Vd when CHF worsen[30].

The degree of imprecision associated with estimation for fixed-effect parameters (θ_n) ranged from 10.87-48.90%. For random-effect parameters, interindividual variability of Vd/F (CV = 107.2%) was estimated with poorer precision than interindividual variability of CL/F (CV = 41.37%). The poor precision of estimating interindividual variability in Vd reflected that most samples were drawn near trough or passed dosing interval as shown in Fig. 1. The interindividual variability of CL/F and Vd/F were determined to be 31.48% and 35.36% as a coefficient of variation in final model, which decreased from basic regression model (51.57% and 103.4%, respectively). The intraindividual variability of 41.7% was higher than all previous reports. High intraindividual variability might be attributed to many factors such as measurement errors, pharmacokinetic model misspecification, day-to-day fluctuations in an individual's pharmacokinetic and especially error in data collection and patient compliance. Since most population studies were outpatients, the error of administration time from parent or patient recall and undetectable noncompliance by using parent or patient interview might occur. However, in the validation group of 57 patients, the predictive performance was no bias between predicted and measured concentrations. But in terms of precision, the prediction was slightly deviated.

Conclusion

The present study presented the population pharmacokinetic parameters of digoxin and variability in pediatrics aged from 0 up to 15 years old. This simple final population model can be used in clinical practice for estimating the initial loading doses or maintenance doses and adjustment in dosage regimen to achieve the target serum digoxin concentration.

Acknowledgements

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เภสัชจลนศาสตร์ประชากรของยาดิจ๊อกซินในผู้ป่วยเด็กไทย

ยุพาพร ปรีชากุล, พีรยา สมสะอาด, เศรษฐสิริ เพชรรัตน์

วัตถุประสงค์: *เพื่อศึกษาหาค่าพารามิเตอร์ ทางเภสัชจลนศาสตร์ประชากรของยาดิจ๊อกซินและปัจจัยที่มีผลต่อค่าพารามิเตอร์ในผู้ป่วยเด็กไทยที่เป็นโรคหัวใจ*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาทางเภสัชจลนศาสตร์ ออกแบบจำลองทางเภสัชจลนศาสตร์ของยาดิจ๊อกซิน ซึ่งเป็นการศึกษาเชิงวิเคราะห์ โดยใช้ข้อมูลจากผู้ป่วยเด็กอายุ 0.1-15.7 ปี จำนวน 130 คน และระดับยาในเลือด 264 ตัวอย่าง ที่เจาะที่เวลาต่าง ๆ หลังจากให้ยา ผู้ป่วยเด็กทุกคนได้รับการรักษาด้วยยาดิจ๊อกซิน ณ ศูนย์หัวใจสิริกิติ์ ภาคตะวันออกเฉียงเหนือ มหาวิทยาลัยขอนแก่น โดยมีช่วงขนาดของการใช้ยา 1.7-13.6 ไมโครกรัม/กิโลกรัม/วัน จากนั้นทำการวิเคราะห์ค่าพารามิเตอร์และออกแบบจำลองทางเภสัชจลนศาสตร์แบบหนึ่งห้องจากข้อมูลโดยใช้โปรแกรม NONMEM และชุดคำสั่ง ADVAN2 TRANS2 ของโปรแกรม*

ผลการศึกษา: *น้ำหนัก อายุ ส่วนสูง และการมีภาวะหัวใจล้มเหลวมีผลต่อพารามิเตอร์ในการกำจัดยา (CL) อย่างมีนัยสำคัญ ส่วนน้ำหนักและการมีภาวะหัวใจล้มเหลวมีผลต่อพารามิเตอร์ในการกระจายตัวของยา (Vd) อย่างมีนัยสำคัญ สมการทางเภสัชจลนศาสตร์ประชากรของค่า CL คือ CL/F (L/h) สำหรับเด็กทารกอายุ 0-1 ปี = 0.322 * WT(kg); CL/F (L/h) สำหรับเด็กอายุมากกว่า 1 ปี = (0.138 * WT(kg) + 0.0319 * HT(cm)) * 0.765^{CHF}; และสมการทางเภสัชศาสตร์ประชากรของค่า Vd คือ Vd/F (L) สำหรับเด็กทุกอายุ = 9.27 * WT(kg) * 1.75^{CHF} ค่าความแตกต่างระหว่างบุคคลของการกำจัดยาและการกระจายตัวของยา คือ ร้อยละ 31.48 และ 35.56 ตามลำดับ และค่าความแตกต่างภายในบุคคล คือ ร้อยละ 41.70 จากการทดสอบแบบจำลองโดยใช้ข้อมูลจากกลุ่มทดสอบ 57 ข้อมูล พบว่าแบบจำลองมีค่าความอคติเท่ากับ -0.049 ng/mL (95% CI: -0.118-0.020) และ ค่าความแม่นยำเท่ากับ 0.269 ng/mL (95% CI: 0.216-0.312)*

สรุป: *สมการอย่างง่ายทางเภสัชจลนศาสตร์ของค่า Vd และ CL ที่ได้จากการศึกษานี้ สามารถนำมาใช้ในทางคลินิกโดยการคำนวณและพิจารณาขนาดยาเริ่มต้นและขนาดต่อเนื่องที่เหมาะสมในการรักษาในผู้ป่วยเด็กแต่ละรายได้ โดยปัจจัยที่มีผลที่ควรคำนึงถึงเมื่อพิจารณาขนาดยาของผู้ป่วยแต่ละรายคือ น้ำหนัก อายุ ส่วนสูง และการมีภาวะหัวใจล้มเหลว*