การทำนายความเข้มข้นของยาคาร์บาร์มาซีปีนในซีรั่มในผู้ป่วยไทยที่เป็นโรคลมชักโดยแบบจำลองเภสัชจลนพลศาสตร์ประชากรที่ปรับแล้ว

PREDICTION OF STEADY-STATE SERUM CARBAMAZEPINE CONCENTRATIONS IN THAI EPILEPTIC PATIENTS BY MODIFIED POPULATION PHARMACOKINETIC MODELS

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บทคัดย่อ

วัตถุประสงค์ของการศึกษาวิจัยครั้งนี้ต้องการทำนายค่าความเข้มข้นของยาคาร์บาร์มาซีปีนในซีรั่มที่สภาวะคงที่โดยอาศัยค่าอัตราการขจัดยา (CL/F) จากแบบจำลองเภสัชจลนพลศาสตร์ประชากรของเกรฟ, ไรทช์, ชาน, เจา 2003 และเจา 2004 และค่าจากแบบจำลองดังกล่าวที่ปรับ นอกจากนี้ยังต้องการเปรียบเทียบค่าอคติ (bias) (mean error, **me**) และค่าความแม่นยำ (precision) (root mean square error, **rmse**) เพื่อเลือกแบบจำลองที่เหมาะสมที่สุด โดยใช้การเก็บข้อมูลระดับยาคาร์บาร์มาซีปีนในซีรั่มของผู้ป่วยโรคลมชักที่มารับรักษา ณ แผนกผู้ป่วยนอกของสถาบันประสาทวิทยา จำนวน 99 ราย และโรงพยาบาลสรรพสิทธิ์ประสงค์ จังหวัดอุบลราชธานี จำนวน 32 ราย รวมทั้งสิ้น 131 ราย โดยการเก็บข้อมูลแบบติดตามไปข้างหน้า โดยเลือกแบบจำลองประชากรที่มีค่าอคติและค่าความแม่นยำใกล้ค่าศูนย์ที่สุด เป็นแบบจำลองที่เหมาะสมสำหรับผู้ป่วยชาวไทยที่เป็นโรคลมชัก นอกจากนี้มีการเก็บข้อมูลเพิ่มเติมอีกจำนวน 40 ราย เพื่อทดสอบแบบจำลอง (model validation) ประชากรที่เลือกแล้วกับแบบจำลองต้นแบบที่ศึกษา

ผลการศึกษาวิจัยพบว่า แบบจำลองประชากรที่เหมาะสมที่สุดสำหรับผู้ป่วยชาวไทยที่เป็นโรคลมชัก ได้จากการปรับแบบจำลองของเจา 2004 โดยแบบจำลองดังกล่าวเป็นดังนี้ CL/F (L/hr) = 0.165 x dose (mg/d) $^{0.41}$ x TBW (kg) $^{0.11}$ x 1.25 ^{VPA} x 1.18 ^{PHT} x 1.27 ^{PB} และเมื่อได้ค่า CL นำไปคำนวณ

ต่อหา C_{ss}^{min} (μg/mL) = Dose (mg/day)/CL (L/day) โดยค่า Mean Error เท่ากับ 0.02 (95%CI -0.3, 0.40) และ ค่า Root Mean Square Error เท่ากับ 2.13 (95%CI 1.83, 2.38) ซึ่งต่ำที่สุดแสดงว่ามีค่าอคติต่ำ และความแม่นยำสูง เมื่อทดสอบโดยใช้ข้อมูลกับผู้ป่วยจำนวน 40 ราย เปรียบเทียบกับแบบจำลองอื่น ๆ พบว่าแบบจำลองที่ปรับแล้วมีค่า Mean Error เท่ากับ -0.96 (95%CI -1.67, -0.26) และมีค่า Root Mean Square Error เท่ากับ 2.39 (95%CI 1.80, 2.85) เมื่อทดสอบความแตกต่างของค่า Mean Error ของแบบจำลองที่ปรับแล้วกับแบบจำลองอื่นทีละคู่ พบว่าแบบจำลองของเจา 2004 ที่ปรับแล้วมีค่า Mean Error ต่ำกว่าแบบจำลองของไรทช์, เจา 2003 และ เจา 2004 อย่างมีนัยสำคัญทางสถิติที่ p=0.004, p<0.001 และ p<0.001 ตามลำดับ และแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ กับแบบจำลองของเกรฟและชาน ส่วนการทดสอบความแตกต่างของค่า Root Mean Square Error ของแบบจำลองของเจา 2004 ที่ปรับแล้ว กับแบบจำลองอื่น ๆ ทีละคู่ พบว่าแบบจำลองที่ปรับแล้ว แตกต่างกันอย่างไม่มีนัยสำคัญกับแบบจำลองของเกรฟ แต่แตกต่างจากแบบจำลองของ ไรทช์, ชาน, เจา 2003 และเจา 2004 อย่างมีนัยสำคัญที่ p=0.034, 0.002, 0.005 และ 0.001 ตามลำดับ

จากผลการศึกษาที่ได้สรุปได้ว่าแบบจำลองของเจา 2004 ที่ปรับแล้ว เป็นแบบจำลองที่เหมาะสมที่สุดสำหรับผู้ป่วยชาวไทยที่เป็นโรคลมชัก สามารถทำนายได้แม่นยำและเที่ยงตรงกว่าแบบจำลองเดิมของเกรฟ, ไรทช์, ชาน, เจา 2003 และเจา 2004

คำสำคัญ : คาร์บามาซีปีน, เภสัชจลนพลศาสตร์ประชากร, โรคลมชัก

Abstract

The aims of this study were to predict serum carbamazepine concentrations in Thai epileptic patients using the estimated total population clearances of Graves, Reith, Chan, Jiao 2003, and Jiao 2004 models and modified forms of these models, and to compare bias (mean error, **me**) and precision (root mean square error, **rmse**) in order to select the most appropriate modified model among these studied models. The models were modified based on prospective observational data from 131 patients (99 patients from the Prasart Neurological Institute, Bangkok and 32 patients from Suppasithiprasong Hospital, Ubonratchathani), using an optimization method available in Excel (Solver Function). Selection of the modified models was performed according to their mean errors (bias) and root mean square errors (precision), the closest of these values to zero in a particular model indicating the most appropriate modified model. Additional prospective data obtained from 40 patients were used for validating the most appropriate modified model and the original studied models.

Based on the prospective data and the lowest **me** and **rmse** values, the most appropriate modified model for Thai epileptic patients was the modified Jiao 2004 population model with clearance (CL) of carbamazepine estimated from the following equations: $CL/F\ (L/hr) = 0.165 \times dose\ (mg/d)^{0.41} \times Total\ body\ weight\ (kg)^{0.11} \times 1.25^{VPA} \times 1.18^{PHT} \times 1.27^{PB}$.

Furthermore, when the prospective test data (n=40) were used for validating this modified model, bias and precision were -0.96 (95%CI -1.67, -0.26) and 2.39 (95%CI 1.80, 2.85), respectively. These values were lower than and significantly different from those of the Jiao 2004 model (p<0.002) and other models (p<0.05), except with those of the Grave model (me= -1.18, p=0.391 and rmse=2.83, p=0.082).

In conclusion, the findings suggest that the most appropriate modified model for Thai epileptic patients is the modified Jiao 2004 model as compared with the Graves, Reith, Chan, Jiao 2003 and Jiao 2004 models.

Keywords: Carbamazepine, Population Pharmacokinetics, Epilepsy

Introduction

Carbamazepine is a narrow therapeutic anti-epileptic drug and has been used as a drug of choice in partial and also generalized tonic-clonic seizures.[1] Additional therapeutic use has also been contributed for the treatment of neuropathic pain and bipolar disorder.[2,3] Variable bioavailability due to its CYP3A4-associated metabolism and auto-induction causes carbamazepine to have variable, but predictable concentrations in serum.[4] Co-medication with other enzyme-inducers or inhibitors also plays a role in variability of serum carbamazepine concentrations in individual patients. The defined therapeutic range of carbamazepine is between 4-12 μg/mL and therapeutic drug monitoring is required to ensure that adverse drug reactions and sub-therapeutic treatment can be avoided.

Attempts have been made to achieve and predict carbamazepine concentrations within a therapeutic range in epileptic patients by employing several population models. These models, namely Graves, Reith, Chan, Jiao 2003, Jiao 2004 models, incorporate covariate factors such as dose, total body weight and other anti-epileptic co-medications into the models to predict clearance and then serum carbamazepine concentrations in epileptic patients.[5-9] Comparison among these population pharmacokinetic models in terms of predictive performance has not been studied and also a population pharmacokinetic model to predict serum carbamazepine concentrations in Thai epileptic patients has not yet been established. The aims of this study were to predict serum carbamazepine concentrations in Thai epileptic patients using Graves, Reith, Chan, Jiao 2003, Jiao 2004 models and modified forms of these models, and to compare bias and precision in order to select the most appropriate modified model among these studied models.

Method

Subjects

Prospective observational serum data of carbamazepine concentrations and characteristic variables from 131 epileptic patients (99 patients from Prasart Neurological Institutes, Bangkok and 32 patients from Suppasithiprasong hospital, Ubonratchathani) were employed for model modification, while other prospective observational data of carbamazepine concentrations from 40 epileptic patients were also used for model validation. This study was approved by the ethic committees of both Prasart Neurological Institute and Suppasithiprasong hospital. The inclusion criteria for selecting patients were as follows: patients receiving the same doses of carbamazepine for at least 4 weeks and/or combining with other anti-convulsants (*i.e.,* phenobarbital, phenytoin, valproicand and felbamate) with good compliance[10], had either immediate released or extended released or syrup dosage forms, age between 1-85 yrs. The exclusion criteria were as follows: patients receiving other medications which affected serum carbamazepine concentrations (*i.e.,* erythromycin, isoniacid, fluoxetine, fluvoxamine, verapramil), being pregnant, having history of liver or kidney diseases, having other diseases such as congestive heart failure and denying to participating in the study. Inform consents were all signed by enrolled patients.

Samples and Assay Method

Blood samples were collected at least after 6-8 hr from last dose (at steady-state, 30 days after first doses) in selected individual patients, and then separated to give serum samples. Serum carbamazepine concentrations from both prospective serum samples were measured by a routine clinical analysis using SYNCHRON LX® System which has good performance as compared with Abbott TDx analyzer. The linearity of serum carbamazepine concentrations analyzed by the system is between 2.00-20.0 μg/mL (8.5-84.64-12 μmol/L) and the limit of quantification (LOQ) is 1 mg/L with %CV less than 10%.

Model Modification and Model Validation

Modification of models was based on an optimization procedure carried by Excel Program (Version 2000) using Solver function. Predicted steady-state trough concentrations of carbamazepine (C_{ss}^{min}) of each model (*i.e.,* Graves's, Reith's, Chan's, Jiao 2003's and Jiao 2004's, pharmacokinetic population models) were estimated by their model parameters (*e.g.,* clearance, CL) by which coefficients of covariates in each model were adjusted sequentially. The best values of the coefficients in each model were selected as

the ones that minimized the differences between the observed and predicted steady-state serum concentrations of carbamazepine. Criteria for minimization of the differences were mean prediction errors (**me**) and root mean square errors (**rmse**) that have been described as bias and precision and provide a good description of predictive performance.[11] The equations estimating bias and precision are as follows:

$$\mathbf{me} = \sum(\text{observed} - \text{predicted})/N$$

$$\mathbf{rmse} = \sqrt{\mathbf{mse}}, \text{ where } \mathbf{mse} = \mathbf{me}^2 + \sum (\mathbf{pe}_i - \mathbf{me})^2$$

These two criteria were automatically changed to the lowest possible along the process of the sequential optimization procedure for each individual model used to predict all 131 prospective data points. The same procedure was also employed for the model validation.

Statistical Data Analysis

Data were presented as mean (95%CI) otherwise stated. One sample t-test was used to compare mean prediction errors (**me**) and mean square errors (**mse**) with zero and to obtain 95%confidence interval for **me** and **rmse** (after taking a square root). Paired t-test was also used for comparing differences of bias and precision among the models. The level of statistical significance was 0.05. All statistical tests were performed using SPSS Version 11.0.

Results

Characteristics of patients for both the model modification set and the validating set were shown in Table 1. All characteristics were comparable, except age**.** Table 2 shows numbers of patients and percentage of other medications given to the patients.

Table 1 Characteristics of patients for both the model modification set and the validation set.

Characteristics	The Model Modification Set	The Model Validation Set	*p*-value
Numbers of Patients (No.)	131	40	
Gender			1.0[a]
Male	65	20	
Female	66	20	
Age (yr)	30 .65±13.71	36.38±13.07	0.023[b]
Weight (kg)	56.67±13.53	61.03±11.27	0.069[b]
Hieght (cm)	158.94±12.09	160.3±9.63	0.471[b]
Serum Carbamazpine Concentrations (μg/mL)	7.53±2.79	6.99±2.69	0.276[b]
Dose of Carbamazepine (mg/day)	866.41±383.43	932.5±381.22	0.357[b]
Dose of Carbamazepine/Body Weight (mg/kg/day)	15.95±7.39	15.49±6.04	0.704[b]

Mean ±SD, a: tested with chi-square, b: tested with unpaired t-test

Table 2 Co-medications of other anti-convulsants with carbamazepine between the two sets of patients.

Anti-Convulsants	The Model Modification Set		The Model Validation Set	
	No	%	No	%
Carbamazepine Monotherapy	55	41.98%	14	35.00%
Carbamazepine Polytherapy	76	58.02%	26	65.00%
Valproic acid (VPA)	40	30.53%	8	20.00%
- VPA >18 mg/kg	*(33)*	*(25.19%)*	*(6)*	*(15.00%)*
Phenytoin (PHT)	10	7.64%	4	10.00%
Phenobarbital (PB)	10	7.64%	11	27.50%
PHT + PHB	9	6.87%	0	0.00%
PHT + VPA	4	3.05%	1	2.50%
- VPA >18 mg/kg	*(3)*	*(2.29%)*	*(0)*	*(0.00%)*
VPA + PB	2	1.53%	2	5.00%
- VPA >18 mg/kg	*(2)*	*(1.53%)*	*(1)*	*(2.50%)*
VPA + PB +PHT	1	0.76%	0	0.00%

The most appropriate modified model for Thai epileptic patients was the modified Jiao 2004 model that estimated the clearance based on the following equation; CL/F (L/hr) = 0.165 x dose (mg/day) $^{0.41}$ x TBW (kg) $^{0.11}$ x 1.25^{VPA} x 1.18^{PHT} x 1.27^{PB}. When the estimated parameter (CL) was used for predicting the trough concentration of carbamazepine via a formulation: C_{ss}^{min}(μg/mL) = Dose (mg/day)/CL (L/day). The modified Jiao 2004 model produced the lowest mean error, 0.02 (95%CI -0.3, 0.40) and root mean square error, 2.13 (95%CI 1.83, 2.38) (Table 3). By using validating data set (n=40), mean error and root mean square error of the modified Jiao 2004 model were -0.96 (95%CI -1.67, -0.26) and 2.39 (95%CI 1.80, 2.85). Mean error of the modified Jiao 2004 was lower than Reith, Jiao 2003 and Jiao 2004 models with statistical significance at $p = 0.004$, $p<0.001$ and $p<0.001$ respectively, but not different from those of Graves and Chan models. Root mean square error of the modified Jiao 2004 model was also lowest (2.39) and different from the Reith, Chan, Jiao 2003 and Jiao 2004 models with statistical significance at $p = 0.034$, 0.002, 0.005 and 0.001, respectively, but not different from Graves model (Table 4)

Table 3 The original Jiao 2004 model and the modified Jiao 2004 model with their associated mean errors (me) and root mean square errors (rmse) using the modification data set (n=131).

Method	Model	Bias (me, μg/mL)	Precision (rmse, μg/mL)
Jaio 2004	CL/F (L/hr) = 0.141 x dose (mg/d) $^{0.406}$ x TBW (kg) $^{0.117}$ x 1.23 ^{VPA} x 1.44 ^{PHT} x 1.26 ^{PB}	-1.07* (-1.47, -0.65)^	2.58 (2.22, 2.87)
Modified Jiao 2004	CL/F (L/hr) = 0.165 x dose (mg/d) $^{0.41}$ x TBW (kg) $^{0.11}$ x 1.25 ^{VPA} x 1.18 ^{PHT} x 1.27 ^{PB}	0.02 (-0.3, 0.40)	2.13 (1.83, 2.38)

*Mean, ^ 95%Confidence Interval

Table 4 The modified Jiao 2004 model and other original models with their associated mean errors and root mean square errors using the validation data set (n=40).

Method	Model	Bias (me, μg/mL)	Precision (rmse, μg/mL)
Modified Jiao 2004	CL/F (L/hr) = 0.165 x dose (mg/d) $^{0.41}$ x TBW (kg) $^{0.11}$ x 1.25 ^{VPA} x 1.18 ^{PHT} x 1.27 ^{PB}	-0.96 (-1.67, -0.26)^	2.39 (1.80, 2.85)
Grave	CL/F (L/hr) = (0.0134 x TBW + 3.58) x 1.42 (PHT only) x 1.17 (PB or FEL) x 1.62 (PHT+PB or FEL) x 0.749 (age>=70)	-1.18 (-2.02, -0.35)	2.83 (2.22, 3.34)
Reith	CL (L/hr) = ((2.24 x surface area (m^2) + (0.047 x dose (mg/kg))	-1.63 (-2.44, -0.82)	2.98 (2.09, 3.66)
Chan	CL (L/d/kg) = 40.7 x A $^{0.494}$ x W $^{-1.17}$ x 1.44 ^{PB}	-0.60 (-1.68, 0.48)	2.94 (2.37, 3.41)
Jiao 2003	CL/F (L/hr) = 0.0722 x dose (mg/kg/d) $^{0.403}$ x TBW (kg) $^{0.697}$ x 1.45 ^{PHT} x 1.17 ^{PB} x 1.21 ^{VPA} x 0.854 ^{E}	-2.01 (-2.70, -1.31)	2.94 (2.37, 40.4)
Jiao 2004	CL/F (L/hr) = 0.141 x dose (mg/d) $^{0.406}$ x TBW (kg) $^{0.117}$ x 1.23 ^{VPA} x 1.44 ^{PHT} x 1.26 ^{PB}	-2.15 (-2.85, -1.45)	3.06 (2.47, 3.55)

*Mean, ^ 95%Confidence Interval

Discussion

Modification and validation of the models based on 131 and 40 patients from Prasart Neurological Institute, Bangkok and Suppasithiprasong hospital, Ubonratchathani was done prospectively and resulted in the most appropriate clearance model for Thai epileptic patients judged by the lowest values of two indexes, mean errors and root mean squared errors as follows:

CL/F (L/hr) = 0.165 x dose (mg/d) $^{0.41}$ x TBW (kg) $^{0.11}$ x 1.25 ^{VPA} x 1.18 ^{PHT} x 1.27 ^{PB}

Previous studies demonstrated that the average population clearance of the drug was 3.3 L/hr based on monotherapy, while polytherapy with other anti-epileptic drugs resulted in increased average population clearance of 5.6 L/hr.[12] Table 5 shows the average population clearances estimated according to the population pharmacokinetic studies used in this study, including the proposed model above.

The proposed model, Jiao 2004, showed that an average population clearance is in accordance with the previous study. It is clear that intra-and inter-individual variability plays an important role in variable response of serum carbamazepine concentrations.[13-17] Factors contributing to both variabilities are daily doses of carbamazepine, patients' weight and concomitant use of other anti-convulsants such as valproic acid, phenytoin and phenobarbital which are usually found in epileptic patients who fail to response to monotherapy by carbamazepine. Phenytoin and phenobarbital has been shown as strong inducers of CYP3A4, a major enzyme system involved in metabolism of carbamazepine in the body.[16,17] In contrast to phenytoin and phenobarbital, valproic acid appears to be involved in displacement of carbamazepine from protein binding sites, thus resulting in increased carrbamazepine clearance.[18] Interplay of these factors, particularly polytherapy of anti-convulsants, were recorded and used in the study models, especially Jiao 2004. It is also noticeable that corresponding variability (%CV see Table 5) was found to be higher in polytherapy than in monotherapy.

Table 5 Estimated Average Population Clearances among the Models Involved

Model		Original Models		Modified Models	
		CL (L/hr)	%CV	CL (L/hr)	%CV
Graves' Model	Monotherapy	4.49	13.18%	4.98	6.46%
	Polytherapy	5.03	18.79%	5.38	10.44%
Reith's Model	Monotherapy	5.76	56.61%	5.16	12.26%
	Polytherapy	5.89	52.97%	5.24	10.69%
Chan's Model	Monotherapy	1.99	32.34%	2.58	31.31%
	Polytherapy	2.28	28.86%	2.57	23.96%
Jiao 2003	Monotherapy	3.61	24.00%	4.04	22.85%
	Polytherapy	4.60	27.99%	5.36	24.66%
Jiao 2004*	Monotherapy	3.67	24.32%	3.99	20.91%
	Polytherapy	4.69	25.96%	5.13	22.13%

* The proposed model

Limitations of this study were 1. Intra- and inter-individual variabilities could not be determined, since modification of the models was based on one single sample (one data point) from individual patient. Suggestions of the programs for genuine population pharmacokinetic study such as NONMEM or PkBUGS should be more appropriate, provided that more data points ($\geq$2 data points) could be obtained.[19,20] 2. elderly patients (>65 yrs) had not been covered in this model, however one can try to apply the model and then adjust it based on concurrent data available at hand when monitoring serum carbamazepine concentrations at the practice site (using the Solver Function of Excel Program). Further development of the program computer based on this modified model has been established (Microsoft Access Programming) and is undergoing for further publication.

This research study was aimed to provide information on the population pharmacokinetics, namely the population clearance of carbamazepine, for effective clinical practice. In particular, for those primary and secondary hospital settings where facilities for therapeutic drug monitoring could be scarce. Dosage regimen and doses can be guided by employing the proposed population clearance equation in order to individualize anti-convulsant therapy appropriately. This would provide a useful guide for medical personnel in rationalizing an effective and safe regimen for carbamazepine therapy.

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