A Computer-based Pharmacokinetic Implementation for Digoxin Therapeutic Monitoring in Pediatric Patients

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ABTRACT

Because of the narrow therapeutic range and large inter-patient variability in digoxin's pharmacokinetics and pharmacodynamics, an appropriate dosage regimen for individuals is needed. However, monitoring and adjusting the optimal individualized dosage regimen requires a knowledge and familiarity of pharmacokinetic equations. The objective of this study was to develop a computer-based pharmacokinetic implementation for individualized digoxin pharmacokinetic parameters, dosage regimen, and predicted concentrations in pediatric patients. The program was developed using Microsoft Access 2000. Validated digoxin pharmacokinetic parameters for pediatrics from a previous study were used to test the computer-based pharmacokinetic program. After entering a patient's data, the program calculated the pharmacokinetic parameters and a dosage regimen for each patient to achieve the therapeutic goals; the predicted concentrations at non-steady state and steady state from selected doses were also calculated. For program testing, 30 pediatric patients from the validation group were used to calculate pharmacokinetic parameters. The mean prediction error (bias) was -0.111 ng/mL (95% CI: -0.218 to 0.004) and precision (RMSE) was 0.315 ng/mL (95% CI: 0.237 to 0.378). Compared to manual calculations, using the computer program required less than one fifth of the time. This simple computer program was developed to assist the pharmacist and healthcare team in terms of accuracy, timesaving, and convenience for digoxin pharmacokinetic calculation and therapeutic monitoring in pediatric patients.

Keywords: Digoxin, Computer-based program, Pharmacokinetic, Pediatric

INTRODUCTION

Digoxin is the most commonly used cardiac glycoside in the treatment of heart failure and cardiac rhythm disturbance in neonates, infants, and children (Latifi et al., 2000). However, digoxin has a narrow therapeutic range and large interpatient variability in its pharmacokinetics and pharmacodynamics, necessitating an appropriate dosage regimen for individual neonate or infant (Suematsu et al., 2001). Monitoring and adjusting the optimal individualized dosage regimen requires a knowledge and familiarity of pharmacokinetic equations. In some situations, this is not always practical for most physicians or pharmacists. As a result, computer-based pharmacokinetic dosing calculators have been developed to assist pharmacists and healthcare teams. Numerous pharmacokinetic software packages for pocket calculators are available such as for aminoglycosides, aminophylline, and phenytoin. Jelliffe et al. (1972) evaluated the use of computer-assisted dosage regimens for digitalis leaf, digitoxin, and digoxin. The computer program computed total body glycoside concentrations correlated with clinical behavior, serum glycoside levels, and myocardial digoxin level. The computer then produced a dosage regimen for the therapeutic goals, adjusted to body weight, renal function, and route of administration. Receiving computer-assisted dosage regimens reduced adverse reactions from 32 of 90 cases (35%) with conventional therapy to 11 of 88 cases (12.5%), with statistical significance ($p<0.001$). More recently, GlobalRPh Inc. also developed a dosing program for calculating dosage regimens in adults. The program can estimate the volume of distribution and clearance and calculate the loading and maintenance dose (McAuley, 2005). After entering the patient's data, the program calculates the ideal body weight, creatinine clearance, and loading and maintenance doses. However, this program is only used for adult patients because the pharmacokinetic parameters of digoxin in adults is different than in pediatrics, especially for clearance and volume of distribution (Park, 1986, Well et al., 1992, Latifi et al., 2000)

A computer-based pharmacokinetic implementation for digoxin in pediatric patients has not yet been developed. To address this, the objective of this study was to develop a computer-based pharmacokinetic implementation for individualized digoxin pharmacokinetic parameters, dosage regimen, and predicted concentrations in pediatric patients using results from a prior study (Preechagoon et al., 2009) of digoxin population pharmacokinetics in pediatric patients with heart disease and the appropriate serum digoxin concentration (SDC)

MATERIALS AND METHODS

The calculation of pharmacokinetic parameters was based on the 1-compartment model for loading dose and maintenance dose equations for individuals to achieve the desired steady-state concentration of digoxin. The program was developed using Microsoft Access 2000. The validated digoxin pharmacokinetic parameters in pediatrics from a previous study (Preechagoon et al., 2009) were used in developing and validating (30 samples) a computer-based pharmacokinetic program. The predicted average concentrations and steady state concentration

calculated from population parameters were compared with the measured concentrations to determine the predictive performance in terms of bias (ME) and precision (MSE and RMSE). There are several known variables influencing the pharmacokinetics of digoxin including age, body weight, height, and presence of congestive heart failure (CHF). These variables are required to perform the dosing calculation. The mathematical backbone of the program is as follows:

(1) The pharmacokinetic parameters of clearance, volume of distribution, elimination rate constant, and half-life were calculated in term of CL/F, Vd/F, ke, and T½, respectively.

- The digoxin CL (clearance) was calculated from population parameters as Equation 1.1 and 1.2.

CL/F (L/h) (0-1year) = 0.322 * WT (kg) Equation 1.1

CL/F(L/h) (>1-15 years)=(0.138*WT(kg)+0.0319*HT(cm)) * 0.765 CHF Equation 1.2

where CL/F is digoxin clearance (L/h), WT is weight in kg, HT is height in cm, CHF is indicator variable with a value of 1 if the patient has congestive heart failure (otherwise it is zero).

- Volume of distribution (Vd) was calculated from population parameters as Equation 1.3.

Vd/F (L) = 9.27 * WT(kg) * 1.75 CHF Equation 1.3

where Vd/F is volume of distribution (L) obtained from final model, WT is weight in kg, CHF is indicator variable with a value of 1 if the patient has congestive heart failure (otherwise it is zero).

- Elimination rate constant (ke) was calculated from Equation 1.4.

$$ke\ (h^{-1}) = \frac{CL}{F} / \frac{Vd}{F} \quad \text{Equation 1.4}$$

- Half-life time (T½) was calculated from Equation 1.5.

$$T½ = 0.693/ke \quad \text{Equation 1.5}$$

(2) the next step of the calculation was divided into two conditions, unknown SDC and known SDC at steady state and post-distribution time.

(2.1) Unknown SDC

(2.1.1) Loading dose and maintenance dose were calculated to achieve desired concentration following loading dose and average concentration at steady state following Equations 2.1 and 2.2, respectively.

$$\text{Loading dose } (\mu g) = \frac{Cdesire * Vd/F}{S} \quad \text{Equation 2.1}$$

$$\text{Maintenance dose } (\mu g) = \frac{CL/F*\tau*Css}{S} \quad \text{Equation 2.2}$$

where C_{desire} is desired concentration following loading dose (µg/L), Css is desired steady state concentration, Vd/F is volume of distribution (L), CL/F is digoxin clearance (L/h), S is salt factor of digoxin = 1, and τ is the dosing interval (h).

(2.1.2) After selecting dosage regimen, concentration predictions

were divided into two states, non-steady state and steady state.

- At non-steady state, the maximum concentration ($C_{max\ (n)}$), minimum concentration ($C_{min\ (n)}$), and concentration at any time ($C_{t\ (n)}$) following n^{th} dose before steady state were calculated by Equations 2.3, 2.4, and 2.5, respectively.

$$C_{max\ (n)}\ (\mu g/L) = \left(\frac{LD}{Vd/F} * e^{-ketl}\right) + \frac{S*Dose}{Vd/F} *(1-e^{-nke\tau})/(1-e^{-ke\tau}) \quad \text{Equation 2.3}$$

$$C_{min\ (n)}\ (\mu g/L) = C_{max\ (n)} * e^{-ke\tau} \quad \text{Equation 2.4}$$

$$C_{t\ (n)}\ (\mu g/L) = C_{max\ (n)} * e^{-ket} \quad \text{Equation 2.5}$$

where $C_{max\ (n)}$ is maximum concentration, $C_{min\ (n)}$ is minimum concentration, and $C_{t\ (n)}$ is concentration at any time, n is number of doses, S is salt factor of digoxin = 1, LD is loading dose, Vd/F is volume of distribution (L), ke is elimination rate constant (h^{-1}), τ is the dosing interval (h), t is number of hours since the last dose to any sampling time, and t1 is number of hours since the loading dose to n^{th} dose.

- At steady state, average concentration at steady state ($C_{pss\ ave}$), maximum concentration at steady state (Cpss max), minimum concentration at steady state ($C_{pss\ min}$), and steady state concentration at various times after administration ($C_{pss\ t}$) were predicted as a function of desired dosage regimen and sampling time after administration followed by Equations 2.6, 2.7, 2.8, and 2.9, respectively.

$$C_{pss\ ave}\ (\mu g/L) = \frac{S*Dose}{CL/F*\tau} \quad \text{Equation 2.6}$$

$$C_{pss\ max}\ (\mu g/L) = \frac{S*Dose}{Vd/F}\ /(1-e^{-ke\tau}) \quad \text{Equation 2.7}$$

$$C_{pss\ min}\ (\mu g/L) = C_{pss\ max} * (e^{-ke\tau}) \quad \text{Equation 2.8}$$

$$C_{pss\ t}\ (\mu g/L) = C_{pss\ max} * (e^{-ket}) \quad \text{Equation 2.9}$$

where $C_{pss\ ave}$ is average concentration at steady state, $C_{pss\ max}$ is maximum concentration at steady state, $C_{pss\ min}$ is minimum concentration at steady state, $C_{pss\ t}$ is steady state concentration at various times after administration, S is salt factor of digoxin = 1, Dose is the maintenance dose of digoxin (µg), CL/F is the total digoxin clearance (L/h), Vd/F is volume of distribution (L) obtained from final model, τ is the dosing interval (h), ke is elimination rate constant (h-1), and t is number of hours since the last dose to any sampling time.

(2.2) Known SDC at steady state and post-distribution time

(2.2.1) For continuing given dosage regimen.

- At non-steady state, $C_{max\ (n)}$, $C_{min\ (n)}$, and $C_{t\ (n)}$ following n^{th} dose before steady state obtained from given dose were calculated by Equation 2.3, 2.4, and 2.5, respectively.

- At steady state, $C_{pss\ max}$ was calculated following Equation 2.10, $C_{pss\ ave}$, $C_{pss\ min}$, and $C_{pss\ t}$ were predicted from Equation 2.6, 2.8, and 2.9 as unknown SDC condition, respectively.

$$C_{pss\ max}\ (\mu g/L) = Cobs * e^{ket} \qquad \text{Equation 2.10}$$

where C_{obs} is the observed concentration at steady state, ke is elimination rate constant (h^{-1}), and t is number of hours since the last dose to true sampling time.

(2.2.2) For adjustment of new dosage regimen, incremental loading dose and maintenance dose to achieve target serum concentration were calculated by Equation 2.11 and 2.2 (as unknown SDC condition), respectively.

$$\text{Incremental loading dose } (\mu g) = \frac{(Cdesire - Cobs)*Vd/F}{S} \qquad \text{Equation 2.11}$$

where C_{desire} is desired concentration following loading dose (µg/L), C_{obs} is observed concentration (µg/L), S is salt factor of digoxin = 1, and Vd/F is volume of distribution (L).

- After selecting the dosage regimen, concentration predictions were calculated for non-steady state and steady state following the equation of unknown SDC condition except Equation 2.3 was replaced with equation 2.12 as follows:

$$C_{max\ (n)}\ (\mu g/L) = \left(Cobs + \frac{LD}{Vd/F}\right) * e^{-ket2} + \frac{S*Dose}{Vd/F} * (1-e^{-nke\tau}) / (1-e^{-ke\tau}) \qquad \text{Equation 2.12}$$

where C_{obs} is observed concentration (ng/mL) of previous dose.

Pharmacokinetic parameters, average steady state concentration, maximum concentration at steady state, minimum concentration at steady state, and steady state concentration at sampling time were calculated manually and with the computer program to compare the time required for each; using ten volunteers (5 pharmacists and 5 pharmacy students), each calculating 10 example cases.

RESULTS

A computer program was developed to calculate pharmacokinetic parameters by utilizing population pharmacokinetic models that were adjusted to a patient's characteristics. After estimating pharmacokinetic parameters, the dosage regimen of digoxin was determined based on mathematical analysis. The user can enter the patient's data into the program. Then the pharmacokinetic parameters and a dosage regimen were calculated for each patient to achieve the therapeutic goals. The user is ultimately responsible for integrating the computer program output with clinical symptoms and selecting the appropriate dosage regimen for each patient. After the user has selected the dosage regimen, the program can also be used to compute the predicted concentration at non-steady state and steady state

from the selected dosage regimen. The user instructions are as follows:

(1) After opening the program, the user chooses the **ENTRANCE** button.

(2) The working screen will be presented (Figure 1). On the top of left side, the user clicks at **KNOWN SDC** if the concentration at steady state was measured and then clicks the **REFRESH** button.

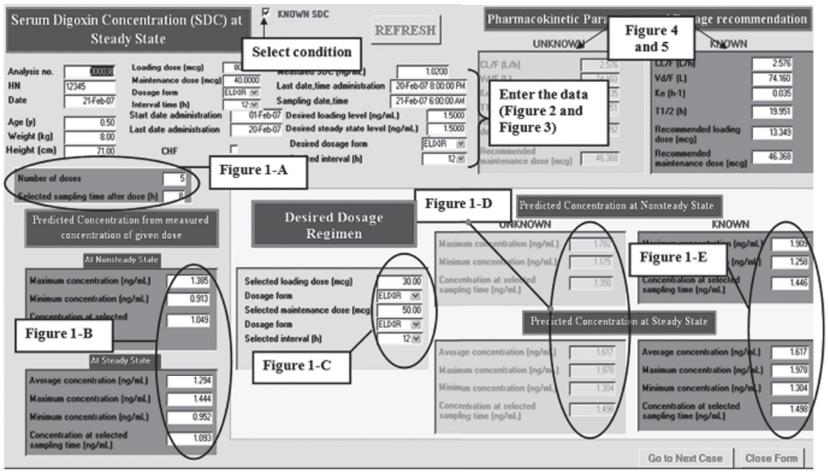

Figure 1. Working screen of the computer program calculation.

(3) The user enters the data into the active cells of each condition.

(3.1) Known SDC at steady state: required input data include hospital number (HN), date, age in years, weight in kg, height in cm, and loading dose and maintenance dose in micrograms (µg). The user chooses the receiving dosage form and interval time of the patient. The start date and time of digoxin administration; the sampling date and time for digoxin assay; and the serum digoxin concentration are required in this condition. The user enters the desired loading concentration, desired steady state concentration, dosage form, and interval time for new dosage regimen and then clicks on the CHF icon if the patient presented CHF (Figure 2).

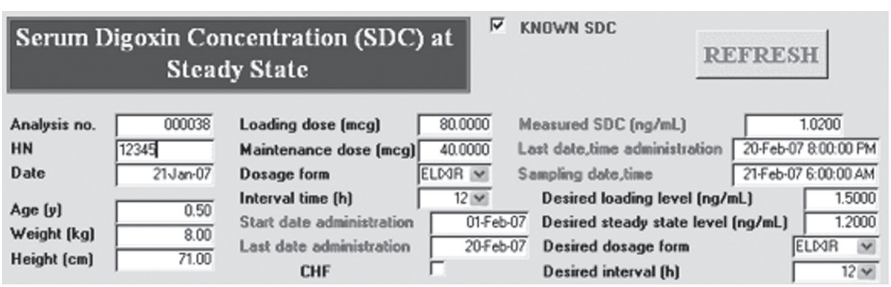

Figure 2. Entering the required input data for known serum digoxin concentration at steady state.

(3.2) Unknown SDC at steady state: required input data include hospital number, date, age in years, weight in kg, height in cm, loading dose and maintenance dose in micrograms (?g), and the receiving dosage form and interval time. The user enters the desired loading concentration, desired steady state concentration, dosage form, interval time for new dosage regimen and then clicks on the CHF icon if the patient presented CHF (Figure 3)

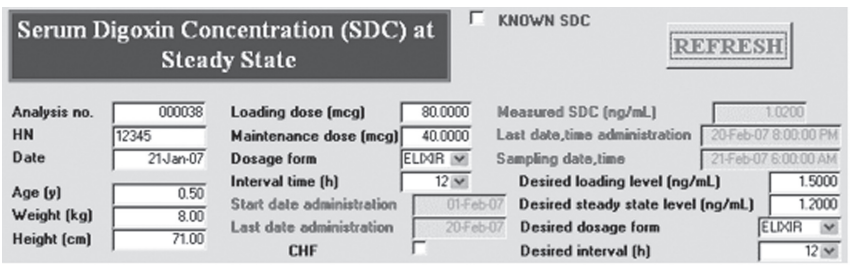

Figure 3. Entering the required input data for unknown serum digoxin concentration at steady state.

(4) After entereing all data, the user clicks the **REFRESH** button at the top of screen. Then the program will calculate the pharmacokinetic parameters of the patient and the recommended loading dose and maintenance dose. The pharmacokinetic parameters will be expressed in terms of CL/F (L/h), Vd/F (L), ke (h^{-1}), and T ½ (h). The recommended loading and maintenance doses to achieve therapeutic goals will be shown in micrograms (μg). Figure 4 and Figure 5 illustrate the active cell of the output for known SDC condition in **KNOWN** box and for unknown SDC condition in **UNKNOWN** box of **Pharmacokinetic Parameters and Dosage Recommendation** box, respectively.

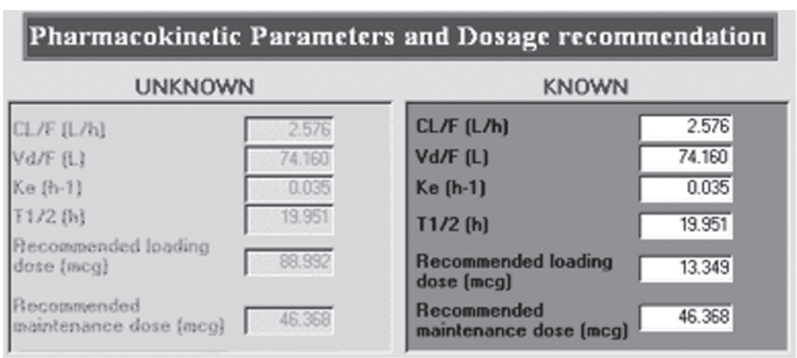

Figure 4. Pharmacokinetic parameters and dosage recommendation for known serum digoxin concentration at steady state.

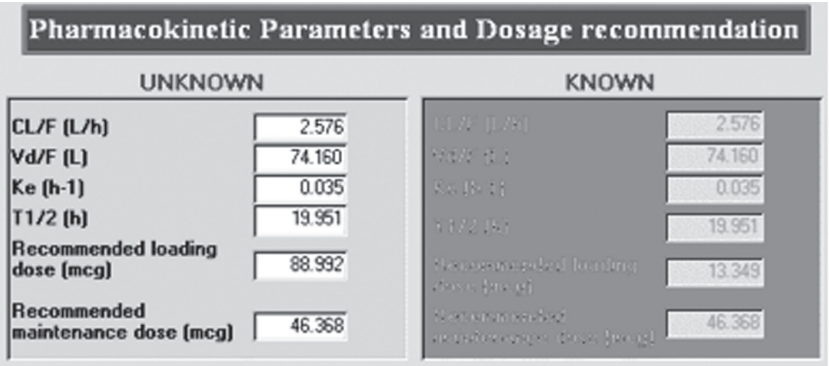

Figure 5. Pharmacokinetic parameters and dosage recommendation for unknown serum digoxin concentration at steady state.

(5) Predicted concentration from measured concentration:

(5.1) If the user wants to know the various predicted concentrations at non-steady state and steady state obtained from a given dose and measured concentration, the user enters the number of doses (n) and selected sampling time after dose (t) in the box at the left side as in Figure 1-A

(5.2) After clicking the **REFRESH** button, the program will present the average concentration, maximum concentration, minimum concentration, and concentration at selected sampling time at steady state and also back calculates the maximum and minimum concentration and concentration at selected sampling time following the nth dose before steady state. The results are presented in **Predicted Concentration from measured concentration of given dose** (Figure 1-B).

(6) Predicted concentration from desired dosage regimen:

(6.1) In this step, the user enters the desired appropriate dosage regimen in the field of selected loading dose, selected maintenance dose, dosage form, and interval time in the **Desired Dosage Regimen** box (Figure 1-C). Then the user selects the number of doses and sampling time after administration for predicted concentration in the box as in Figure 1-C.

(6.2) The user clicks the REFRESH button again.

(6.3) The computer program will calculate and present the predicted concentrations in the active cell both at non-steady state following the nth dose and at steady state obtained from the selected dosage regimen divided by unknown SDC (Figure 1-D) and known SDC condition (Figure 1-E).

(7) The user then clicks **Go to Next Case** if the calculation was completed.

(8) Finally, the user clicks **Close form** at the bottom to exit the program.

For program validation, the mean prediction error, a convenient measure of bias, for predicted average concentrations and predicted concentrations at sampling time were -0.111 ng/mL (95% confidence interval: -0.218 to 0.004) and 0.056 ng/mL (95% confidence interval: -0.005 to 0.163), respectively. The mean squared prediction error (MSE) and root mean squared prediction error (RMSE) are measures of precision. The MSE was 0.099 ng/mL (95% confidence interval,

0.056 to 0.143) and 0.089 ng/mL (95% confidence interval: 0.035 to 0.142) for predicted average concentrations and predicted concentrations at sampling time, respectively. The RMSE was 0.315 ng/mL (95% confidence interval: 0.237 to 0.378) and 0.298 ng/mL (95% confidence interval: 0.187 to 0.377) for predicted average concentrations and predicted concentrations at sampling time, respectively.

Pharmacokinetic parameters, average steady state concentration, maximum concentration at steady state, minimum concentration at steady state, and steady state concentration at sampling time were calculated manually and using the computer program. Time consumption for calculation was tested from 10 cases by 5 pharmacists and 5 pharmacy students. The average time consumption for manual calculation and computer program calculation was 5.65 minutes and 0.97 minutes, respectively.

DISCUSSION AND CONCLUSION

The performance of the computer program was tested using patient data from 30 individuals in the validation group. The mean prediction error (ME) between measured concentrations and predicted average concentrations (-0.111 ng/mL, 95%CI: -0.218 to 0.004) was slightly negative bias. This could be because some of the samples were drawn at near trough concentrations or the sampling time was longer than the dosing interval, causing lower concentrations than the average predicted concentration. For concentrations at various sampling times and concentrations at non-steady state, the equations were complex and difficult to calculate. Manual calculation takes more time, especially for those pharmacists who do not have knowledge of and familiarity with pharmacokinetic equations. For parameter calculations and concentration predictions at steady state, the computer program reduces the time required from over five minutes (5.65 min) for the manual calculation to less than one minute (0.97 min). It also reduces errors. Before adopting this program for clinical use, it needs to be evaluated further in clinical studies.

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