Population Pharmacokinetics of Digoxin in Korean Clearance After The Multiple Intravenous Administrations

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Background : Digoxin possesses a narrow therapeutic range and causes serious adverse effects at toxic concentrations. In the evaluation study of the digoxin dosing methods, foreign published methods showed poor predictability in Koreans.

Methods : We have determined the population pharmacokinetic parameters of digoxin after multiple intravenous administrations in Korean patients by using NPEM. The measured CLcr was compared with the estimated CLcr value, using Jelliffe's equation in seven healthy volunteers and fifteen patients.

Results : From the regressive analysis, modified Jelliffe equation was developed as follows : $CLcr = 1.41 \times BSA \times \{98 - 0.8(Age - 20)\} / Scr / 1.73 - 18.18$ ($R^2 = 0.768$, $p < 10^{-4}$) where age is in years and Scr is in mg/dl and BSA is body surface area (m^2). In analysis of the bias and the predictive accuracy of the two equations, modified equation was evaluated to be more accurate with -4.36 mean error and 27.98 root mean squared error, compared with Jelliffe's equation (13.33 and 29.01 , respectively). Twenty serum concentrations from 17 patients were used to generate pharmacokinetic parameter estimates for digoxin, using NPEM. NPEM generated a population mean value for V_s ($7.25 \pm 1.52 L/kg$) and K_s ($0.000223 \pm 0.0000386 min/ml/hr$).

Conclusion : The relationship between volume of distribution and weight was $V = 7.25 \times Wt$. The relationship between K_e and $CLcr$ was $K_e = 0.000223 \times CLcr + 0.00656$.

KEY WORDS : Digoxin population pharmacokinetics · Creatinine clearance nonparametric expectation maximization.

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INTRODUCTION

The availability of a population pharmacokinetic study enhances the ability of a clinician to achieve therapeutic serum concentrations early in pharmacotherapy. Several methods for estimating population pharmacokinetic values have been employed. The naive pooling and the standard 2-stage approach are traditional methods. These methods, however, are restricted in that they require significant amounts of data to analyze the pharmacokinetic parameters. Often these methods are applied only to intensively studied healthy volunteers or to very small patient groups. The resulting expense of these approaches limits their broad availability also¹⁾.

The introduction of the nonlinear mixed effect model has allowed the use of routine data in the identification of population pharmacokinetic values of interest²⁻⁵⁾. However this parametric approach requires an assumption that the underlying population distribution is normal or will be normal after suitable transformations^{6,7)}.

The nonparametric expectation maximization program developed by Schumitzky and Jelliffe^{8,9)}, does not assume the true population distribution. The main advantage of this approach is that it allows for non-normal distributions. The method has been used to evaluate population parameter values in groups of patients receiving gentamicin¹⁰⁻¹²⁾, and in a group of patients with human immunodeficiency virus and cytomegalovirus receiving ganciclovir¹³⁾.

An accurate estimate of renal function is imperative for ascertaining the fate of drugs that are eliminated principally by the kidney. The use of renal creatinine clearance (CL_{Cr}) as a measure of kidney function is widely accepted¹⁴⁾. The CL_{Cr} can be determined by measuring the creatinine concentration in

urine collected over a 24-hour period. This method is restricted in that the test results are not readily available and the accuracy of the measurement depends on the completeness of urine collection in a 24-hour period. Several formulas have been developed for estimating CL_{Cr} from serum creatinine concentration (Scr) and other easily obtained values such as height, weight, age and surface area^{7,15,16)}. However, many of the existing formulas were derived from populations with restricted ranges for some of these variables. Because some of the variables may lack deviation in a particular patient group, it is necessary to identify a best formula for use in specific populations. In addition, these formulas are derived from foreign populations. Jelliffe's equation⁷⁾ or Cockcroft and Gault's formula¹⁵⁾, widely used in clinical environment, are from foreign populations as well. Because these equations can not accurately extrapolate the information in Korean population, they may not be useful predictors.

Digoxin is widely prescribed for the treatment of congestive heart failure and supraventricular tachyarrhythmias^{17,18)}. It is a difficult drug to dose because of its narrow therapeutic range and wide variation in the pharmacokinetic characteristics. For a given daily dosage, steady-state serum digoxin concentrations vary greatly from one patient to another. Therefore, the clinicians need methods to predict digoxin pharmacokinetic values and an appropriate dosage regimen for individual patients on pharmacotherapy¹⁹⁻²¹⁾. Many attempts in foreign nations have been made to improve the ability to predict individual digoxin requirement²²⁻²⁴⁾, but none in Korean population. In the evaluation study²⁵⁾ of digoxin dosing methods, the seven published methods showed poor predictability in Koreans. Also, ethnic differences in drug disposition²⁶⁾ stimulate a need for

the population pharmacokinetic study in Koreans.

The purpose of this paper was to determine the population pharmacokinetic parameters of digoxin after the multiple intravenous administration in Korean patients. Measured CLcr was compared with a CLcr value estimated by using Jelliffe's equation⁷⁾ in Korean healthy volunteers and patients.

METHOD

Determination of Creatinine Clearance

Population

Seven healthy volunteers and fifteen hospitalized patients (less than 65 years old) were enrolled in this study. Excluded from this study were patients who had muscular dystrophy, thyroid dysfunction and hepatic failure (bilirubin or serum transeaminase concentration > three times the upper limit of normal). Similarly, patients with conditions known to interfere with creatinine measurement, such as hyperglycemia (glucose > 200mg/dl), massive hemolysis, diabetic ketoacidosis or hyperlipidemia (total cholesterol > 200mg/dl, triglyceride > 160mg/dl) were excluded from participation²⁷⁾. None of the volunteers and patients received cefoxitin, cephalothin, cimetidine, trimethoprim, androgens and levodopa.

Calculation of creatinine clearance

The urine was collected for 24 hours and the serum samples were obtained at 8:30 AM of the urine collection day. The serum and urine creatinine concentration were measured by Jaffe reaction on a HITACHI analyzer. The following equation was utilized to calculate the 24-hour urine collection :

$$\text{CLcr (ml/min)} = \frac{\text{Ucr (mg/dl)} \times \text{Uvol (ml)}}{\text{Scr (mg/dl)} \times \text{time (min)}}$$

where CLcr = creatinine clearance, Ucr = urine creatinine concentration, Uvol = urine volume, Scr = serum creatinine.

Each the same participant's measured CLcr was compared with a CLcr value for the same participant estimated by using Jelliffe's equation. Jelliffe's equation (1973) was :

$$\text{CLcr (ml/min)} = \frac{98 - [0.8 \times (\text{age} - 20)]}{\text{Scr}} \times \frac{\text{BSA}}{1.73}$$

$$\text{BSA (m}^2\text{)} = W^{0.5378} \times H^{0.3964} \times 0.024265$$

where age is in years, Scr in mg/dl, BSA body surface area, W actual body weight in kg and H height in cm.

Analysis of correlation and predictive error

The estimated CLcr values were plotted against the measured CLcr values and the regression equation by using least square method was calculated. From this equation, new modified formulae of CLcr estimation in Korean was developed. To evaluate the modified formulae on predictivity, the squared correlation (R^2) was calculated by analysis of variance. The mean error value and the root mean squared error value were compared²⁸⁾ between two formulae, Jelliffe's equation and modified Jelliffe's equation. The mean error was calculated for each of these two formulas by using the prediction error, the difference between the estimated and the measured CLcr values, by using the following equation : Mean error = $(1/n) \sum (\text{prediction error})$

where n is the sample size and $\sum$ is the total amount. The root mean squared error was calculated as follows :

$$\text{Mean square error} = (1/n) \sum (\text{prediction error})^2$$

$$\text{Root mean squared error} = \sqrt{(\text{mean square error})}$$

Determination of digoxin population pharmacokinetic parameters

Patients

Patients, ranging from 20 to 65 years of age, who received digoxin intravenous solution (0.25mg/2ml, Asia Pharmaceutical Company in Seoul Korea) from Seoul National University Hospital were selected. The inclusion criteria^{17,19,20)} were as follows :

1. Stable renal function with estimated $\text{CLcr} > 20 \text{ ml/min}$
2. Not on hemodialysis or peritoneal dialysis
3. Normal serum level of potassium (3.5–5 mEq/L)
4. Not concurrently receiving cefoxitin, cephalothin, cimetidine, trimethoprim, androgens, levodopa, steroids, amiodarone, quinidine, spironolactone and verapamil for at least seven consecutive days prior to the study
5. Free from active state of thyroid dysfunction, muscular dystrophy and hepatic dysfunction

Data collection

The data collected by chart-review included the following : age, sex, height, weight, admitting diagnosis, concurrent medications, serum creatinine, potassium values, the date, time, dose, route and duration of digoxin therapy, and the date and time that serum digoxin concentration was drawn. The CLcr were estimated by using a modified formulae of Jelliffe's equation.

The serum digoxin concentrations were measured by the fluorescence polarization immunoassay method on a TDX system (Abbott lab. Irving TX). The assay pattern was determined by the use of the replicate serum digoxin concentrations⁹⁾. The first order

equation for assay error pattern is as follows :

$$\text{SD}(\text{ng/ml}) = 0.115 + 0.017 \times C$$

where S.D. is the standard deviation and C is the observed digoxin concentration.

NPEM pharmacokinetic analysis

The individual patient data were entered into the USC PACK database program PASTRX[®]. A total of 20 digoxin concentrations were obtained in seventeen patients. The data from PASTRX were downloaded into NPEM for calculation of the slope (V_s : L/kg) of volume of distribution to body weight and the slope (K_s : min/ml/hr) of the relationship between elimination rate constant (K_e : hr^{-1}) and creatinine clearance (CLcr : ml/min). The intercept (K_i : hr^{-1}) was fixed at 0.00656, corresponding to a half-life of 105.6 hours, assuming that digoxin exhibits a minimal nonrenal clearance²⁹⁾. As described above, following one-exponentially decay model was assumed :

$$K_e(\text{hr}^{-1}) = K_s \times \text{CLcr} + K_i$$

$$V(L) = V_s \times W_t$$

The user-supplied boundaries for the V_s were 0.0 to 20 L/kg of body weight and for the K_s were 0.0 to 0.0005 min/ml/hr. In this study, the run was set to permit a maximum of 100 iterative cycles, or a log-likelihood function value of less than 0.001 units from the previous cycle[®].

RESULTS AND DISCUSSION

Determination of creatinine clearance

The description of seven healthy volunteers and fifteen hospitalized patients (14 men and 8 women) is shown in Table 1. The Mean demographics were

Table 1. Demographics of the study to determine the creatinine clearance in Korean population. (n=22)^a

Descriptor	Range	Mean±S.D.
Age (years)	22-65	40.2±14.5
Height (cm)	151-183	166.1±9.8
Weight (kg)	43-81	58.5±10.8
Serum creatinine concentration (mg/dl)	0.5-3.8	1.21±0.79
Measured creatinine clearance (ml/min)	9.79-181.62	89.99±48.40
Estimated creatinine clearance (ml/min)	19.51-117.66	76.66±30.06

^a 7 healthy volunteers, 15 patients/14 men, 8 women

Fig. 1. Correlation of estimated versus measured creatinine clearance using Jelliffe's equation (1973). ($Y=1.41 X-18.18$, $R^2=0.768$, $p<0.0001$), CLcr : creatinine clearance(ml/min)

Fig. 2. Correlation of estimated versus measured creatinine clearance using the modified Jelliffe's equation. ($Y=1.01 X-0.01$, $R^2=0.768$, $p<0.0001$), CLcr : creatinine clearance(ml/min)

age 40.2 ± 14.5 years, height 166.1 ± 9.8 cm, and weight 58.5 ± 10.8 kg. The measured CLcr values ranged from 9.79 to 181.62 ml/min. The ranges of Scr values were 0.5-3.8 mg/dl.

In this study, the age-range of persons was restricted from twenty to sixty five years because several studies had reported low predicti in the fo-

rmulae of CLcr³⁰). Hepatic disease or muscular dystrophy were reported to interfere with the synthesis of creatinine and thus the spontaneous production of creatinine. So the patients, had these diseases, were excluded from the study. For androgens and levodopa, their high concentrations have been reported to cause falsely elevated values of creatinine²⁷).

Table 2. Demographics of the study to determine the population pharmacokinetic parameters of digoxin in Korean patients. (n=17)^a

Descriptor	Range	Mean ± S.D.
Age (years)	32–65	50.3 ± 10.7
Height (cm)	145–176	163.7 ± 9.2
Weight (kg)	44–88	61.6 ± 11.8
Serum creatinine concentration (mg/dl)	0.6–1.6	0.92 ± 0.32
Creatinine clearance (ml/min)	42.03–207.82	98.94 ± 45.13
Digoxin daily dose (mg/day)	0.156–0.625	0.357 ± 0.143
Serum digoxin concentration (ng/ml)	0.3–1.6	0.95 ± 0.45
Sampling time after administration (hrs)	6–46	16.1 ± 10.5

^a11 men, 6 women

Table 3. Population pharmacokinetic parameters of digoxin in Korean patients (n=17)^a

Parameter	Vs ^b	Ks ^c
Mean	7.25	0.000223
S.D.	1.52	0.0000386
C.V.	21.03	17.33
Median	7.13	0.000219
Mode	7.4	0.000234
Skewness	–1.06	–1.48
Kurtosis	2.88	4.17

^a11 men, 6 women

^bVs : L/kg : the slope of volume of distribution to body weight

^cKs : min/ml/hr : the slope of the relationship between elimination rate constant and creatinine clearance

And the drugs of cefoxitin, cephalothin, cimetidine and trimethoprim have been reported to increase serum creatinine concentration through competition for secretion by the kidney tubules³¹. For these reasons, the patients, had taken the medications, which may be able to induce false results, were not selected.

Figure 1. represents the plot of the measured versus the estimated CLcr values from Jelliffe's equation.

The simple linear regression equation by using the least square method was $Y = 1.41 X - 18.18$ ($R^2 = 0.768$). According to the analysis of variance, the squared correlation value was statistically significant at F value = 66.32 and $p = 0.0001$. From the regression equation, following modified formulae was developed.

$$CL_{cr} \text{ (ml/min)} = 1.14 \times \frac{[98 - 0.8 \times (\text{age} - 20)] \times BSA}{Scr \times 1.73} - 18.18$$

where age is in years and Scr is in mg/dl and BSA is body surface area (m^2).

Figure 2. shows the plot of measured versus estimated CLcr values using the modified Jelliffe's equation. The simple linear regression equation by using the least square method was $Y = 1.01 X - 0.01$. The squared correlation (R^2) value 0.768, was statistically significant at $p = 0.0001$.

To evaluate predictive performance, the degree of association along a particular line, the identity line, (perfect prediction) was assessed²⁸. The mean error value of Jelliffe's equation for estimating CLcr was 13.33 and the modified equation was –4.36. This means that Jelliffe's equation overestimated the true clearance values and the modified equation

Fig. 3. Marginal density distributions for the slope (V_s) of volume of distribution with respect to body weight. The x-axis represents V_s and the y-axis represents the fraction of population having the particular values of V_s

underestimated. The results imply that the modified formulae was less bias than Jelliffe's equation. The root mean squared error was 29.01 for Jelliffe's equation and 27.98 for modified equation, that is, it can be guessed that the modified formulae is more accurate than Jelliffe's equation. According to the result of these predictive error analysis, it is thought that the modified formulae was more valuable in estimation of CLcr in Korean adult less than 65 years.

To increase the validity of the results, further data should be collected with a larger sample size. A further study should estimate the influence of gender, age, weight, and height on modified Jelliffe method and how these factors affect the result.

Determination of digoxin population pharmacokinetic parameters

Presently, several computer programs, such as including NONMEM, NPML and NPEM³²⁾ for popula-

Fig. 4. Marginal density distributions for the slope (K_s) of elimination constant with respect to creatinine clearance. The x-axis represents K_s and the y-axis represents the fraction of population having the particular values of K_s

tion modeling exist. Although all these programs estimate the population pharmacokinetic parameters, they differ in several respects. First, NONMEM is based on user-defined parametric distributions. Without prior knowledge, the program simply assumes the posited parameter distribution. The potential advantages of NPEM include its ability to determine parameter distributions without prior knowledge and its relative ease of use. A disadvantage, however, is that, unlike NONMEM, NPEM presently is limited to a one- or two-compartment model with linear pharmacokinetics. In considering these respect, NPEM was selected for the study of digoxin, reported with linear pharmacokinetics³³⁾.

Twenty serum concentrations from 17 patients (eleven men, six women) were used to generate pharmacokinetic parameter estimates for digoxin, using NPEM. Mean demographics were age 50.3 ± 10.7 years, height 163.7 ± 9.2 cm, weight 61.6 ± 11.8 kg and creatinine clearance 98.94 ± 45.13 ml/min.

Fig. 5. Three dimensional surface plots of the joint density functions over the Vs versus Ks. The z-axis represents the fraction of population having the particular values of Vs and Ks

Sampling time intervals after a digoxin intravenous administration ranged from six to forty-six hours. The daily dose was 0.357 ± 0.143 mg/day and serum digoxin concentration ranged from 0.3 to 1.9 ng/ml. The description of patient population is shown in Table 2.

The distribution of digoxin is influenced by several physiologic variables, particularly potassium level and renal function. Acute hyperkalemia is associated with decreased distribution of ^3H -digoxin to several tissues in the dog, including the heart and skeletal muscle. The volume of distribution of digoxin decreases in chronic renal failure, although the mechanism is not clear yet. For these reasons, the patients with normal potassium level and $\text{CLcr} > 20\text{ml/min}$, were selected in this study.

In parameterization of volume of distribution with respect to body weight and the relationship between elimination rate constant and creatinine clearance, mean, standard deviation (S.D.), percentage coefficient of variation and other distribution characteristics are presented in Table 3. NPEM generated a population mean value for Vs (7.25L/kg) and Ks (0.000223min/ml/hr). The relationship between Ke and CLcr was $\text{Ke} = 0.000223 \times \text{CLcr} + 0.00656$.

The marginal distribution for Vs is depicted in Figure 3. Much of the population distribution is located between 7.1 and 9.5L/kg. Another small mode is located between 3.8 and 5.0L/kg. In Figure 4, the marginal distribution for Ks is shown. The population distribution lies between 0.00021 and 0.00027min/ml/hr and another small mode is located approximately between 0.0001 and 0.0002min/ml/hr. The three-dimensional plot of the joint probability density function, using the volume with respect to weight and the slope of the relationship between elimination rate constant and creatinine clearance is presented in Fig 5.

One of the reasons of these small modes, drug interaction may be considered. In this study, one case out of four with diltiazem coadministration was chiefly included the small mode group in Vs and Ks. Another person who took phenytoin together, had values belonged to the small mode group in Vs and Ks. This result suggests that coadministration of diltiazem or phenytoin with digoxin, may decrease the clearance of digoxin, in some cases. But the reports about the effect of diltiazem and phenytoin on digoxin were controversial³⁴⁻³⁶. In addition, the study about phenytoin interaction reported that concomitant administration of phenytoin resulted in a reduction in digoxin elimination half-life and AUC with delayed onset, thus the possibility of drug-interaction

was considered to be low. Further study with larger population could present the reality of these small mode groups in Ks and Vs.

In parameterization of volume of distribution with respect to body weight and the relationship between elimination rate constant and creatinine clearance, the population parameters studied by Paulson³⁷⁾ and Koup³⁸⁾ are different from those of this result. These studies, however, were developed by vector regression analysis and by the data from oral administration and renal failure patients.

The accuracy assessment of the population parameters in this result, by Bayesian estimation, was not available, because the other data of serum digoxin concentrations after intravenous administration of digoxin, were not able to be collected, yet. Further studies will be required to provide more information regarding the accuracy of the population parameters after intravenous administration and the estimation of the population parameters after oral administration of digoxin in Korean.

CONCLUSION

In the study for the determination of creatinine clearance in Korean population, following modified formulae was developed.

$$CL_{Cr} \text{ (ml/min)} = 1.14 \times$$

$$\frac{[98 - 0.8 \times (\text{age} - 20)] \times \text{BSA}}{\text{Scr} \times 1.73} - 18.18$$

where age is in years and Scr is in mg/dl and BSA is body surface area(m²)

NPEM generated a population mean value for Vs (7.25 ± 1.52L/kg) and Ks (0.000223 ± 0.0000386min/ml/hr) from the population pharmacokinetic study of digoxin in Korean patients. The relationship between volume of distribution and weight was V=7.

25 × Wt. The relationship between Ke and CL_{Cr} was Ke = 0.000223 × CL_{Cr} + 0.00656. To increase the validity of the results, further data should be collected with a larger sample size.

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