Evaluation of Equations for Prediction of Serum Digoxin Concentration at Digoxin Clinic in Community Hospitals

นิพนธ์ต้นฉบับ

Original Article

มยุลา โลมรัตน์[1]*, พีรยา ศรีผ่อง[1], จันทร์ทิพย์ กาญจนศิลป์[1] และ ยุพาพร ปรีชากุล[2]

[1] ภาควิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ มหาวิทยาลัยมหาสารคาม อ.กันทรวิชัย จ.มหาสารคาม 44150
[2] ภาควิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น อ.เมือง จ.ขอนแก่น 40002

* **ติดต่อผู้นิพนธ์:** lomamayula@gmail.com

วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2558;10(3):81-86

Mayula Lomarat[1]*, Peeraya Sriphong[1], Jantip Kanjanasilp[1] and Yupaporn Preechagoon[2]

[1] Department of Clinical Pharmacy, Faculty of Pharmacy, Mahasarakham University, 44150 Thailand
[2] Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University, 40002 Thailand

* **Corresponding author:** lomamayula@gmail.com

Thai Pharmaceutical and Health Science Journal 2015;10(3):81-86

บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินสมการที่เหมาะสมที่สุดสำหรับคนไทยในการคำนวณค่าการกำจัดยาดิจ๊อกซิน ซึ่งได้แก่ Sheiner, Sheiner 1977, Jusko, Yukawa (1997 และ 2001), Bauer, Nagaraja, Nakajud และสมการสำหรับทำนายระดับยาในเลือด ได้แก่ Bauman **วิธีการศึกษา:** ทำการศึกษาโดยการเจาะวัดระดับยาดิจ๊อกซินในเลือดผู้ป่วยที่รับประทานยาอย่างสม่ำเสมอติดต่อกันเป็นเวลาอย่างน้อย 7 วัน จำนวน 37 ราย จากโรงพยาบาลชุมชน 3 แห่ง ระหว่างมกราคมถึงกันยายน พ.ศ. 2556 **ผลการศึกษา:** พบว่าผู้ป่วยส่วนใหญ่เป็นเพศหญิง (ร้อยละ 67.6) มีอายุเฉลี่ย 64.32 ± 10.4 ปี น้ำหนักเฉลี่ย 52.03 ± 10.9 กิโลกรัม มีภาวะไตวายอยู่ในระยะที่ 3 (Clcr เท่ากับ 30 – 59 ml/min) (ร้อยละ 62.2) ใช้ยาดิจ๊อกซินเพื่อรักษาภาวะ Atrial fibrillation (ร้อยละ 56.8) ได้รับยาดิจ๊อกซินขนาด 125 ไมโครกรัม วันละ 1 ครั้ง (ร้อยละ 67.6) ผู้ป่วยส่วนใหญ่มีระดับยาดิจ๊อกซินในเลือดอยู่ในช่วงการรักษา (0.5 – 2.0 ng/ml) (ร้อยละ 78.4) พบว่าสมการของ Yukawa 2001 มีความถูกต้องและไม่มีอคติในการทำนายระดับยาดิจ๊อกซินในเลือด ซึ่งมีค่า mean prediction error (MPE) = 0.08 (95%CI = -0.05 - 0.21) และ mean absolute error (MAE) = 0.21 (95%CI = 0.11 - 0.31) **สรุป:** สมการของ Yukawa 2001 เหมาะสมสำหรับการคำนวณค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาดิจ๊อกซิน คือค่า clearance เพื่อนำไปใช้ทำนายระดับยาดิจ๊อกซินในเลือดต่อไป

คำสำคัญ: ดิจ๊อกซิน การทำนาย ระดับยาดิจ๊อกซินในเลือด, สมการ

Abstract

Objective: To evaluate the calculation equation that was most suitable for predicting serum digoxin in Thai patients. The equations included those of Sheiner, Sheiner 1977, Jusko, Yukawa (1997 and 2001), Bauer, Nagaraja, Bauman and Nakajud. **Materials and Method**: Blood samplings were collected from 37 patients who received digoxin at least 7 consecutive days at 3 community hospitals from January and September 2013. **Results:** The results revealed that most of the patients were female (67.6%), with an average age of 64.32 ± 10.4 years, average weight of 52.03 ± 10.9 kg, renal function in stage 3 (Clcr 30 – 59 ml/min) (62.2%), having atrial fibrillation (56.8%) and receiving digoxin dose of 125 mcg/day (67.6%). Most of serum concentrations were in therapeutic level (0.5 – 2.0 ng/ml) (78.4%). It was shown that Yukawa 2001 equation had no bias [mean prediction error = 0.08 (95%CI = -0.05 - 0.21)] and more accuracy [mean absolute error = 0.21 (95%CI = 0.11 - 0.31)] than the other equations. **Conclusion**: The Yukawa 2001 equation was the most suitable method to be used along with the provision of pharmaceutical care for patients using digoxin at digoxin clinic in community hospitals.

Keywords: digoxin, prediction, serum digoxin, equation

Introduction

Digoxin is an inotropic agent primarily used to treat heart failure (HF) and atrial fibrillation (AF).[1] Since digoxin has a narrow therapeutic index (0.5 – 2.0 ng/ml), serious toxic effect may occur even if the drug is used in a recommended dose as it has a large inter-patient variability in its pharmacokinetic property. Digoxin had a large volume distribution and is renally excreted. Factors associated with inter-patient variability included age, weight, disease state and renal function.[2,3] Co-administration of interacting drug such as amiodarone, verapamil, spironactone increases serum digoxin concentration. Serum digoxin monitoring is an important process for optimizing digoxin therapy. However, in Thailand, particularly at the community hospital, due to financial barriers, digoxin concentration monitoring is not always accessible in a routine practice.[4] Many equations have been developed to predict serum digoxin; nevertheless, there was a lack of predictive performance evaluation of these equations for Thai patients using digoxin. The purpose of this study was to evaluate the equations most suitable for calculating digoxin clearance including those of Sheiner, Sheiner 1977, Jusko, Nakajud, Yukawa (1997 and 2001), Bauer, Nagaraja and an equation for predicting serum digoxin concentrations of Bauman.

Materials and Methods

Data source

The present study was a cross-sectional observational study. The study protocol was approved by the Ethic Committee of Human Research of Mahasarakham University

(0133/2555). The electronic medical records of patients who received digoxin tablet over a 9-month period (January to September 2013) were used to screen for eligible patients. This screening procedure yielded 74 potentially eligible patients. The medical records of these patients were then reviewed following inclusion criteria: age 18 years or older, receiving stable oral digoxin dose at least 1 month, receiving digoxin at least 7 consecutive days, and having serum digoxin concentration of $\geq$ 0.3 ng/ml. The patients had given informed consent. Patients were excluded from the study if any of these exclusion criteria were met: the presence of end-stage renal function (GFR $\leq$ 15 ml/min/1.73 m^2), having active hepatitis, biliary obstruction, or severe liver disease, or having a serum digoxin concentration of < 0.3 ng/ml.

Digoxin assay

All blood samples were drawn before the morning dose for assay (22 – 24 hours after previous dose). Serum digoxin concentrations were determined by the Chemiluminescent Microparticle Immunoassay (Abbott Architect Digoxin System). The lower limit of detection for this assay is 0.3 ng/ml and $\leq$ 10% total coefficient of variation (CV). Spironolactone and canrenone does not interfere with the determination of digoxin concentration by this method.

Description of the prediction methods

Steady state serum digoxin concentrations (SDC) was calculated by using the digoxin clearance from equations including those of Sheiner, Sheiner 1977, Jusko, Nakajud, Yukawa (1997 and 2001), Bauer, and Nagaraja. The Bauman equation was used to predict serum digoxin concentrations.

Steady state digoxin serum concentration was calculated by using the following equation:

$C_{ave\text{-}ss}$predicted = [MD * F] / [Cl * τ]

Digoxin clearance was predicted by 8 equations as follows:

Sheiner:

No CHF: CL(L/day) = [Clcr(ml/min/kg)] + 0.8] * BW(kg) * (factors) * 1.44

CHF: CL (L/day) = [0.9(Clcr(ml/min/kg))] + 0.33] * BW(kg) * (factors) * 1.44

Jusko:

CL = [(A * CrCl) + B] * C

Bauer:

CL [L/h] = [2.37 + 0.0797*Clcr] * 0.68^{VER} * 0.511^{QUI}

CL (L/h) = 0.795 * $Scr^{-0.650}$ * $WT^{0.533}$ * 0.71^{VER} * 0.595^{QUI}

Shiener 1977:

CL (L/h) without CHF = 0.06 * CrCL+0.05 * TBW

CL (L/h) CHF = 0.053 * CrCL + 0.02 * TBW

Yukawa 1997:

CL (L/day) = 106.0[1-0.00475*AGE]*$TBW^{0.310}$*$Scr^{-0.569}$* 0.858^{GEN} * 0.895^{SPI} * 0.813^{CHF}*0.824^{DFAC}

CL (L/day) = 29.6*CLcr0.526*0.9^{SPI}*0.814^{CHF}*0.833^{DFAC}

Yukawa 2001:

CL (L/h) = [0.036 * TBW + 0.112*CLcr] * 0.77^{SPI} * 0.784^{CCB}

Nagaraja:

CL = 0.053 * CL_{CR} + 2.06

Nakajud:

CL/F (L/hr) = 0.122 * CrCl

Digoxin serum concentrations were predicted by equations as follows:

Bauman:

Cpe = 1.345 + [0.287 * Dose] – [0.007 * Clcr] – [0.011 * IBW]

where,

$C_{ave\text{-}ss}$predicted = predicted concentration at steady state, MD = Maintenace dose, F = Bioavailability, CL = Digoxin Clerance, τ = Dosing interval, CHF = congestive heart failure, CrCl = normalized creatinine clearance [ml/min], BSA = Body surface area (square meters), A = 0.88, for patient with Acute CHF, otherwise=1, B = 23, for patient with Acute CHF, otherwise = 40, C = correction factor for interacting drugs (quinidine = 0.65, spironolactone = 0.75, verapamil = 0.7), VER = 1 for combination with verapamil, 0 for otherwise, GEN = 1 for combination with gentamicin, 0 for otherwise, QUIN = 1 for combination with quinidine, 0 for otherwise, Scr = serum creatinine, SPI = 1 for combination with spironolactone, 0 for otherwise, WT = total body weight [kg], AGE = age (year), DFAC = 1 for half a tablet, 0 for one tablet, CHF = 1 for patient with Acute CHF, 0 for otherwise, CCB = 1 for combination with calcium antagonist (diltiazem, nifedipine, verapamil), 0 for otherwise, Cpe = Expected plasma concentration, Clcr = Creatinine clearance, Dose = Maintenance dose of digoxin, IBW = Ideal body weight.

Statistical analysis

Continuous data were presented as mean $\pm$ SD. Categorical data were presented as numbers and percentages. The correlations between the observed and the predicted serum digoxin concentrations by the different equations were tested by Pearson's correlation coefficient. The predictive performance of each equation was also evaluated by calculating the mean prediction error (MPE) and mean absolute error (MAE). MPE, which describes the bias that may be present, and MAE, a measure of accuracy, were calculated by the following equations:

$$MPE = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{Cp_{ei} - Cp_{oi}}{Cp_{oi}}\right]$$

$$MAE = \frac{1}{N}\sum_{i=1}^{N}\left[Cp_{oi} - Cp_{ei}\right]$$

Where,

n = number of non-missing data points

N = number of non-missing data points

Cp_{ei} = Expected concentration

Cp_{oi} = Observed concentration

Results

From a total of 74 patients, 37 were excluded from the analysis: digoxin was discontinued by physician in 9 patients, 6 patients were lost follow up, 2 patients had GFR of < 15 ml/min and 20 patients had digoxin concentrations of < 0.3 mcg/ml. The remaining 37 patients had digoxin concentrations that met the inclusion criteria. Of these 37, 25 were female (67.6%) (Table 1). Thirty-four patients (91.9%) had indication for atrial fibrillation. Twenty-five patients (67.6%) were receiving digoxin 125 mcg once daily, while 12 patients (32.4%) were receiving 250 mcg once daily. Laboratory analyses revealed that 27 patients (73.0%) had a normal potassium concentration, and 23 patients (62.2%) had creatinine clearance range between 30 and 59 ml/min. There were 10 patients (27.0%) having underlying hypertension and 24 patients (64.9%) receiving antiplatelet agents.

Table 1 Baseline characteristics.

Characteristics	Number (%) (N = 37)
Female gender	25 (67.6)
Age [years], mean ± SD	64.32 ± 10.4
Weight [kg], mean ± SD	52.03 ± 10.9
Height [cm], mean ± SD	156.32 ± 6.1
Indication	
Atrial fibrillation	34 (91.9)
Congestive heart failure,	3 (8.1)
Digoxin dose [mcg/day]	
125	25 (67.6)
250	12 (32.4)
Potassium concentrations	
Low	10 (27.0)
Normal	27 (73.0)
Renal function (ml/min)	
Clcr ≥ 90	1 (2.7)
Clcr 60 – 89	7 (18.9)
Clcr 30 – 59	23 (62.2)
Clcr 15 – 29	6 (16.2)
Comorbidity	
Hypertension	10 (27.0)
Diabetes mellitus	7 (18.9)
Thyrotoxicosis	3 (8.1)
Hyperlipidemia	2 (5.4)
Mitral stenosis	2 (5.4)
Gout	1 (2.7)
Ischemic heart disease	1 (2.7)
Asthma	1 (2.7)
Concomitant drug	
Diuretics	16 (43.2)
ACEIs	12 (32.4)
Beta-blockers	10 (27.0)
Calcium channel blockers	10 (27.0)
Antiplatelet agents	24 (64.9)
Anticoagulants	18 (45.9)
Vitamins and minerals	22 (71.0)
Lipid-lowering agents	14 (43.2)
Antidiabetics	6 (16.2)
Proton pump inhibitors	7 (18.9)
Benzodiazepines	3 (8.1)
Antithyroid agents	3 (8.1)
Nitrates	69 (16.2)
Uricosuric agents	1 (2.7)
Xanthine oxidase inhibitors	1 (2.7)
Corticosteroids inhalants	1 (2.7)
Beta2 agonists	1 (2.7)
Xanthine derivatives	1 (2.7)
Tricyclic antidepressants	1 (2.7)

In terms of digoxin concentrations, the steady state digoxin concentrations for analysis ranged from 0.3 to 1.7 ng/ml (mean ± SD: 0.73 ± 0.32 ng/ml).

Correlation between the observed and predicted digoxin concentration

Overall, 29 out of 37 measured serum digoxin concentrations (78.4%) were in the therapeutic range (0.5 – 2.0 ng/ml) and 8 measured concentrations (21.6%) were in the sub-therapeutic range (< 0.5 ng/ml). Signs and symptoms of disease of all patients were controlled and there were also no signs and symptoms of digoxin intoxication and adverse events. The mean ± S.D., minimum and maximum measured serum digoxin concentrations were 0.73 ± 0.32, 0.3 and 1.7 mcg/ml, respectively. The minimum – maximum observed and predicted serum digoxin concentrations are shown in Table 2.

Table 2 The minimum – maximum of observed and predicted serum digoxin concentrations (SDC).

Equation/variable	Minimum – Maximum SDC (mcg/L)	Mean ± SD (mcg/ml) of SDC
Observed concentrations	0.3 – 1.7	0.73 ± 0.32
Sheiner	0.6 – 6.30	1.88 ± 1.07
Jusko	0.53 – 2.63	1.11 ± 0.46
Bauer	0.39 – 1.90	0.81 ± 0.33
Sheiner1977	0.47 – 2.17	0.94 ± 0.39
Yukawa1997	0.32 – 1.23	0.55 ± 0.18
Yukawa2001	0.32 – 2.56	0.79 ± 0.41
Nagaraja	0.55 – 2.40	1.08 ± 0.43
Nakajud	0.49 – 4.62	1.36 ± 0.78
Bauman	-0.6 – 0.78	0.48 ± 0.17

Figure 1 shows the linear-regression analyses between the observed and predicted serum digoxin concentrations for the different tested equations. The Nakajud equation showed the strongest correlation (r^2 = 0.576; *P* <.001) in comparison to the other tested equations (with r^2 of all other equations in the range of 0.47 to 0.52). The Bauman equation which was

used to predict digoxin serum concentrations had an r^2 of 0.199 (*P*-value = 0.06).

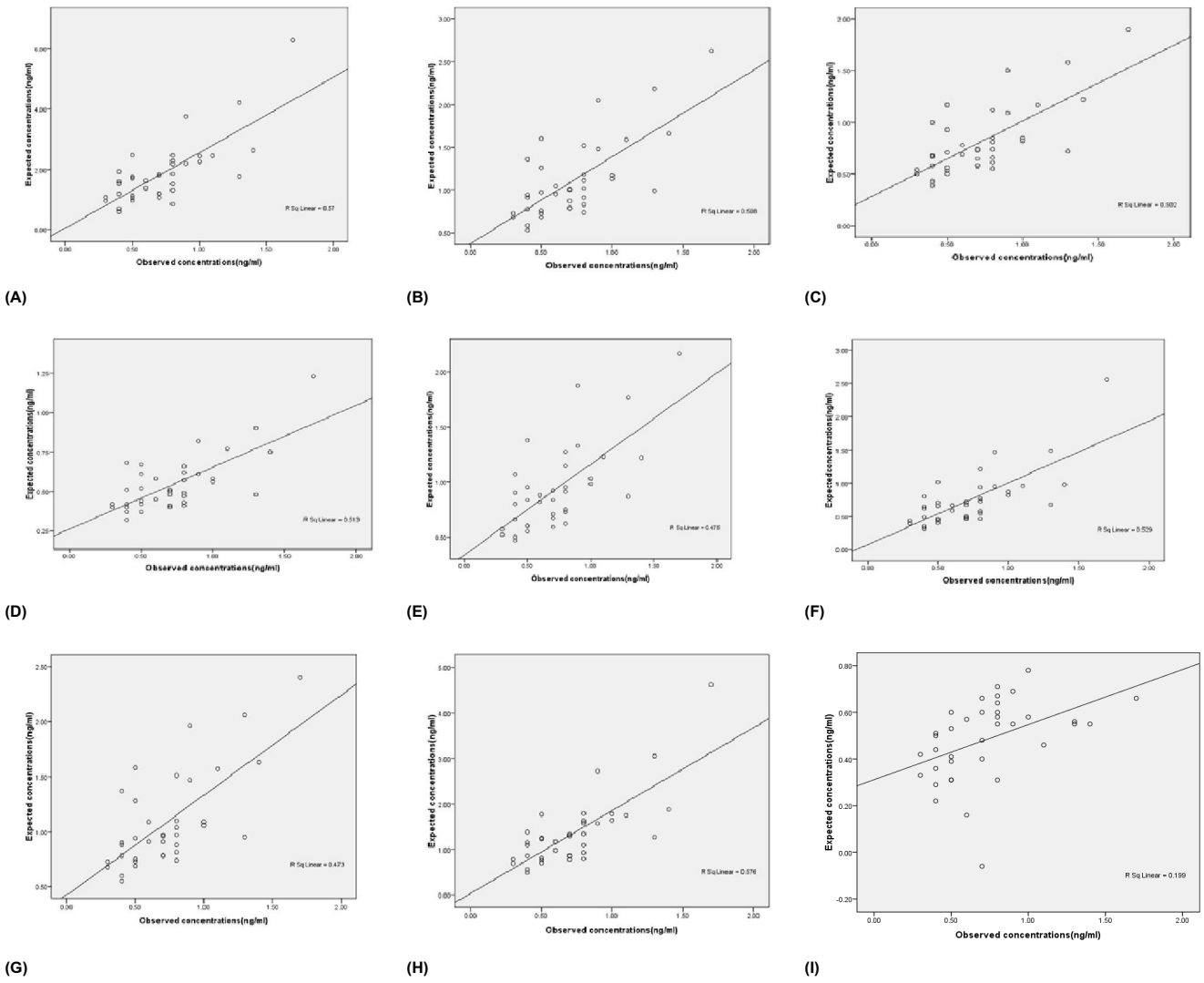

Figure 1 Linear-regression analyses showing the correlation between the observed and predicted SDC (ng/ml) according to; the Sheiner equation (A), the Jusko equation (B), the Bauer equation (C), the Sheiner 1977 equation (D), the Yukawa 1997 equation (E), the Yukawa 2001 equation (F), the Nagaraja equation (G), the Nakajud equation (H) and the Bauman equation (I). Note that the Nakajud equation shows the best correlation in the linear-regression.

A comparison between the measured and predicted SDCs for the different equations were also tested by the mean absolute error (MAE) and mean prediction error (MPE), which demonstrated the lowest values, meaning higher accuracy and less bias (Table 3). The MAE and MPE (with 95% confidence interval) for each equation were more likely to over-predict except the Bauman equation which had a lower prediction error. However the Yukawa 2001 equation showed the best predictive performance.

Table 3 Mean prediction error (MPE) and mean absolute error (MAE).

Equations	MPE (95%CI)	MAE (95%CI)
Sheiner	1.67 (1.28 - 1.92)	1.15 (0.87 - 1.44)
Jusko	0.65 (0.45 - 0.85)	0.41 (0.31 - 0.51)
Bauer	0.21 (0.07 - 0.36)	0.20 (0.10 - 0.30)
Sheiner1977	0.39 (0.22 - 0.56)	0.27 (0.17 - 0.37)
Yukawa1997	-0.16 (-0.26 - -0.06)	0.23 (0.13 - 0.33)
Yukawa2001	0.08 (-0.05 - 0.21)	0.21 (0.11 - 0.31)
Nagaraja	0.62 (0.42 - 0.82)	0.38 (0.28 - 0.48)
Nakajud	0.93 (0.70 – 1.15)	0.63 (0.51 - 0.83)
Bauman	-0.26 (-0.36 - -0.15)	0.27 (0.17 - 0.37)

Discussion and Conclusion

In current study measuring predictive performance using mean absolute error (MAE) and mean prediction error (MPE), the Yukawa 2001 equation had lowest bias (MPE = 0.08, 95%CI = -0.05 - 0.21) and provided the most accuracy (MAE = 0.21, 95% CI = 0.11 - 0.31) compared to the other equations. As shown in Table 2, the performance of the Sheiner, Sheiner 1977, Jusko, Nakajud, Yukawa (1997 and 2001), Bauer, and Nagaraja tended to over-predict serum digoxin concentration because these equation were created from heart failure that had a lower digoxin clearance than atrial fibrillation who were subjects in current study.

Most of serum digoxin concentrations were in therapeutic level (0.5 – 2.0 ng/ml) (78.4%). Measured serum digoxin concentration in current study (0.73 ± 0.32 mcg/L, range: 0.3 – 1.7 ng/ml) was lower than previous study because most of patients were outpatients with atrial fibrillation. This finding suggested that serum digoxin concentration in admitted patients with congestive heart failure were higher than in patients with atrial fibrillation and serum digoxin concentration in in-patients were higher than in outpatients that were found in previous studies.[5,6] Several studies have found that congestive heart failure is an important factor in estimating digoxin clearance. Sheiner et al found that digoxin clearance was lower in patients with congestive heart failure than in patients without congestive heart failure.[6] Naffs et al found that digoxin clearance was lower in patients with congestive heart failure than in patients with atrial fibrillation (2.88 ± 1.226 vs 4.26 ± 2.16 L/h).[7] Congestive heart failure was known to cause reduced gastric emptying and malabsorption of drug.[8] From linear-regression analysis in our study, the observed and predicted serum digoxin concentrations from most equations were correlated. This indicates that the predicted concentration was closely correlated to the observed concentration.

In current study, the predictive performance of Sheiner 1977 was relatively low with MAE of 0.27 (95%CI = 0.17 - 0.37) and MPE of 0.39 (95%CI = 0.22 - 0.56), showing less accuracy and more bias than previous study. El-sayed et al[9] found that Sheiner 1977 equation in CHF had ME = -0.03 (-0.08 – 0.01), MSE = 0.01 (0.01 – 0.02) and non-CHF had ME = -0.05 (-0.09 – 0.01), MSE = 0.03 (0.02 – 0.04) because of difference in method to evaluate creatinine clearance. El-sayed used the 24-hr urine collected method to evaluate creatinine clearance while our current study calculated creatinine clearance by using Crockcroft and Gault equation. The performance of Jusko, Bauer, Yukawa 1997, Nagaraja and Nakajud equation tended to over-predict serum digoxin concentration because the equation was created from in-patients with congestive heart failure who were admitted whereas most of the patients from the study were outpatients with atrial fibrillation known to have serum digoxin concentration lower than in admitted patients with congestive heart failure.[5,7,8,10-12] The Yukawa 2001 equation was found to have MPE = 0.08 (95% CI = -0.05 - 0.21) and MAE = 0.21 (0.11 - 0.31) that were similar to previous study because Yukawa equation was performed by adjusting several factors such as body weight, and drug co-administration (spironolactone, diltiazem, nicardipine, nifedipine and verapamil) in the equation.[13] The Bauman equation predictive performance was reflected as MAE = 0.27 (95% CI = 0.17 - 0.37) and MPE = -0.26 (95% CI = -0.36 – -0.15) which was close to the result from Buaman (root mean square error of 0.375). However this result was less accurate and more biased than Muzzarelli study conducted in Caucasians (root mean square error of 0.17), implying that these differences might be due to different ethnic groups,[14,15] which were also related to pharmacogenetic expression. This could be explained by previous studies showing that the patients with multidrug resistance protein1 (MDR1) genotype C3435T SNP homozygous TT had 20% serum digoxin concentration higher than heterozygous CT and homozygous CC [TT > CT > CC]. The genotype TT was found in 20% Chinese, 24% German, 28% British but not found in Ghanaian[16-20], however there was no such study in Thai patients.

Our study was conducted in a routine healthcare practice and patient compliance was assessed before collecting blood sample. There were a few limitations of the study. The current study used population digoxin bioavailability parameter values for calculation because there were no bioequivalence data from the digoxin brand used the 3 community hospitals. However the 3 hospitals used the same brand. Therefore, future study should use digoxin bioavailability from a drug company. In addition, the study recruited too small sample size. The number of eligible subjects should be increased. Patients with congestive heart failure should also be included in future studies.

Conclusion

The Yukawa 2001 equation showed the best predictive performance which could be incorporated to the provision of pharmaceutical care at digoxin clinic in community hospitals for better care of all patients using digoxin. This finding could help reduce financial problems of those patients who cannot access standard routine digoxin serum monitoring.

Acknowledgements

This study was financially supported by the Faculty of Pharmacy, Mahasarakham University and Pathumratcha-wongsa hospital.

References

1. Kelly RA, Smith TW. Pharmacological treatment of heart failure In: Hardman TG, Limbird LE (eds.). Goodman & Gilman's the pharmacological basis of therapeutics, 9th ed. New York. McGraw-Hill, 1996.
2. Yukawa E, Honda T, Ohdo S, Hiuchi S, Aoyama T. Population-based investigation of relative clearance of digoxin in Japanese patients by multiple trough screen analysis: an update. *J Clin Pharmacol* 1997; 37:92-100.
3. Yukawa E, Mine H, Higuchi S, Aoyama T. Digoxin population pharmacokinetics from routine clinical data: role of patient characteristics for estimating dosing regimens. *J Pharm Pharmacol* 1992;44:761-765.
4. Soto E. The use of digitalis a prospective study of weekly interruption digoxin dosage. *Rev Espan Cardiol* 1990;43:123-128.
5. Sheiner LB, Rosenberg B, Marathe VV, Perk C. Differences in serum digoxin concentrations between outpatients and inpatients: an effect of compliance? *Clin Pharmacother* 1974;15:239-246.
6. Sheiner LB, Rosenberg B. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J Pharmacokinet Biopharm* 1977;5:445-479.
7. Naafs MAB, van der Hoek C, van Duin S. Decreased renal clearance of digoxin in chronic congestive heart failure. *Eur J Clin Pharmacol* 1985;29:249-252.
8. Shammas FV, Dickstein K. Clinical pharmacokinetics in heart failure: an updated review. *Clin Pharmacokinet* 1988;15:94-113.
9. El-Sayed YM. Predictive performance of four pharmacokinetic methods for calculating digoxin dosage. *J Clin Pharm Ther* 1995;20(5):297-304.
10. Nagaraja YJP, Jeon S, Sand CD, Derendorf H. Population pharmacokinetics of digoxin in Korean patients. *Inter Clin Pharmacol Ther* 2000;38:291-297.
11. Nakajud P, Preechagoon Y, Wongwipaporn C, Ariyapim N. Population pharmacokinetic analysis of digoxin for designing appropriate dosage regimen in Thai patients. The 3rd Annual Northeast Pharmacy Research Conference 2011, 2011.
12. Bauer LA, Horn JR, Pettit H. Mixed-effect modeling for detection and evaluation of drug interactions: digoxin-quinidine and digoxin-verapamil combinations. *Ther Drug Monitor* 1996;18(1):46-52.
13. Yukawa E, Suematu F, Yukawa M, et al. Population pharmacokinetics of digoxin in Japanese patients: a 2-compartment pharmacokinetic model. *Clin Pharmacokinet* 2001;40(10):773-781.
14. Ieiri I, Takane H, Otsubo K. The MDR1 (ABCB1) gene polymorphism and its clinical implications. *Clin Pharmacokinet* 2004;43:553-576.
15. Kurata Y, Ieiri I, Kimura M, et al. Role of human MDR1 gene polymorphism in bioavailability and interaction of digoxin, a substrate of P-glycoprotein. *Clin Pharmacokinet Ther* 2002;72:209-219.
16. Muzzarelli S, H. Stricker, O. Pfister P, et al. Individual dosage of digoxin in patients with heart failure. *Q J Med* 2011;104:309-17.
17. Bauman JL DR, Viana M, et al. A method of determining the dose of digoxin for heart failure in the modern era. *Arch Intern Med* 2006; 166:2539-2545.
18. Li Yan-Hong, Wang Yng-Hua, Li Yan, Ling Y. MDR1 gene polymorph-isms and clinical relevance. *Acta Genetica Sinica* 2006; 33(2):93-104.
19. Ameyaw MM, Regateiro F, Li T, et al. MDR1 pharmacogenetics: frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity. *Pharmacogenetics* 2001;11:217-221.
20. Kurzawski M, Bartnicka L, Florczak M, Gornik W, Drozdzik M. Impact of ABCB1(MDR1) gene polymorphism and P-glycoprotein inhibitors on digoxin serum concentration in congestive heart failure patients. *Pharmacol Reports* 2007;59:107-111.

Editorial note

Manuscript received in original form on December 25, 2014; accepted in final form on July 20, 2015