약학박사 학위논문

한국 입원 환자에서 디곡신의 집단 약동학에 대한 영양 요인의 영향 분석

A Population Pharmacokinetic Analysis of the Influence of Nutritional Status of Digoxin in Hospitalized Korean Patients

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서울대학교 대학원

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최수안

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이 논문을 약학박사학위논문으로 제출함

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ABSTRACT

A Population Pharmacokinetic Analysis of the Influence of Nutritional Status of Digoxin in Hospitalized Korean Patients

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Background: Safe and effective use of digoxin in the hospitalized populations requires information about the drug's pharmacokinetics and the influence of various factors on drug's disposition. However, no attempts were made to link an individual's digoxin requirements with nutritional status.

Objectives: The main goal of this study is to estimate the population pharmacokinetics of digoxin and identify nutritional status that explains pharmacokinetic variability in hospitalized Korean patients.

Methods: Routine therapeutic drug monitoring data from 106 patients

who received oral digoxin at Seoul National University Bundang Hospital were retrospectively collected. The pharmacokinetics of digoxin was analyzed with a one-compartment open pharmacokinetic model using Nonlinear Mixed Effects Modeling (NONMEM) and a multiple trough screen approach.

Results: The effect of demographic characteristics, and biochemical and nutritional indices were explored. Estimates generated by NONMEM indicated that apparent clearance (CL/F) of digoxin was influenced by the renal function, serum potassium, age, and percent of ideal body weight (PIBW). These influences could be modeled by following equation CL/F (L/h) = $1.36\times (CCR/50)^{1.580} \times K^{0.835} \times 0.055\times (AGE/65) \times (PIBW/100)^{0.403}$. The inter-individual variability (CV) for CL/F was 34.3% and the residual variability (SD) between observed and predicted concentrations was 0.225 μg/L. The median estimates from a bootstrap procedure were comparable and within 5% of the estimates from NONMEM. Correlation analysis with the validation group showed a linear correlation between observed and predicted values.

Discussion: The use of this model in routine TDM requires that certain conditions be met that are consistent with the conditions of the sub-populations in the present study. Therefore, the authors advocate further studies to elucidate the effects of various nutritional status on digoxin pharmacokinetics.

Conclusion: The present study established important sources of variability in digoxin pharmacokinetics and showed the relationship between pharmacokinetic parameters and nutritional status in hospitalized Korean patients.

Keywords : Digoxin, Nonlinear Mixed Effects Modeling, population pharmacokinetics, NONMEM, nutritional status

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INTRODUCTION

Digoxin is one of the commonly prescribed cardiac medications and an integral part of the treatment for heart failure and atrial fibrillation.[1] However, the drug is difficult to administer, because it lacks a clear relationship between the dose and desired effect. Furthermore, routine dosage of the drug can cause toxicity due to a narrow therapeutic index and inter-/intra-individual variability in its pharmacokinetics.[1] Therefore, individualized dosage regimen of digoxin is of great significance.

It is important to recognize how the pharmacokinetics of digoxin varies in hospitalized patients in order to administer the drug safely and effectively. It is also critical to understand the effect of various clinical factors on the pharmacokinetics of digoxin in performing therapeutic drug monitoring (TDM),[2, 3] that improves patient care and contributes to decrease to suspected digoxin toxicity. Among various clinical factors, demographics have a critical impact on the pharmacokinetic parameters of digoxin and nutritional problems including malnutrition are highly prevalent in hospitalized patients. Especially, nutrition problems are related to increased morbidity, length of hospital stay, costs and mortality.[4, 5]

Hanratty and associates show that the pharmacokinetics of digoxin is affected by aging-related changes including nutritional status such as body mass or weight.[6] This contributes to the development of toxicity in older patients. Moreover, Korean population has less mean digoxin

dosage and concentration compared to other population[7] and epidemic obesity or muscle mass is different between asian and western population.[8]

Previously, the population pharmacokinetics of digoxin were examined using the computer program NONMEM, developed by Beal and Sheiner.[9] Several studies have investigated various races-, and age-groups, and pediatric patients in an effort to identify important sources of pharmacokinetic variability of digoxin.[10-12] But, no attempts were made in these studies to link an individual's digoxin pharmacokinetics with nutritional status. Therefore, this study examines relationship between the digoxin pharmacokinetics and pathophysiological and nutritional status. The previous studies also didn't explain the differences among various race estimates as well as models of digoxin population pharmacokinetics in Korean patients. The main purpose of this study is to estimate and identify influential factors associated with pharmacokinetic parameters in hospitalized Korean patients.

METHODS

Data Sources

The usual oral adult maintenance dosage of digoxin administered as tablet is 0.125-0.5 mg once daily. Data sources (255 observations) of population group were retrospectively collected from 106 patients at Seoul National University Bundang Hospital (a 900-bed, tertiary care academic medical center in South Korea) who were administered a tablet form of digoxin (Digosin; CJ Pharmaceutical Co. Ltd, Korea). The patients were all hospitalized and under the supervision of medical and nursing staff such that the administration of treatment and compliance were standardized.[13] Additionally, we analyzed 43 samples (16 patients) as the validation group for a predictive performance study and the patient information is given in Table 1. We reconfirmed, from electronic medical records, basic information on the patients and pathologies from blood samples. The collected data were (1) demographic data; age, gender, total body weight and height, (2) clinical data; indication for digoxin, laboratory data of routine care (creatinine clearance, K; serum potassium, WBC; white blood cell, lymphocyte) (3) medication history; dosage regimen of digoxin, concomitant medications, date and time of administration, sampling time of digoxin (4) nutritional data; serum albumin, cholesterol, percentage of ideal body weight (PIBW), total lymphocyte count (TLC), nutritional risk index (NRI).

The percent of ideal body weight (PIBW) reflects chronic nutritional status more accurately than other nutritional factors.[14] At the time of the hospital admission, the recent change in patients' weight is more suitable to examine acute nutritional status.[14] The NRI, used in the Veterans Administration Cooperative Group study of perioperative parenteral nutrition, stratified operative morbidity and mortality.[15,16]

NRI = [1.519 × albumin (mg/dl)] + [41.7 × present/usual body weight (kg)]

Derivation of NRI (score of > 100, no risk; 97.5 to 100, mild risk; 83.5 to 97.5, moderate risk; 83.5, severe risk) is based on serum albumin and weight change, so NRI is a valid measure of health status and contains a nutritional dimension.[16] Malnutrition leads to decline in immune function. TLC is calculated by multiplying the white blood cell count by percentage of lymphocytes and one of the clinical measures of immune function that have been used as nutritional screening or assessment parameters.[5] The nutritional data used in the present study intended to reflect both acute and chronic nutritional status, severity of illness as well as the risk of malnutrition.

The present study excluded patients who had any major disorders of the hepatic, gastrointestinal, or hematopoietic systems, exhibited fluctuating or rapidly deteriorating renal function,[11] and who were taking drugs that may interact with digoxin (for example, amiodarone, quinidine, cholestyramine or phenytoin). This was done to eliminate

the effects of non-renal excretion, malabsorption of digoxin and misinterpretation of nutritional factor such as TLC. The digoxin concentrations for TDM were measured in terms of one trough level, based on the concentration of the steady state (chronic user or after 10 doses at least) that has completed volume of distribution in order to ensure the accuracy of measurements. We kept reliable sampling points and excluded patients with uncertain sampling records. Also, multiple trough screen approach is applied to estimate the pharmacokinetic parameters of a population using sparse data collected during routine clinical care. We equally applied the criteria regarding the data collection between the population and validation group.

The study was conducted in accordance with the Declaration of Helsinki and its amendments[17] and was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (B-1009-112-107). We submitted the waiver of informed consent for data collection and analyses according to HRPP (Human Research Protection Program) based on 45 CFR 46 subpart A 46.116. We didn't have patients' signed consents. However, our study was approved by IRB. IRB imposes a strict limitation on retrospective data collection without signed consent. Consequently, we were able to see only their clinical data but not individual information. The entire process about retrospective data collection was acceptable only after the

representative researcher had submitted a written declaration.

The measurement of digoxin in serum was carried out by a TDx digoxin assay kit from Abbot Laboratories for fluorescence polarization immunoassay (FPIA). The minimum detectable concentration for digoxin was 0.2 μg/L, and the coefficients of variation (CV) both between runs and within runs were less than 10% for concentrations between 0.5 and 5.0 μg/L.

Population Pharmacokinetic Model

Population pharmacokinetic modeling was performed using the NONMEM program (Version VI) developed by Sheiner and Beal.[18] The Xpose and Perl-speaks-NONMEM (PsN) modules were used for graphic and statistical model analysis.[19, 20] The principle of the extended non-linear least squares was applied to estimate the population pharmacokinetic parameters using the patient's sparse plasma concentration data, pathological factors, physiological factors and co-administration.[21] A one-compartment pharmacokinetic model using the subroutines ADVAN2 and TRANS2 (first-order absorption) was used to fit the data.[12] Data were parameterized in terms of apparent clearance (CL/F, L/h), apparent volume of distribution (Vd/F, L), and absorption rate constant (Ka, h^{-1}). The absorption rate constant of digoxin can be calculated from plasma concentration

values 1 h after dosing.[22] However, each patient contributed to only one data point and it was impossible to build an absorption model using the limited data,-; therefore, the model was simplified by fixing Ka to 1.63 h^{-1} based on values reported in the literature.[22, 23]

The inter-individual variability was best explained by exponential error model according to the following equations:

$CL/F_{ij} = TVCL * EXP(\eta_{iCL})$

$Vd/F_{ij} = TVV * EXP(\eta_{iVd})$

where CL/F_{ij} is the jth true CL/F for ith individual, Vd/F_{ij} is the jth true Vd/F for ith individual, TVCL is typical value of CL/F, TVV is typical value of Vd/F predicted by a regression model, and η_{iCL}, η_{iVd} are random variable distributed with zero means and respective variance of ω^2_{CL} and ω^2_{Vd} respectively. The residual (error) variability was also best explained by additive error model and can be expressed as follows:

$C_{ij} = C_{predij} + \varepsilon_{ij}$

where C_{ij} is the jth observed concentration for the ith individual, C_{predij} is the digoxin concentration predicted by the pharmacokinetic model, and ε_{ij} is a difference value between C_{ij} and C_{predij} and randomly distributed term of zero mean and variance σ^2 which represented the residual intra-individual variability.[24] This type of error is caused by influences such as assay variability, misspecification of the suggested pharmacokinetic model, and timing errors in drug administration or

blood sampling.[10]

Data Analysis Procedure

Initially, base regression analysis (without covariate) was applied to the data in order to develop a fixed-effect model. Ranges derived from the literature were used for initial estimates of digoxin pharmacokinetic parameters. Parameter-covariate relationships were initially explored by visual inspection and linear regression. The covariate model was established using a forward-inclusion/backward-elimination method incorporating a stepwise approach. Each covariate was added into the basic model and the change in objective function value (OFV) was considered for candidate covariate (preliminary screening phase). Next, the candidate covariates were sequentially added to the basic regression model, and the apparent influence of each covariate on digoxin disposition was determined based on the change OFV (forward stepwise fashion). The covariates screened were age, gender, weight, creatinine clearance (CCR), serum potassium, albumin, cholesterol, PIBW, TLC, NRI, and indication for digoxin. In order to identify potentially significant covariates, differences in OFV associated with a p-value of <0.05 (>3.84 for 1 degree of freedom) was required in the processes of stepwise modeling.[13] The other factors were added

cumulatively to the reduction in OFV until there was no further reduction in the OFV. Then the backward elimination process was used to identify the significant covariates for the final model. The imprecision (uncertainty) in parameter estimation of the model was calculated by dividing the standard error of each by its value (RSE%, relative standard error) and expressed as a percentage of coefficient of variation (CV%). Scatterplots of observed versus predicted concentrations (PRED) and individual concentrations (IPRED) were also created to check the goodness-of-fit in final model.

Validation

Model evaluation and validation are important components in determining model appropriateness.[13] Therefore, model qualification was conducted to assess the model capacity to predict the individual observations. The bootstrap method was applied as an internal validation approach to assess the stability of the final parameter estimates and to confirm the robustness of the final model. It was performed with the assistance of PsN (Perl-speak-NONMEM; http://psn.sourceforge.net). The final model was used to repeatedly fit the 1000 bootstrap data sets, and parameters were estimated for each data set.[25] The median and 95% confidence interval were calculated for each pharmacokinetic parameter.

Visual predictive check (VPC) as diagnostic plot was also assessed to confirm model performance. The final model was assessed by an inspection of standard diagnostic plots of observed concentration versus population and individual predicted concentration and separate plots of weighted residual versus model-predicted concentration.[26] After the population model was determined, clinical information of the validated group were input into the NONMEM program to estimate the individually predicted values of the serum concentrations and compared with measured values. The linear relation was also analyzed between the predicted and observed concentrations.

RESULTS

The demographic characteristics of the study population are summarized in Table 1. There were 106 patients in the study, with the mean age being 73 years, and mean dosage being 0.133 ± 0.053 mg/day. A total of 255 blood samples were analyzed, yielding a digoxin concentration of 0.866 ± 0.341 μg/L (mean ± SD).

Figure 1 shows the correlation between daily dose and serum concentration of digoxin. For a given daily dose, the steady-state serum concentration of digoxin has a wide range of level and the poor correlation (r = 0.136) implies that it is impossible to predict serum concentrations on the basis of the daily digoxin dose alone. Therefore, the authors applied population pharmacokinetic modeling using NONMEM, which is a better approach for predicting drug concentration and optimizing the dosage regimen of digoxin.

We determined values of sigma (σ^2), omega (ω^2), theta (θ) and error model in order to explain the best structural (base) model. The exponential error model was suitable to explain inter-individual variability and the additive error model was suitable to explain residual variability in Vd/F and CL/F. There were many indicators of the improvement of fit resulting from the addition of certain parameters to the model- including a decrease in the standard error of the estimates, reduction in variability, reduction in weighted residuals, uniformity of physiological plausibility, and the scatterplot of weighted residuals versus predicted concentrations. The base

model of Vd/F was markedly affected by CCR, weight, serum potassium, age, and cholesterol and the base model of CL/F was markedly affected by CCR, serum potassium (K), age, PIBW, TLC, and albumin. However, when these factors were stacked, Vd/F and CL/F were significantly affected by weight and the combination of CCR, K, age, PIBW. NONMEM analysis steps of the covariates are summarized in Table 2. The population estimates for Vd/F and CL/F were 735 L, 1.36 L/h, respectively. The inter-individual variability (CV) was 56.8% for Vd/F and 34.3% for CL/F. The residual variability (SD) between the observed and predicted concentrations was 0.225 μg/L. The final regression model is Ka = 1.63 (h^{-1}, fixed), $Vd/F = \theta_2 \times (weight/55)^{\theta 4}$ (L), $CL/F = \theta_3 \times (CCR/50)^{\theta 5} \times K^{\theta 6} \times \theta_7 \times (AGE/65) \times (PIBW/100)^{\theta 8}$ (L/h).

The observed versus population predicted concentrations (PRED) and individual predicted concentrations (IPRED) of final model were showed as scatterplot in Figure 2. The final model was improved, as the identity line of the scatterplot appeared together with a narrow gap and the number of points that were far from the identity line was reduced. Figure 3 shows weighted residual versus predicted concentration obtained from the base model was compared with the final model. In the scatterplot of the final model, the large positive residuals were cleared. These observations suggest that the resultant model fit the observed data well. Additionally, we assessed VPC to confirm model performance (Figure 4). Most of the observed

concentrations fall within the 90% predicted intervals obtained from the stimulated data represented by the shaded area.

The parameter estimates of the final model using the original data set, the median parameter estimates, and the 95% confidence intervals obtained from bootstrap replications with successful runs are shown in Table 3. The median parameter estimates were within 20% of those obtained with the original data set. The accuracy of the pharmacokinetic model was acceptable on the basis of the reasonably close agreement between corresponding pairs of bootstrap samples and the final model parameters.

Clinical information of the validation group is presented in Table 1. The individual values of digoxin steady-state serum concentration from the validation group had been predicted by the established final model. Correlation analysis showed a linear correlation between observations and predicted values ($y = 0.681x + 0.292$, $r = 0.743$, $p < 0.001$), indicating that the model may be helpful in clinical practice to predict digoxin serum concentration.

DISCUSSION

To our knowledge, this is the first study to identify the influence of nutritional and demographic variables on pharmacokinetics of digoxin in hospitalized Korean patients by using NONMEM. Estimates generated by NONMEM indicated that digoxin CL/F (L/h) was influenced by CCR (ml/min), serum potassium (mmol/L), age (years), and PIBW (%). The relative influence of each variable can be represented by the following equation: $CL/F = 1.36 \times (CCR/50)^{1.580} \times K^{0.835} \times 0.055 \times (AGE/65) \times (PIBW/100)^{0.403}$. Vd/F (L) can be represented by the following equation: $Vd/F = 735 \times (weight/55)^{0.902}$.

Digoxin exhibits a narrow therapeutic index and large inter/intra-patient variability in disposition, which requires that doses be carefully adjusted per an individual patient's needs, in order to minimize digoxin toxicity.[27] It is important to understand the effect of various clinical factors on the pharmacokinetics of digoxin. Both demographic factors and nutritional status considerably influences the absorption, plasma protein binding, distribution, biotransformation and excretion of drugs.[28, 29] Albumin, NRI, and TLC were not significantly associated with change in digoxin pharmacokinetic parameters in the present study. Malnutrition is a progressive condition and evaluation of an influence of malnutrition on drug pharmacokinetics is confounded by issues of time. These nutritional factors have been referred to as acute-phase state and are decreased in serum concentration in response to acute inflammation, liver and renal

function, hydration and blood loss.[5, 30] In comparison to population group, validation group shows significant difference in acute nutritional factors such as albumin and NRI. Because acute nutritional factors can be altered based on clinical signs and severity of disease, they are not suitable to explain the impact of the nutrition on digoxin PK in acute phase. Therefore, acute-phase nutritional factors have limitation in explaining to influence on pharmacokinetics of digoxin in hospitalized patients.

About half of the total body digoxin load is bound to skeletal muscle, whereas only 1% is in circulation.[29] When analyzed in tissue obtained intraoperatively and postmortem, a high amount of digoxin was found distributed in muscle, with lesser amounts in plasma and other body constituents.[31] Therefore, small changes in the fraction bound to skeletal muscle could profoundly affect the concentration of the drug in serum. The somatic protein status as represented the weight is equivalent to the skeletal muscle mass that declines in response to malnutrition or catabolic conditions.[32] We analyzed the effect of PIBW, as an indication of chronic nutritional status and change of patients. PIBW is an appropriate factor for use in investigation of the relationship between digoxin's CL/F and nutrition, because being chronically underweight has a substantial impact on digoxin's CL/F. PIBW may also indicate muscle wasting, an effect of muscle mass reduction, as well providing an accurate measurement of renal

function. Ferrara et al.[33] studied a model based on body composition and bioelectric impedance analysis (BIA) to predict digoxin kinetics in the elderly. Their findings indicated that digoxin levels, calculated via BIA, may be sufficiently reliable in the majority of patients, because exact plasma creatinine monitoring was predicted by measuring variability of muscle wasting. Asian populations are lean when compared with western population.[8] Also, Yoon et al.[34] studied the epidemic obesity in Asia, this showed the prevalence of overweight and obese adults between Korea and USA (27.4%:34% and 3.2%:30%, respectively).[35] This is also related to the fact that PIBW is the influence factor on digoxin pharmacokinetics in Korean.

The final regression model suggests that clearance of digoxin is associated by CCR. In other studies, decreases in the volume of distribution of digoxin in patients with renal impairment have been reported.[36] A study by Reuning et al.[37] suggested that possible explanations for the decrease in the volume of distribution of digoxin in cases of renal failure include: reduction of the tissue mass (*e.g.*, skeletal muscle), and decrease in digoxin binding to other organs than skeletal muscle.[38-40] However, Jogestrand and Ericsson[38] found that the ratio of the concentration of digoxin in biopsied skeletal muscle to its serum concentration did not differ significantly between patients with renal failure and subjects with normal renal function. Reduced body tissue mass due to chronic renal failure was evidently not an

important factor. In the present study, CCR also has not significant effect on the Vd/F of digoxin.

It is widely accepted that age influences digoxin distribution.[6] This is mainly because of the influence of lean body mass, which decreases by approximately 20% from the age of 20 years to the age of 70 years.[6] A loss of skeletal muscle is common in the elderly.[41] The volume of distribution of digoxin reduces with age, which may result in its higher serum concentrations. However, our study does not show an effect of age on Vd/F, and only shows covariation of CL/F with age, possibly due to the reduction of aging-associated glomerular filtration.

Several previous studies have suggested that congestive heart failure (CHF) is an important factor in digoxin clearance estimation.[13, 26] In adults, Sheiner et al.[9] found that digoxin clearance in patients with CHF was significantly lower than that in patients without CHF. In subsequent studies, it was reported that digoxin clearance was reduced by 19% and 11.8% in adults and infants with CHF, respectively.[13, 42] However, in the present study, no effect of CHF on CL/F of digoxin is apparent.

Some reports have suggested that when digoxin is taken orally with calcium-channel blockers (CCBs), such as verapamil and diltiazem, and spironolactone (SPI), the serum concentration of digoxin increases, potentially resulting in an increased risk of digoxin toxicity.[6, 11] However, in the present study, parallel treatment with

these drugs is not common and do not affect CL/F of digoxin.

Table 4 shows various population estimates and models of digoxin population pharmacokinetics. The differences apparent therein may be related to population sizes, the length of disease course or its severity, and the methods of population analysis. Further, 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.[44] It is possible that in patients not adhering to the data predicted by the model there may be alterations in digoxin handling due, for example, to P-gp polymorphism, a variable resulting in more than 30% variability in steady-state digoxin levels.[45] There are 50 single nucleotide polymorphism (SNPs) in the *MDR1* gene, and the exon 26 C3435T SNP is associated with a change in the oral absorption of digoxin.[45, 46] The distribution of C3435T polymorphism is significantly influenced by ethnicity. There is no study about genetic metabolic efficiency on digoxin serum concentration in Korea patients yet. However, there are other studies associated with MDR1 gene polymorphism presented MDR1 C3435T polymorphism in Korean. They showed C as the dominant allele.[47, 48] The causative molecular genetic mechanism of the effects of this polymorphism is unknown.[45] C3435T polymorphism in Korean helps explaining the observed differences with other studies, but the exact causes of the above CL/F differences require further exploration.

Conventional compartmental analysis of digoxin levels has reported a two-compartment model in healthy adults.[49] However, population analysis of sparse data has found a one-compartment model adequate for explaining the pharmacokinetics of digoxin.[9] Because of the limited sampling strategy used in the TDM laboratory, this study also decided the performance of population pharmacokinetic analysis in the light of a multiple-trough screening approach to digoxin concentration. Furthermore, one-compartment model was easy application for TDM service in the clinical practice.

No models of digoxin pharmacokinetics have suggested a relationship with nutritional status. Our study may explain the effect of chronic nutritional status on the pharmacokinetics of digoxin. This also explains the reason for lower mean digoxin dosage and concentration in Korean population. Multiple factors should still be considered with regard to digoxin dosage adjustment, such as other drug interactions, effects of absorption in gastrointestinal disease, and other intensive care environments exist. Also, MDR1 C3435T polymorphism in Korean needs to be considered in order to prove the effect on digoxin pharmacokinetics more precisely. In addition to monitoring of digoxin concentration, each patient's clinical status and drug toxicity should also be monitored. Its pharmacologic and clinical effects correlate not with serum digoxin concentration but with those in the peripheral nonserum compartment.[7] Our study did not analyze

the peripheral concentration. Thus, the use of this model in routine TDM requires that certain conditions be met that are consistent with the conditions of the sub-populations in the present study. The authors advocate further studies to elucidate the effects of various nutritional parameters on digoxin pharmacokinetics and to validate with larger validation population.

CONCLUSION

Using NONMEM, estimates of digoxin population pharmacokinetics were derived from a population of hospitalized Korean patients for the first time. Renal function, serum potassium, age, and PIBW were identified as significant covariates for digoxin CL/F. The present study established important sources of variability in digoxin pharmacokinetics and showed the relationship between pharmacokinetic parameters and nutritional status in hospitalized Korean patients.

TABLES

Table 1. Demographic data of the patients

Characteristics	Population group[a]	Validation group	*P* value
Number of patients	106	16	
Number of samples	255	43	
Samples per patients (mean, range)	2.40 (1-10)	2.68 (1-8)	
Digoxin dose (mg/day)	0.133 ± 0.053	0.113 ± 0.066	0.057
Serum digoxin concentration (μg/L)	0.866 ± 0.341	0.693 ± 0.380	0.003
Gender (n(%))			
Male	58 (54.7)	8 (50.0)	
Female	48 (45.3)	8 (50.0)	
Age (years)	72.8 ± 13.0	70.1 ± 12.5	0.252
Weight (kg)	57.3 ± 12.0	54.2 ± 12.9	0.113
Percent of ideal body weight (%)	99.7 ± 17.0	103.0 ± 21.8	0.328
Indications (n(%))			
Artrial fibrilation	55 (51.9)	13 (81.2)	
Heart failure	12 (11.3)	2 (12.5)	
Others[b]	39 (36.8)	1 (6.3)	
Concomitant medications (n(%))			
Calcium-channel blockers	19 (17.9)	3 (18.7)	
Spironolactone	3 (2.8)	0 (0)	
Creatinine clearance[c] (ml/min)	51.5 ± 24.6	42.9 ± 27.6	0.065
Serum potassium (mmol/L)	4.28 ± 0.57	4.05 ± 0.57	0.023
Serum albumin (g/dl)	3.41 ± 0.54	2.87 ± 0.45	< 0.001
Serum cholesterol (mg/dl)	148.3 ± 40.5	126.1 ± 34.8	0.002
TLC[d] (cells/mm^3)	1536.4 ± 921.4	1159.9 ± 517.1	0.013
NRI[e]	92.5 ± 8.4	72.9 ± 6.8	< 0.001

[a] Mean ± standard deviation unless otherwise stated

[b] Cor-pulmonale, myocardial infarction, ventricular septal defect, post-operation

[c] Estimating creatinine clearance (CL_{CR}) by the Cockcroft and Gault method

[d] Total lymphocyte count = [white blood cell × % lymphocyte]/ 100

[e]Nutritional risk index = [1.519 × serum albumin(mg/dl)] + 41.7 × [present /usual body weight(kg)]

Table 2. Summary of the covariate model results by forward and backward stepwise

Model	OFV	ΔOFV	p-value
Basic model	-250.134		
$Vd/F = 588*(CCR/50)^{0.845}*(ABW/60)^{0.686}$ $CL/F = 3.49*(CCR/50)^{0.678}$	-282.084	31.95	<0.001
$Vd/F = 535*(CCR/50)^{0.922}*(ABW/60)^{0.520}$ $CL/F = 0.139*(CCR/50)^{0.737}*PIBW^{0.700}$	-286.566	36.43	<0.001
$Vd/F = 607*(CCR/50)^{0.640}*(ABW/60)^{0.840}$ $CL/F = 0.206*(CCR/50)^{1.190}*K^{0.674}$	-334.887	84.75	<0.001
$Vd/F = 822*(ABW/60)^{0.975}$ $CL/F = 4.98*(CCR/50)^{1.608}*K^{0.861}*0.013*(AGE/65)$	-350.485	100.35	<0.001
$Vd/F = 735*(ABW/60)^{0.902}$ $CL/F = 1.36*(CCR/50)^{1.580}*K^{0.835}*0.055*(AGE/65)$ $*(PIBW/100)^{0.403}$	-353.167	103.03	<0.001

Vd/F, CL/F = volume of distribution, clearance, where F is bioavailability; OFV = objective function value; ΔOFV = decrease in OFV; CCR = creatinine clearance; ABW = actual body weight; PIBW = percent of ideal body weight; K = serum potassium.

Table 3. Population pharmacokinetic parameters from final model and bootstrap validation

Parameter	Final Model	Bootstrap			Difference
	Estimate (%RSE)	SE	Median	95% CI	(%)
Pharmacokinetic parameters					
Ka (θ_1)	1.63 (fixed)				
Vd/F (θ_2)	735 (12.91)	94.9	724	453,919	-1.5
Effect of ABW (θ_4)	0.902 (54.21)	0.489	0.917	0.138,1.920	1.6
CL/F (θ_3)	1.36 (23.68)	0.322	1.410	0.836,2.278	3.5
Effect of CCR (θ_5)	1.580 (34.68)	0.548	1.590	0.521,2.310	0.6
Effect of K (θ_6)	0.835 (21.44)	0.179	0.815	0.550,1.050	-2.4
Effect of AGE (θ_7)	0.055 (51.74)	0.028	0.056	0.033,0.092	3.1
Effect of PIBW (θ_8)	0.403 (90.82)	0.366	0.509	0.030,0.981	20.7
Interindividual variability (%)					
Vd/F ($\omega_{Vd/F}$)	56.83 (37.50)	33.3	59.2	21.7,91.0	3.9
CL/F ($\omega_{CL/F}$)	34.26 (24.32)	16.6	33.6	22.7,40.2	-2.0
Residual variability (SD, μg/L)					
Additive error (σ)	0.225	0.091	0.218	0.172,0.255	-3.2

Ka (hr^{-1}) = absorption rate constant; Vd/F (L), CL/F (L/hr) = volume of distribution, clearance, where F is bioavailability; CCR = creatinine clearance; ABW = actual body weight; PIBW = percent of ideal body weight; K = serum potassium; %RSE = percent of relative standard error (standard error/estimate × 100); SE = standard error; CI = 2.5^{th} and 97.5^{th} percentiles of bootstrap distributing of parameter estimates; Difference (%) = (bootstrap median value – estimate from final model)/bootstrap median value × 100.

Table 4. Previously documented methods for estimating digoxin population pharmacokinetic parameters in adults

Sheiner et al.; 1-compartment model[9]

CL (L/h) = 0.06 × CCR + 0.05 × TBW for CHF absent

CL (L/h) = 0.053 × CCR + 0.02 ×TBW for CHF present

Vd (L) = 3.12 × CCR + 3.84 × TBW

F = 0.6

Nagaraja et al.; 1-compartment model[43]

CL (L/h) = 0.053 × CCR + 2.06

Vd (L) = 6.63 × CCR + 10.82 × TBW -343

Ka (h^{-1}) = 0.546 – 0.103 × drug – 0.092 × sex

Yukawa et al.; 2-compartment model[11]

CL (L/h) = (0.036 × TBW + 0.112 × CCR) × 0.77^{SPI} × 0.784^{CCB}

V_1 = 1.83 L/kg, V_2 = 22.6 L/kg, Q = 0.629 L/kg

Xiao-dan et al.; 1-compartment model[23]

CL/F (L/h) = 5.9 × [1- 0.412×SPI] × [1- 0.0101×(TBW-62.9)]
× [1- 0.0012×(CCR-126.8)]

Yukawa et al.; 1-compartment model[13]

CL/F (L/h) = 0.588 × $TBW^{0.189}$ × $SCr^{-0.163}$ × $(AGE/65)^{-0.152}$ × 0.957^{CCB} × 0.941^{CHF}
× 0.965^{sex} × $C_{trough}^{-0.180}$

CCR = creatinine clearance; TBW = total body weight; CHF = 1 for presence of congestive heart failure; drug = 0 for no, 1 for yes; sex = 0 for male, 1 for female; SPI = 1 for combination with spironolactone; CCB = 1 for combination with calcium-channel blockers; SCr = serum creatinine; C_{trough} = elderly clearance factor

FIGURES

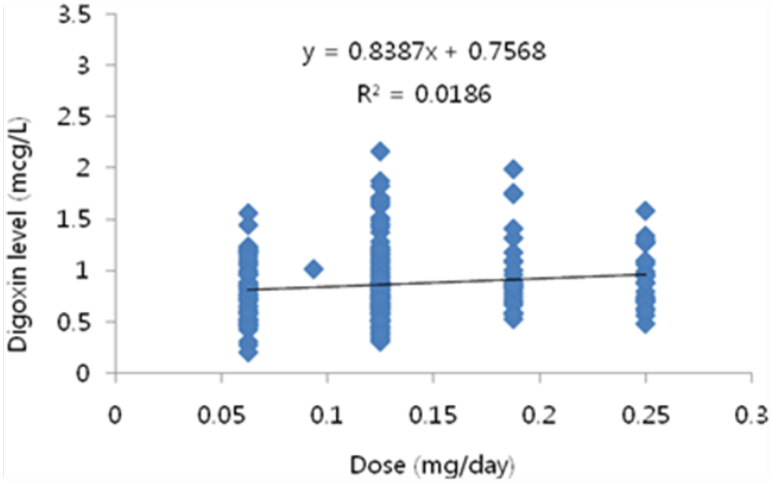


Figure 1. Correlation between daily dose and serum concentration of digoxin.

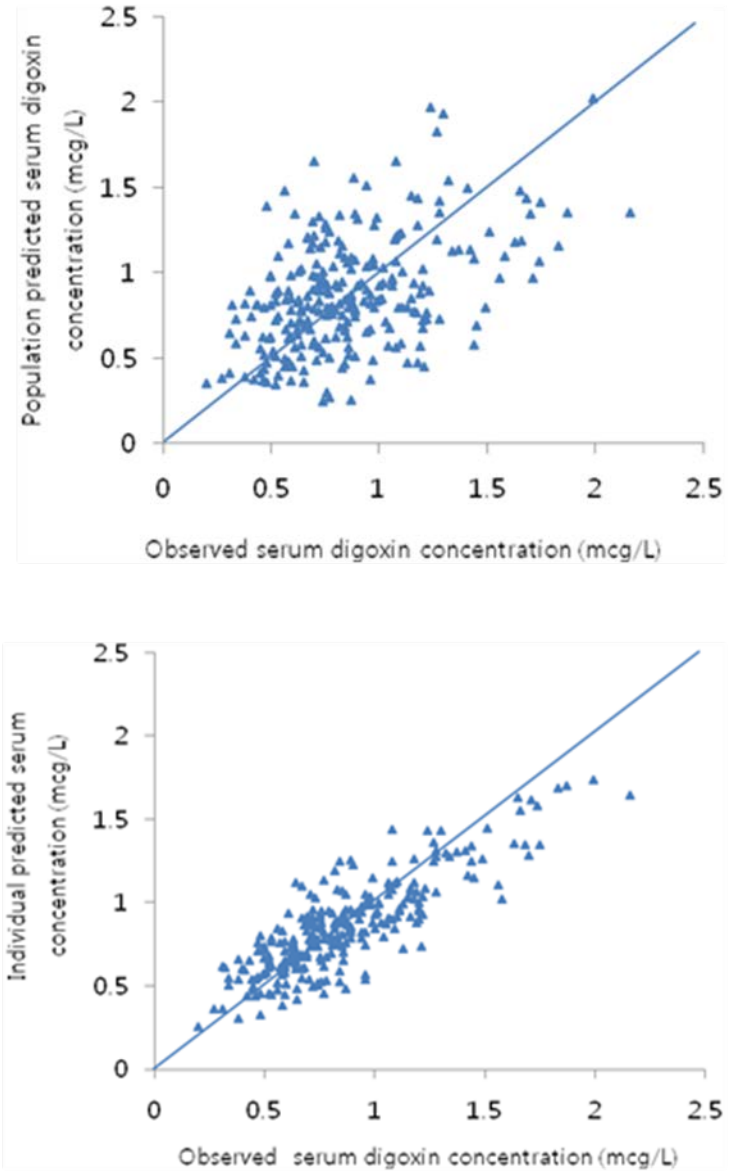
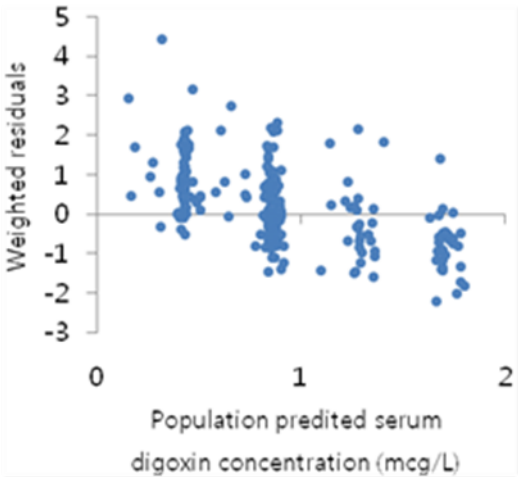


Figure 2. The observed versus population predicted concentrations (PRED)-upper and individual predicted concentrations (IPRED)-lower of final model, where solid lines represent line of identity.



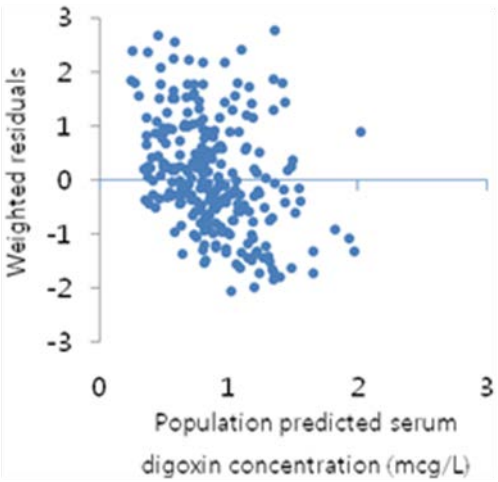


Figure 3. Comparison of scatterplot of weight residuals versus predicted concentration obtained from base model (upper) and final model (lower).

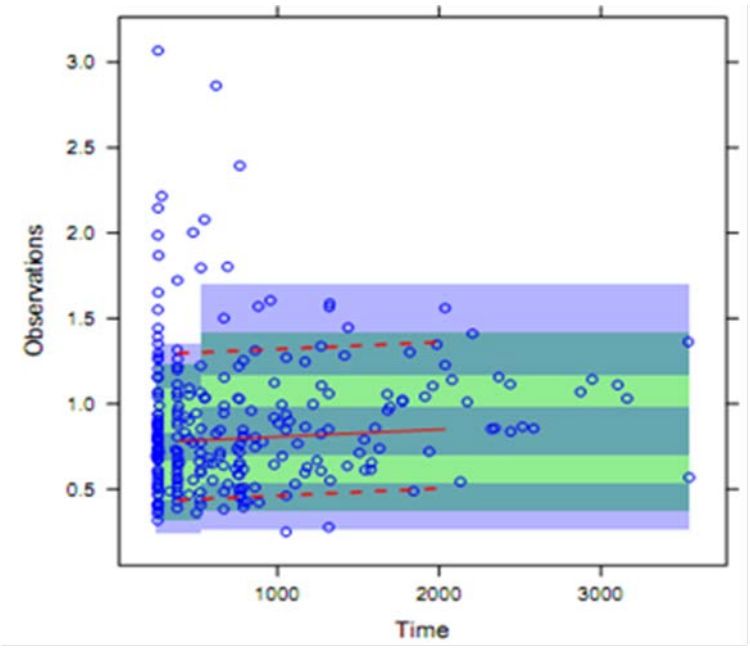


Figure 4. Visual Predictive Check of final model.

The solid red line represents the median observed concentration, and the semitransparent dark-green field represents a 95% confidence interval for the median. The observed 5% and 95% percentiles are presented with dashed red lines, and the 95% confidence intervals for the corresponding model predicted percentiles are shown as semitransparent dark-green. The observed concentrations are presented by the blue circles.

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APPENDIX

The Effect of Nutritional Factors on Volume of Distribution of Digoxin in Korean Adult Patients

;A Population Pharmacokinetics Analysis Using Nonlinear Mixed-Effect Modeling

Soo An Choi, B.Sc.Phm., BCOP, BCNSP, Wan Gyoon Shin, Pharm.D., Ph.D

Abstract

Optimal use of digoxin in the malnourished populations requires information about the drug's pharmacokinetics and the influence of various factors on drug's disposition. However, because of sampling restrictions, it are not conducted pharmacokinetic studies of digoxin according to various nutritional status and in malnourished patients. The main goal of this study is to estimate and identify influence of nutritional status on digoxin pharmacokinetic parameters in Korean patients. Data sources (287 observations) were retrospectively collected from 108 patients receiving oral digoxin in Seoul National University Bundang Hospital between January, 2008 and December, 2009, using routine therapeutic drug monitoring data. The pharmacokinetics of digoxin was analyzed with a one-compartment open pharmacokinetic model using Nonlinear Mixed Effects Modeling (NONMEM). We evaluated the degree of malnutrition and nutritional risk more specifically by assuming there is a relationship between digoxin's Vd and skeletal muscle reduction. Estimates generated by NONMEM indicated

that the volume of distribution (Vd) of digoxin was influenced by the nutritional factors such as albumin, NRI (nutritional risk index). These influences could be modelled by equation CL = 5960*(creatinine clearance/59) $^{0.741}$, Vd = 688000*e $^{0.0759 * albumin}$. The interindividual and intraindividual variability for Vd were 49.5%, 23.74% as estimated coefficient variation. The present study established important sources of variability in digoxin pharmacokinetics. Clinical application of this model may help calculate digoxin dose requirements according to nutritional status affecting digoxin volume of distribution, and it will also be useful for therapeutic drug monitoring.

Introduction

Digoxin is one of commonly prescribed cardiac medications as an integral part of the treatment for heart failure and atrial fibrillation.[1] However, because digoxin has a narrow therapeutic index and inter-/intra-individual variability in its pharmacokinetics[1], it is a difficult drug to administer. Digoxin toxicity is well recognized.[2,3] Although the incidence has been decreased to 2-5% in recent studies,[2,4] digoxin has been considered still as a common cause for patient's emergency room visits and long-term hospital stay.[5]

Because of the lack of a clear relationship between the digoxin dose and the desired effect, serum digoxin level is the most widely used parameter in routine therapeutic drug monitoring.[6] It improves patient care and contributes to decrease the suspected digoxin toxicity.[7] It is therefore important to understand how the pharmacokinetics of digoxin may be altered in the hospitalized patients.

Malnutrition is highly prevalent in hospitalized patients and related to increased morbidity, mortality, length of hospital stay and costs.[8,9] We clinically experienced that pharmacokinetic parameters and concentration of digoxin were unpredictable in malnourished or serious ill patients than other hospitalized patients. The overall apparent distribution of digoxin to various organs and tissues appears to be largely related to the body distribution.[1,10] Skeletal muscle-bound digoxin appears to account for about 50% of apparent digoxin in the body. Accordingly, small variations in the occupancy of digitalis binding sites in skeletal muscle can influence the serum

concentrations available for binding to the heart. Also, the somatic protein status as represented the weight is equivalent to the skeletal muscle mass which declines in response to malnutrition or catabolic conditions.[11] We have now examined the pharmacokinetics of digoxin with nutritional factors and how the degree of malnutrition or nutritional risk may affect the drug's pharmacokinetics more specifically by assuming there is a relationship between volume of distribution (Vd) of digoxin and skeletal muscle reduction. Previously, the population pharmacokinetics of digoxin were examined using the computer program NONMEM, developed by Beal and Sheiner.[12] Various race, old and pediatric group were targeted in several studies for explaining important source of variability.[13-15] However, at that time, no attempt had been made to link the relationships between individual digoxin requirements and nutritional status. Therefore, the main goal of this study was to estimate and identify the influence of nutritional factors on pharmacokinetic parameters in Korean adult patients.

Methods

Data Sources

Data sources (287 observations) were retrospectively collected from 108 patients in Seoul National University Bundang Hospital (a 900-bed, tertiary care academic medical center in South Korea) between January, 2008 and December, 2009, who were administered a tablet form of digoxin (Digosin;

CJ Pharmaceutical Co. Ltd, Korea). The patients were all hospitalized and under the supervision of medical and nursing staff such that the administration of treatment and compliance were standardized. We reconfirmed, from electronic medical records, basic information on the patients and pathologies from blood samples. The collected data were (1) demographic data; age, gender, total body weight and height, (2) clinical data; indication for digoxin, laboratory data of routine care (creatinine clearance, serum potassium, WBC; white blood cell, lymphocyte) (3) medication history; dosage regimen of digoxin, concomitant medications, date and time of administration (4) nutritional data; serum albumin, cholesterol, percentage of ideal body weight (PIBW), total lymphocyte count (TLC), nutritional risk index (NRI).

Albumin has been used to assess nutritional status, specifically protein nutriture. Despite considerable published information to the contrary, albumin has been assumed to reflect a reservoir of protein in conditions of adequate nutrition and a deficit of protein in conditions of inadequate nutrition. Decreased albumin levels correlate with poor clinical outcomes, increased length of stay, increased risk for complication, and death. Anthropometric measurements such as height and weight are the most useful way to assess changes in nutritional status of an individual in the clinical setting.[16] Especially, weight is one of the best parameters for evaluating a change in nutritional status when change from usual weight of an individual is quantified. The NRI, used in the Veterans Administration Cooperative Group study of perioperative parenteral nutrition, stratified operative morbidity and mortality using serum albumin and the ratio of current weight

to usual weight.[17,18] Comparison of a patient's current weight during the course of admission to their usual weight before admission is generally more useful than comparing current weight to an "ideal" or desirable weight.[16]

NRI= [1.519×albumin(mg/dl)] + [41.7×present/usual body weight(kg)]

NRI score of > 100 indicates no risk; 97.5 to 100, mild risk; 83.5 to 97.5, moderate risk; 83.5, severe risk. Derivation of NRI is based on serum albumin and weight change, so NRI is a valid measure of health status and contains a nutritional dimension.[18] Malnutrition leads to decline in immune function. TLC is calculated by multiplying the white blood cell count by percentage of lymphocytes and one of the clinical measures of immune function that have been used as nutritional screening or assessment parameters.[9] Thus, the nutritional data chosen in present study intend to reflect the various nutritional status, severity of illness and risk of malnutrition.

There were excluded patients who have any major disorders of the hepatic or gastrointestinal or hematopoietic systems, or with fluctuating or rapidly deteriorating renal function and exhibit interactions with digoxin (for example, amiodarone, quinidine, cholestyramine or phenytoin). This is to eliminate the effects of the non-renal excretion, malabsorption of digoxin and misinterpretation of nutritional factor such as TLC. The samples were concentrations for therapeutic drug monitoring measured as one trough level. It was based on the concentration of the steady state (chronic user or after 10 doses at least) that has completed distribution in order to ensure the measurement accuracy. The present study was approved by the IRB (Institutional Review Board of the Seoul National University Bundang

Hospital) about the data collections and analysis. (2010. 10.12 B-1009-112-107)

The measurement of digoxin in serum was carried out by a TDx digoxin assay kit from Abbot Laboratories for fluorescence polarization immunoassay (FPIA). The minimum detectable concentration for digoxin was 0.2 ng/ml, and the coefficients of variation both between runs and within runs were less than 10% for concentrations between 0.5 and 5.0 ng/ml.

Population Pharmacokinetic Model

Population pharmacokinetic modeling was performed by using NONMEM program (Version VI) developed by Sheiner and Beal. Pharmacokinetic parameters were estimated by using the first-order estimation method with the POSTHOC option. Because of the sparse nature of the data, a one-compartment pharmacokinetic model with using the subroutines ADVAN2 and TRANS2 (first-order absorption) was performed to fit the data.[15] Data was parameterized in terms of clearance (CL), volume of distribution (Vd), and absorption rate constant (Ka). Because each patient contributed to only one data point and it was impossible to build an absorption model by the limited data, the model was simplified by fixing Ka to 0.7 h^{-1} based on literature values.[19]

The initial program run computed an overall population analysis of pharmacokinetic parameters and minimum value of the objective function. The interindividual variability was best explained by exponential error model according to the following equations:

CL_{ij} = TVCL*EXP(η_{iCL})

Vd_{ij} = TVV*EXP(η_{iVd})

where CL_{ij} is the jth true CL for ith individual, Vd_{ij} is the jth true Vd for ith individual, TVCL is typical value of CL, TVV is typical value of Vd predicted by a regression model, and η_{iCL}, η_{iVd} are random variable distributed with zero means and respective variance of ω^2_{CL} and ω^2_{Vd} respectively. The residual (error) variability was also best explained by additive error model and can be expressed as follows:

$C_{ij} = C_{predij} + \varepsilon_{ij}$

where C_{ij} is the jth observed concentration for the ith individual, C_{predij} is the digoxin concentration predicted by the pharmacokinetic model, and ε_{ij} is a difference value between C_{ij} and C_{predij} and randomly distributed term of zero mean and variance σ^2 which represented the residual intraindividual variability. This type of error is caused by influences such as assay variability, misspecification of the suggested pharmacokinetic model, and timing errors in drug administration or blood sampling.

Data Analysis Procedure

In the first step, the data were used to develop the basic regression model (without covariate) for fixed effect model. Literature ranges were used for initial estimates of digoxin pharmacokinetic parameters. Then each covariate was added into the basic model and the change in objective function value (OFV) was considered for candidate covariate (preliminary screening phase). Next step, the candidate covariate was added to the basic regression model,

in turn, and the apparent influence of covariate on digoxin disposition was observed by the changing of the OFV (forward stepwise fashion). Covariates screened were age, gender, weight, creatinine clearance (CCR), serum potassium, albumin, cholesterol, PIBW, TLC, NRI. The difference between OFVs for a model containing n covariates and that containing n-1 covariates by more than 10.83 ($\chi 2$ distribution, $p< 0.001$; 1 degree of freedom) was considered to be significant and added to the model. The other factors were added cumulatively to the reduction in OFV from the preliminary screening phase until there was no further reduction in the OFV. 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 (RSE%, relative standard error).

Validation

Model evaluation and validation are important components in determining model appropriateness. Therefore, model qualification was conducted to assess the model capacity to predict the individual observations. A scatter distribution of the observed concentration values against the predicted values was plotted. The base structural model and final model were validated by comparison with the data from validation data set. The bootstrap method was applied as an internal validation approach to assess the stability of the final parameter estimates and to confirm the robustness of the final model. It was performed with the assistance of PSN (Perl-Speak-NONMEM; http://psn.sourceforge.net). The final model was used to repeatedly fit the

1000 bootstrap data sets, and parameters were estimated for each data set. The median and 95% confidence interval were calculated for each pharmacokinetic parameter.

Results

The demographic data of the patients are presented in Table 1. The number of patient was 108 and the mean age was 73 years, mean dosage was 0.135 ± 0.054 (mg/day). The number of old age patients, defined as older than 65 years old, was 89. Out of 108, 36 patients had heart failure and 56 of them had atrial fibrillation. A total of 287 blood samples were provided, with a mean ± SD digoxin concentration of 0.859 ± 0.384 mcg/L. Nutritional status of study subjects was evenly distributed, based on data of serum albumin, cholesterol, PIBW, NRI.

Figure 1 shows the correlation between daily dose and serum concentration of digoxin. For a given daily dose, the steady-state serum concentration of digoxin has a wide range of level and the poor correlation (R=0.1315) implies that it is impossible to predict serum concentrations on the basis of the daily digoxin dose alone. Therefore, we decided to apply the population pharmacokinetic modeling using NONMEM, which is a better approach to predict drug concentration and optimize dosage regimen of digoxin.

We determined values of sigma, theta and error model in order to explain the best structural (base) model. We chose a statistical regression model that could significantly reduce the objective function value (OFV) through the

process of trial and error. Table 2 presents NONMEM output of base model. The exponential error model was suitable to explain inter-individual variability and the additive error model was suitable to explain residual variability in Vd and CL. The estimated coefficient of variation was 40% and 52.2% in Vd and CL respectively.

As a preliminary analysis, we utilized covariates modeling that is presented in Table 3. The model was constructed by including covariates such as age, creatinine clearance (CCR), weight, percentage of ideal body weight, albumin, NRI, TLC, cholesterol, serum potassium, sex in the base model. It was also analyzed the relationship between those covariate and the pharmacokinetic parameters. We found out that estimate of CL was improved dramatically by inserting CCR in centered power model. Vd was improved significantly with only CCR though OFV was minimized with albumin, NRI, creatinine clearance in power, proportional and exponential model (table 3). Other covariates failed to reduce significant OFV or estimate the standard error in modeling of Vd and CL.

Table 4 shows the combination modeling of Vd and CL by continous variable analysis. We inserted NRI, albumin, CCR on Vd and CCR on CL and OFV was reduced by more than 10.83 (χ^2, $p<0.001$, 1 degree of freedom) from the base model. Parameter estimation was also optimized from FO to FOCE (first-order conditional estimation). Compared to the base model, the albumin, NRI, creatinine clearance turned out to be significant factors to explain the variability of digoxin pharmacokinetics. However, both albumin and NRI didn't reduce RSE of Vd as much as we expected. The reason was that this study didn't only include full pharmacokinetic data but also used

clinical therapeutic drug monitoring data. Also, theta value of NRI was beyond the scope of acceptable clinical range. Creatinine clearance (CCR) reduced RSE of Vd and CL in comparison with the base model and obtained the reliability. However, CCR's result also had limitations to explain the Vd and CL at the same time as a single factor because of the correlation in Vd and CL (correlation matrix of estimate = −0.0319) as showed on NONMEM results. Therefore, the relationship between nutritional covariates and volume of distribution was suitable for being described by only albumin in the present study with the full regression of the following model:

$$Vd\ (ml) = 688000 * e^{0.0759 * albumin}$$

$$CL\ (ml/min) = 5960 * (CCR/59)^{0.741}$$

Our model presented with albumin did not identify relationship between degree of malnutrition and Vd of digoxin, so we reanalyzed this model by categorical variables (Table 5). By this analysis, PIBW, age and sex were found to be covariates that have a significant effect. However, compared with the base model, RSE was not improved as well as showing correlation so that those were not chosen for final covariates. The amount of uncertainty (RSE%) associated with estimation of the coefficient of this model (covariate; albumin): θ_2, θ_3 were 11.24%, 5.15%, respectively and for interindividual variability of Vd and CL were 45.74% and 23.56%, respectively. Vd tended to be decreased as albumin decrease. This shows that digoxin's Vd is affected by nutritional status and severity of illness. Thereby it is more suitable to explain digoxin's Vd as categorized albumin level reflects degree of malnutrition rather than albumin value. As NRI decreases (<97.5), it also tended to have an influence on Vd. This shows that

digoxin's Vd is affected by nutritional risk. In other words, it is showed that digoxin's Vd is affected by the risk of malnutrition and severity of malnutrition and illness, which are expressed as NRI and albumin. The relationship between degree of malnutrition (albumin), nutritional risk (NRI) and Vd was described by the full regression of the following models:

Vd (ml) = 788000*(EXP(0.019)*B))*(EXP(0.106)*C))*(EXP(0.219)*D))

CL (ml/min) = 5790*(CCR/59)** $^{0.739}$

Vd (ml) =

832000*(EXP(-0.265)*B))*(EXP(0.036)*C))*(EXP(0.643)*D))*(EXP(0.02)*E))

CL (ml/min) = 5750*(CCR/59)** $^{0.710}$

The bootstrap validation is performed as the determination of the stability and the evaluation of the performance of model. A total 1000 bootstrap samples was generated by repeated random sampling from the original data set. The final pharmacokinetic model was fitted repeatedly to the 1000 bootstrapped samples. The parameter estimates of the final model using the original data set and the median parameter estimates and 95% confidence intervals obtained from bootstrap replications with successful runs (both estimation and covariate step were successfully converged) are shown in Table 6. The 95% confidence interval from bootstrap included the parameter values of the final model. The accuracy of pharmacokinetic model was acceptable according to the reasonably close agreement between corresponding pairs of bootstrap and final model parameters.

The diagnostic plots of predicted versus observed concentrations indicated adequacy of the derived NONMEM model. Scatterplot between pairs of

measured concentration and predicted concentration obtained from base model (without covariate) was compared with final model (Figure 2). The final model is proven to be improved as the scatter plot of the identity line appears together with the narrow gap and scattered points that used to be far from the identity line have been reduced. Figure 3 shows weighted residual versus predicted concentration obtained from the base model was compared with the final model. The scatterplot of the final model indicated an improvement in much closer to the line of identity. This suggests that the resultant model fits the observed data well.

Discussion

This study was the first to identify the relationship between nutritional factors such as albumin, NRI and volume of distribution of digoxin in Korean patients with NONMEM.

Digoxin exhibits a narrow therapeutic index and large inter/intra-patient variability in the disposition, which requires that the doses be carefully adjusted to an individual patient's needs for minimizing digoxin toxicity. It would be helpful to understand the effect of various clinical factors on the pharmacokinetics of digoxin. These can be assessed by the population pharmacokinetic analysis of digoxin. The demographic factors are critical factors to the impacts on pharmacokinetic parameters of digoxin. Especially, nutritional status including malnutrition considerably influence on the absorption, plasma protein binding, distribution, biotransformation and

excretion of drugs. Generally, the major pathophysiological changes in malnutrition related to drug disposition are alterations of drug-protein binding.[20] These were focused on measuring various proteins quantitatively. The binding of digoxin to plasma proteins is independent of concentration over a wide range and only 20 to 25% of digoxin is bound to plasma proteins.[21] Albumin is important binding protein. Among the various nutritional parameters proposed, serum albumin is a good marker of nutritional status and visceral protein stores.[22] Therefore, we analyzed in different perspectives with albumin, not as a drug-binding protein but a nutritional factor. Albumin was the significant covariate of Vd in the final model and was proven to have an impact according to degree of malnutrition through categorical variables analysis. The estimated effect of albumin is 0.019 (if albumin < 2.8 mg/dl, B=1, C,D=0), 0.106 (if 2.8-3.5 mg/dl, C=1, B,D=0), 0.219 (if > 3.5 mg/dl, D=1, B,C=0) and this was expressed as the exponential value on Vd of digoxin. We came into conclusion that digoxin's Vd was reduced more at the lower level of albumin with poor nutritional status and serious illness.

About half of the total body digoxin load is bound to skeletal muscle, whereas only 1% is in the circulation.[21] Although the concentration of digoxin in skeletal muscle is low compared with myocardial tissue, it is the single largest pool in the body because of the total body skeletal muscle mass.[23] The binding capacity of the skeletal muscle pool is 52-fold higher than that of the heart ventricular muscle pool. When analyzed in tissue obtained intraoperatively and at postmortem, digoxin is highly distributed into muscle, with lesser amounts in plasma & other body constituents.[23] Therefore, small

changes in the fraction bound to skeletal muscle could profoundly affect the concentration of the drug in serum. The somatic protein status as represented the weight is equivalent to the skeletal muscle mass which declines in response to malnutrition or catabolic conditions.[11] As assumed in our study, if there were equal pattern of distribution, shortage weight in skeletal muscle tissue would result in the decline of digoxin's distribution space. Therefore, we undertook an analysis of PIBW (percent of ideal body weight), NRI (Nutrition Risk Index) effects, it contained influences the degree and change of weight on Vd of digoxin. If NRI is less than 97.5, which identifies moderate or major nutritional risk, it has more influence on Vd (Table 5). The estimated effect of NRI expressed as the exponential value was -0.265 (NRI < 83.5), 0.036 (NRI < 83.5-97.5) and this shows that digoxin's Vd is affected by the risk of malnutrition. In this study, we couldn't find the impact of weight that is expressed as PIBW, but this resulted from the fact that there were no differences in nutritional status due to the characteristics of our patient group. Thereby it is more appropriate to explain the relationship between digoxin's Vd and nutritional factors that reflect severity of illness rather than weight or PIBW itself.

Digoxin is excreted predominantly in the urine as an unchanged drug and eliminated only small amount by hepatic metabolism. Principal elimination (57-80%) of digoxin takes place by renal excretion,[24] hence renal function of a patient reflected by the creatinine clearance (CCR) plays a major role in determining the clearance of digoxin. At present study, multiple linear regressions using all the potential covariates showed that CL significantly correlated with creatinine clearance ($CCR_{)}$. The final regression model

suggested that pharmacokinetic parameters of digoxin were influenced by creatinine clearance. In other studies, decrease in volume of distribution of digoxin in the case of patients with renal impairment has been reported.[1,25] Study by Reuning et al suggested possible explanations of the decrease in the volume of distribution of digoxin in renal failure are: (1) reduction of the tissue mass (*e.g.* skeletal muscle), (2) reduced digoxin binding to other organs than skeletal muscle.[26-29] However, Jogestrand and Ericsson found that the ratio of biopsied skeletal muscle digoxin concentration to serum concentration was not significantly different in patients with renal failure than in subjects with normal renal function.[27] A reduced tissue mass (e.g., skeletal muscle) because of chronic renal failure also did not seem to be an important factor. Renal dysfunction may also cause decreased binding of digoxin to tissues.[30] But, our study showed that it was the decreased binding capacity of digoxin by skeletal muscle reduction, as represented poor nutritional status (albumin) and increased nutritional risk (NRI), that explained the apparent reduction of digoxin's Vd regardless of renal function. With increasing aging, lean body mass tends to decrease, adipose tissue tends to increase, although overall total body weight tends to decrease. It is generally known that age influences digoxin distribution. This is mainly in relation to lean body mass, which decreases by approximately 20% from the ages of 20 to 70 years.[10] A loss of skeletal muscle is common in older persons.[30] The volume of distribution for digoxin reduces with age and possibly results in higher serum concentrations. This could also suggest another basis in explaining the effect of reduced skeletal muscle mass on the Vd of digoxin. Subjects of our study included many older people, but we

didn't find out any significant effect of age on the pharmacokinetic parameters of digoxin by demographic characteristic compromised of their good nutritional status. In addition to, we could not choose an age as covariate in categorical analysis by observed the correlation. Hence, further studies are necessary to conclusively determine the effects of age on pharmacokinetic parameters of digoxin, ideally containing various subgroup age.

Conventional compartmental analysis of digoxin levels has reported a two-compartment model in healthy adults.[24] However, population analysis of sparse data has found a one-compartment model adequate for explaining the pharmacokinetics of digoxin.[12] Because of the limited sampling strategy that we used in the therapeutic drug-monitoring laboratory, this study also decided the performance of population pharmacokinetic analysis in the light of a single-trough screening to digoxin concentration. Furthermore, one-compartment model was easy application for therapeutic drug monitoring service in the clinical practice. Population analysis of digoxin in other studies done using NONMEM.[13-15] The observed differences might be due to different disease severity, population size, ethnic differences, age and/or the method of population analysis. Population pharmacokinetics of digoxin has been reported in a Korean patient population (n=15).[31] However, this study used a nonparametric expectation procedure, for the population modeling. In this method, no distribution model was assumed for interpatient variability and the error model.

Multiple factors should be considered for digoxin dosage adjustment, as other drug interactions, effects of absorption in gastrointestinal disease, and

other intensive care environments exist. Therefore, the sum of the effects of these covariates on digoxin cannot be predictable. Not only monitoring of digoxin concentration but also patient's clinical status and drug toxicity should be accomplished. Pharmacokinetic parameters of drug tend to be altered especially among the special populations such as the pediatric group, advanced age and physiologic change of malnutrition. The present study showed not only that digoxin's Vd is related to nutritional factors such as albumin and NRI but also Vd is affected by the degree of those factors represented the severity of illness and reduction of lean body mass. As proved in the study, it is well-known that digoxin's PK is affected by malnutrition and severity of illness. However, it is meaningful enough to make sense that this study analyzed the degree of malnutrition and the degree of nutritional risk more specifically by assuming there is a relationship between digoxin's Vd and skeletal muscle reduction.

Conclusion

This population pharmacokinetic model of digoxin by presented nutritional factors was developed for the first time with the NONMEM in Korean patients. The present study established important sources of variability in digoxin pharmacokinetics. Clinical application of this model may help calculate digoxin dose requirements according to degree of malnutrition affecting digoxin volume of distribution, and it will also be useful for therapeutic drug monitoring

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Table 1. Demographic data of the patients

Characteristics	
Number of patients	108
Number of samples	287
Samples per patients (mean)	2.65
Gender (n(%))	
Male	58 (53.7)
Female	50 (46.3)
Age (years, mean±SD[a])	72.8 ± 13
Weight (kg, mean±SD)	57.29 ± 11.99
Percent of ideal body weight (mean±SD)	100.08 ± 17.21
Digoxin dose (mg/day, mean±SD)	0.135 ± 0.054
Serum digoxin concentration (mcg/L)	0.859 ± 0.384
Indications (n(%))	
Heart failure	36 (33.3)
Atrial fibrillation	56 (51.9)
Others[b]	16 (14.8)
Creatinine clearance[c] (ml/min, mean±SD)	59.32 ± 24.7
Serum potassium (mmol/L, mean±SD)	4.3 ± 0.6
Serum albumin (g/dl, mean±SD)	3.4 ± 0.54
Serum cholesterol (mg/dl, mean±SD)	147.8 ± 40.43
TLC[d] (cells/mm^3, mean±SD)	1543.34 ± 915.78
NRI[e] (mean±SD)	92.58 ± 8.33

[a] Standard deviation

[b] Cor-pulmonale (4), myocardial infarction (2), ventricular septal defect (7), post-operation (3)

[c] Estimating creatinine clearance (CL_{CR}) by the Cockcroft and Gault method

[d] Total lymphocyte count = [white blood cell × % lymphocyte]/ 100

[e] Nutritional risk index = [1.519 × serum albumin(mg/dl)] + 41.7 × [present / UBW(kg)]

Table 2. NONMEM output of base model

Parameter	Final Parameter Estimate			
	Population mean	%RSE	IIV (%CV)	%RSE
Ka (hr^{-1})	3[a]	-	-	-
Vd (ml)	93800	15.45	40	68.75
CL (ml/min)	4830	6.9	52.2	20.32

[a] Fixed value

RSE= relative standard error, IIV = interindividual variability, CV = coefficient of variation associated with parameter estimation

Table 3. Preliminary screening of covariates by ADVAN2 TRANS2: effect on objective function value changing of addition of significant covariates in the base model

Hypothesis	Equation	OFV	LRT	p-value	Conclusion
Base model (ADVAN2 TRANS2)	Ka = θ_1(fixed 3) Vd = θ_2 CL = θ_3	-262.876			
Vd (volume of distribution)					
Did NRI influence Vd?	θ_2*NRI**θ_4	-263.511	-0.635	>0.05	No
	θ_2+ NRI*θ_4	-263.358	-0.482	>0.05	No
Did albumin influence Vd?	θ_2*ABM**θ_4	-264.274	-1.398	>0.05	No
	θ_2+ ABM*θ_4	-263.803	-0.927	>0.05	No
	θ_2*(EXP(θ_4)*ABM)	-263.463	-0.587	>0.05	No
Did creatinine clearance influence Vd?	θ_2*CCR**θ_4	-294.524	-31.648	<0.001	Yes
	θ_2+ CCR*θ_4	-296.287	-33.411	<0.001	Yes
CL (clearance)					
Did creatinine clearance influence CL?	θ_3*CCR**θ_5	-339.909	-77.033	<0.001	Yes
	θ_3*(CCR/59)**θ_5	-339.909	-77.033	<0.001	Yes
	θ_3+ CCR*θ_5	-334.662	-71.786	<0.001	Yes

OFV = objective function value; Ka = absorption rate constant; LRT = Likelihood ratio test

ABM = serum albumin, NRI = nutritional risk index, CCR =creatinine clearance

Table 4. Continous variables analysis as the final model in Korean population Pharmacokinetic parameters for digoxin

Hypothesis	Equation	OFV	LRT	Estimation	Conclusion
Base model (ADVAN2 TRANS2)	Ka = θ_1(fixed 3) Vd = θ_2, CL = θ_3	-262.876			
Did NRI influence Vd?	θ_2*NRI**θ_4	-341.527	-78.651	FO	Yes
Did creatinine clearance influence CL?	θ_3*(CCR/59)**θ_5	-356.917	-94.041	FOCE	Yes

Parameters	Meaning	Estimated value	Variability estimation	
			SE	RSE[a](%)
θ_1	Absorption rate constant	Fixed 3.0	-	-
θ_2	Volume of distribution	11500	43900	381.74
θ_3	Clearance	5940	305	5.13
θ_4	Coefficient of NRI in Vd	0.963	0.849	88.16
θ_5	Coefficient of CCR in CL	0.744	0.13	17.47
ω^2_{Vd}	Interindividual variability (CV%) in Vd	0.303 (55)	0.125	41.25
ω^2_{CL}	Interindividual variability (CV%) in CL	0.158 (39.74)	0.0383	24.24
σ^2	Intraindividual variability (CV%)	0.0552 (23.5)	0.00869	15.74

Did albumin influence Vd?	θ_2*(EXP(θ_4)*ABM)	-340.534	-77.658	FO	Yes
Did creatinine clearance influence CL?	θ_3*(CCR/59)**θ_5	-355.063	-92.187	FOCE	Yes

Parameters	Meaning	Estimated value	Variability estimation

			SE	RSE[a](%)
θ_1	Absorption rate constant	Fixed 3.0	-	-
θ_2	Volume of distribution	688000	153000	22.23
θ_3	Clearance	5960	299	5.02
θ_4	Coefficient of ABM in Vd	0.0759	0.0686	90.38
θ_5	Coefficient of CCR in CL	0.741	0.128	17.27
ω^2_{Vd}	Interindividual variability (CV%) in Vd	0.299 (54.7)	0.148	49.50
ω^2_{CL}	Interindividual variability (CV%) in CL	0.155 (39.37)	0.0368	23.74
σ^2	Intraindividual variability (CV%)	0.0561 (23.7)	0.00933	16.63
Did creatinine clearance influence CL?	θ_2*CCR**θ_4	-344.7	-81.824	FO	Yes
Did creatinine clearance influence CL?	θ_3*(CCR/59)**θ_5	-363.705	-100.829	FOCE	Yes

Parameters	Meaning	Estimated value	Variability estimation	
			SE	RSE[a](%)
θ_1	Absorption rate constant	Fixed 3.0	-	-
θ_2	Volume of distribution	101000	59500	58.99
θ_3	Clearance	5990	309	5.16
θ_4	Coefficient of CCR in Vd	0.561	0.14	24.96
θ_5	Coefficient of CCR in CL	0.644	0.119	18.48
ω^2_{Vd}	Interindividual variability (CV%) in Vd	0.423 (65)	0.147	34.75
ω^2_{CL}	Interindividual variability (CV%) in CL	0.162 (40.24)	0.032	19.75
σ^2	Intraindividual variability (CV%)	0.0506 (22.49)	0.0075	13.39

OFV = objective function value; Ka = absorption rate constant; LRT = Likelihood ratio test;

FO = First-order estimation method; FOCE = First-order conditional estimation

SE= standard error; RSE= Relative standard error (RSE%=SE/value*100)

ABM= serum albumin, Vd= volume of distribution (ml), CCR= creatinine clearance, CL= clearance (ml/min), CV%= coefficient of variation, TV= typical value, NRI = nutritional risk index

Table 5. Categorical variables analysis in Korean population pharmacokinetic parameters for digoxin

Parameter	Final parameter estimate			
	Population mean	%RSE*	IIV(%CV)	%RSE*
CL (ml/min)	5790	5.15	41.23	23.56
Effect of CCR	0.739	16.1		
Vd (ml)	788000	11.24	54.25	45.74
Effect of albumin	0.019/0.106/0.219			
RV (%CV)	0.0575		24.33	15.13
CL (ml/min)	5750	4.9	41.38	21.83
Effect of CCR	0.710	13.96		
Vd (ml)	832000	12.14	53.78	60.63
Effect of NRI	-0.265/0.036/0.643/0.02			
RV (%CV)	0.0528		23.28	15.98
CL (ml/min)	5760	4.8	40.66	23.79
Effect of CCR	0.743	15.34		
Vd (ml)	605000	42.81	59.94	44.95
Effect of PIBW	0.472/0.072/0.415/0.424			
RV (%CV)	0.0549		23.75	16.81
CL (ml/min)	5830	4.8	40.80	
Effect of CCR	0.727	15.68		22.4
Vd (ml)	819000	83.88	56.84	
Effect of sex	0.172/-0.0678			43.75
RV (%CV)	0.0569		24.19	15.62
CL (ml/min)	5810	7.78	40.66	25.42
Effect of CCR	0.748	18.18		
Vd (ml)	813000	610	59.83	47.38
Effect of age	0.0624/0.098			
RV (%CV)	0.0568		24.17	15.44

*Relative standard error (RSE%=SE/value*100)

Random-effects models : $Vd = TVVd * EXP(\theta_2)$, $CL = TVCL * EXP(\theta_3)$

Where, CL = clearance (ml/min), Vd= volume of distribution (ml), CCR= creatinine clearance, CV%= coefficient of variation, PIBW = percent of ideal body weight, NRI = nutritional risk index

@ Categorical variables range : a = albumin (mg/dL) < 2.8, 2.8~.3.5, >3.5

b = NRI < 83.5, 83.5~97.5, 97.5~100, > 100

c = PIBW (%) ≥ 69, 70~79, 80~89, ≤ 90

d = sex ; male, female

e = age (years) < 65, ≥ 65

Table 6. Population pharmacokinetic parameters from final model and bootstrap validation

Parameter	Final model*		Bootstrap#		
	Estimate	Standard Error	Medians	95% Confidence Interval	
Continous variable model					
Vd (ml)	688000	153000	605000	230975	944050
Effect of ABM	0.0759	0.0686	0.115	0.00902	0.42705
CL (ml/min)	5960	299	5900	5339	6480
Effect of CCR	0.741	0.128	0.7605	0.50495	1.02
Categorical variable model					
Vd (ml)	788000	88600	798500	505275	1109250
Effect of ABM	0.019	0.0128	0.00901	-0.16385	0.08958
	0.106	0.0764	0.09945	-0.26085	0.44963
	0.219	0.164	0.1985	-0.459175	0.65248
CL (ml/min)	5790	298	5780	5210	6400
Effect of CCR	0.739	0.119	0.7355	0.50553	0.398385

*obtained from the original data

#Mean calculated from 1000 bootstrap

ABM= serum albumin, Vd= volume of distribution (ml), CL= clearance (ml/min), CCR= creatinine clearance

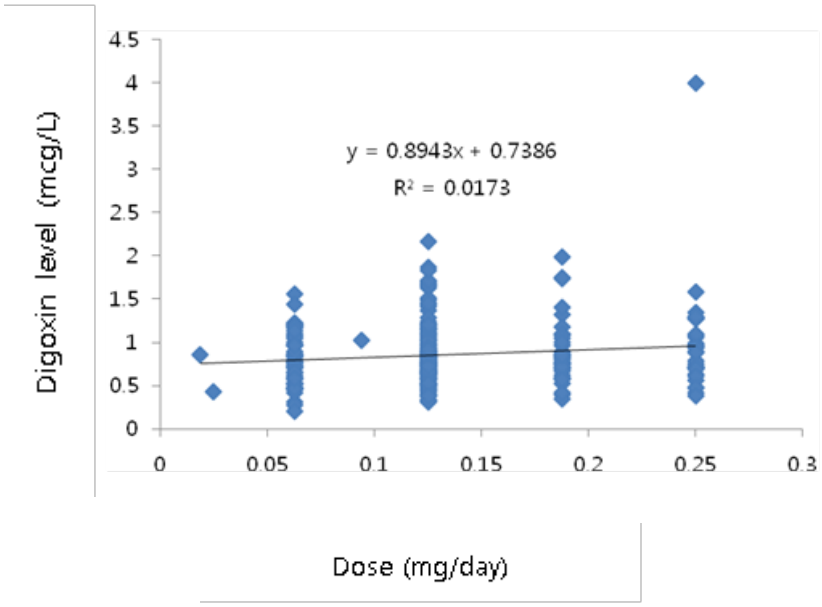
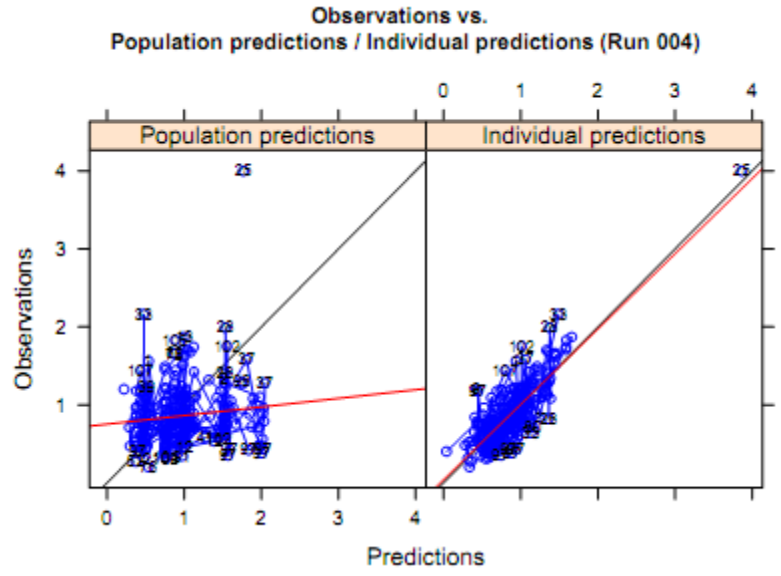
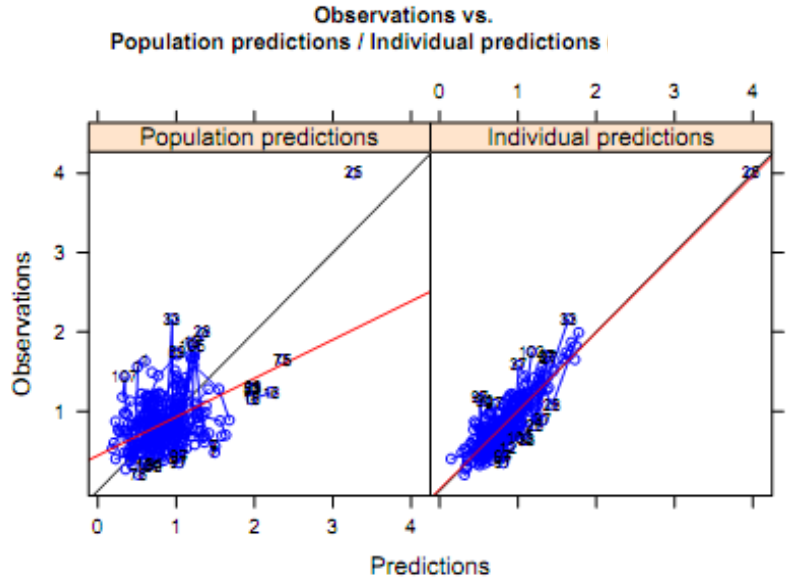


Figure 1. Correlation between daily dose and serum concentration of digoxin.



Base model



Final model

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

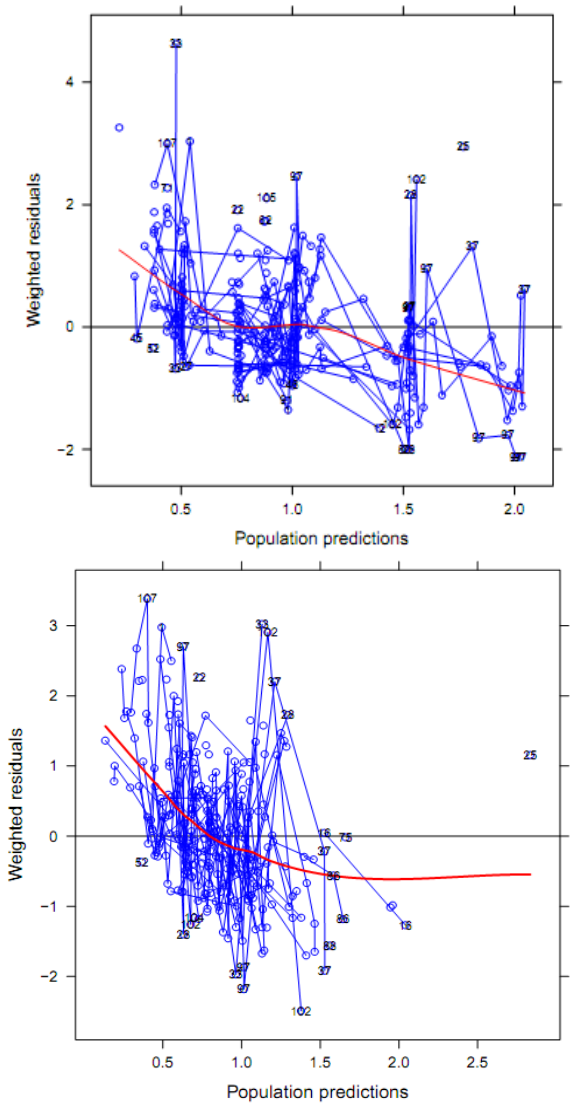


Figure 3. Comparison of scatterplot of weight residuals versus predicted concentration obtained from base model and final model.

국문 초록

입원 환자들에서 안전하고 효과적인 디곡신의 투여를 위해서는 약물의 체내 동태와 이에 영향을 미치는 다양한 요인들의 영향을 아는 것이 필요하다. 하지만, 이러한 영향 요인들에 대한 연구들은 개인별 영양 상태와 디곡신의 요구량에 대한 관계를 밝히고자 시도하였던 적이 없다. 이에 본 연구에서는 한국 입원 환자들을 대상으로 디곡신의 약동학을 예측하고 이러한 다양성에 영향을 미치는 요인 중 영양 상태와의 관계를 규명하고자 하는 것을 목적으로 하였다.

분당서울대학교병원에서 경구로 디곡신을 투여 받은 106명(255개의 혈중 농도)의 치료 농도 모니터링 결과를 후향적으로 검토하였다. 디곡신의 약동학은 비선형 혼합효과 모델링을 이용하여 1-구획 약동학적 모델과 다중 최저농도 접근법으로 분석하였다.

환자들의 개별 특성과 생화학적, 영양학적 지표를 공변량으로 보고 다양한 관계를 탐색하였다. 비선형 혼합효과 모델링에 의해 측정된 디곡신의 청소율은 신기능, 혈중 포타슘 농도, 연령과 이상 체중비에 영향을 받았다. 이러한 영향은 다음과 같은 식으로 나타낼 수 있다. CL/F (L/h) = $1.36\times (CCR/50)^{1.580} \times K^{0.835} \times 0.055\times (AGE/65) \times (PIBW/100)^{0.403}$ 청소율에 대한 개체내 다양성(CV)은 34.3%였고 관찰 농도와 예측 농도 사이의 잔차 다양성(SD)은 0.225 μg/L였다. 부트스트랩을 통한 중앙값은 비선형 혼합효과 모델링의 측정치 5%내에

있으므로 본 모델의 예측이 적절함을 입증할 수 있다. 또한, 다른 실험군을 통한 상관성 분석을 통해서도 관찰치와 본 모델을 적용한 예측치 사이에 선형 상관성이 있음을 밝힘으로서 그 유효성을 입증하였다.

디곡신의 일상적인 치료 농도 모니터링에 본 모델을 적용하기 위해서는 이 연구와 동일한 조건의 환자군을 만족해야 할 것이므로 좀 더 다양한 영양 상태의 효과들을 입증하기 위한 전향적 약동학적 연구들이 필요하겠다.

본 연구는 디곡신의 약동학적 다양성을 설명함에 있어 영양 상태라는 중요한 변수를 확립하였다는 것에 큰 의의가 있으며 이로서 한국 입원 환자에서 약동학적 모수들과 영양 상태와의 관계를 보여주었다.

주요어 : 디곡신, 비선형 혼합효과 모델, 집단 약동학, 영양 상태

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감사의 글

드디어 이 감사의 글을 쓰면서 한동안 큰 숙제였던 박사논문에 마침표를 찍고 있습니다.

이 논문이 완성되기까지 언제나 묵묵히 기다려주시며 격려해주신 신완균교수님 감사 드립니다. 약학을 선택하고 병원에서 임상을 공부하고 수많은 업무를 하면서 가장 큰 인생의 열쇠를 제게 주셨습니다. 사회에 첫발을 내딛고 묵묵히 열심히 하는 것이 제일인 줄만 알았던 제게 먼저 손을 내밀어 주시고 항상 따뜻하게 인도해주셨던 이병구교수님 감사 드립니다. 병원 업무를 하면서 열심히 하였다고 너그럽게 논문 심사해주신 이명걸교수님, 오정미교수님, 김은경교수님, 김대덕교수님 감사 드립니다.

학교를 마치며 무엇을 해야 할 지 아니 하고 싶은지를 모른 채 언니의 권유로 시작한 서울대병원에서의 인턴, 레지던트 생활은 제 인생에 큰 나침반이 되는 시간이었습니다. 하루하루가 즐겁고 앎에 대한 기쁨으로 순식간에 지나가버린 2년은 앞으로 계속 임상약학을 해야겠다는 내 인생의 소명처럼 느껴지며 자연스레 시작된 병원약사의 길을 안내하였습니다. 다양한 임상 업무를 해내는 내내 많은 갈증이 있었고 여러 가지 시험에도 도전하게 되었지만 무엇보다 학교에서 정식으로 학위를 마치고 좀 더 이 분야의 전문가로서 떳떳하고자 시작한 학업이었습니다. 이제 마무리를 짓고 큰 숙제 하나를 해내는 오늘이지만 한편, 그 동안 병원 업무에 밀려 제대로 하지 못했던 학위논문을 병원을 그만두고 나서야 완성할 수 있어서 스스로의 부족함에 아쉬움이 남는 순간입니다.

이 논문을 쓰기 시작하였던 곳인 분당서울대병원 식구들에게 감사의 말을

전합니다. 이제 곧 병원을 그만 둔지도 1년이 되어가지만 여전히 갈 때마다 이곳이 친정이라며 따뜻하게 맞아주시는 이은숙 부장님 항상 불평과 불만이 많았던 저에게 끝까지 웃으면서 격려해주셨던 것 잊지 않겠습니다. 감사합니다. 언제나 할말 많은 주임약사를 데리고 일하시느라 고생하셨던 이정화팀장님, 남궁형욱팀장님, 최경숙팀장님 역시 감사 드립니다. 사실 병원 식구들 일일이 나열하고 싶은 사람들이 너무 많지만 하나하나 나열하지 못함을 이해하여 주기 바랍니다. 언제나 잘한다며 격려해주었던 선배약사님들, 내가 있어서 힘이 난다던 후배약사님들(특히, 숙, 홍), 사실 언제나 제가 그들 때문에 힘이 났었습니다. 마지막까지 동고동락을 같이했던 외래약국 식구들 모두 모두 감사합니다. 이것으로 인연은 끝이 아니라 시작으로 생각하며 항상 도움이 되는 선배약사가 또 후배약사가 되겠습니다.

이 논문을 마무리 지었던 곳인 임상약학실 선후배에게도 감사의 말을 전합니다. 작년 8월 갑자기 나타나 책상 하나 자리잡고 앉아서 도움도 못되고 있을 때 매일 따뜻한 얼굴로 맞아주고 오히려 챙겨주었던 고마운 식구들, 제가 온 것이 오히려 든든하다고 힘주셨던 류윤미선생님, 가끔 마주쳐도 환하게 인사해주시던 강병철선생님, 무엇이든지 물어봐도 좋았던 최청암, 슬그머니 신경 써주는 이정윤, 꿋꿋이 열심히 하는 모습을 오히려 배우고 싶었던 정옥분, 함께 한 시간은 짧지만 항상 반겨주었던 김정아, 타지에 와서 너무 열심히 하는 모습에 반하게 했던 김은혜, 혼자서도 무엇이든 잘하는 긍정의 아이콘 공지선, 병원 다니면서 열심히 석사 마무리 지은 윤한샘, 오랜만에 온 연건동에서 무엇보다 낯설지 않아 반가웠던 최정윤 이외에도 김아정선생님, 문미라선생님, 김은아선생님 모두모두 감사 드립니다.

언제나 멀리서 응원해주는 후배 민경이, 병원을 그만두어도 항상 먼저 연락하며 힘이 되어주는 여러 후배약사들 모두가 생각납니다. 매번 전화로 메일로

이것저것 물어보는데도 항상 친절히 답해주었던 휘열군(윤박사님)에게 누구보다 고맙다고 전하고 싶습니다.

이 세상에 태어나 오늘의 제가 있게 해준 가족들, 언제나 저의 기쁨과 슬픔을 함께 해주었기에 하루하루 버틸 수 있었습니다. 둘째 딸이 하는 거라면 뭐든지 믿고 이해해주신 부모님 감사 드리며 이 논문을 부모님께 바칩니다. 앞으로 더욱 열심히 사는 훌륭한 약사가 되어 부모님의 은혜에 꼭 보답하겠습니다. 무엇보다 같은 약사로서 많은 고민을 함께 나눌 수 있어서 좋았던 우리 수임언니, 나의 멘토로 항상 함께 해주어 너무 고맙고 나보다 더 속상해 해주고 화내주어서 언니 때문에 힘을 낼 수 있었던 것 같습니다. 우리 언니는 잘할 수 있다며 무조건 믿어주는 셋째 동생 안나, 이제는 언니가 무조건 믿어주겠다고 얘기하고 싶습니다. 혼자서 먼 미국에서 악착같이 공부해서 열심히 그리고 멋지게 해내고 있는 우리 막냉이 선정, 언니가 오히려 배울 점이 많은데도 항상 언니 최고라고 해주어서 너무 고맙습니다. 또한, 내 인생의 새로운 식구들, 언제나 연구도 진료도 게을리하지 않으며 저에게 모범을 보여주시는 우리 형부, 세상에서 이모가 가장 사랑하는 우리 조카 승준이, 채빈이 그 존재만으로도 감사 합니다.

이렇게 감사의 글을 쓰는 순간에도 참 부끄럽다는 아직 많이 부족하다는 생각을 합니다. 이제야 겨우 내가 아는 것들을 연구해 보고자 하는 마음도, 요령도, 자신감도 생긴 것 같아 이 논문은 무엇보다 제 인생에서 새로운 출발을 다짐케 하는 시작인 것 같습니다. 이 다짐을 잊지 않고 앞으로 더욱 열심히 연구하고 공부하는 약사로 평생 살겠습니다. 다시 한번 엄마, 아빠, 언니, 동생들, 형부, 조카들, 나의 가족에게 사랑한다고 고맙다는 말을 가슴 깊이 전합니다.