เภสัชจลนศาสตร์ประชากรของยาวอริโคนาโซลในผู้ป่วยเด็กชาวไทย ที่เป็นโรคราแอสเปอร์จิลลัสชนิดรุกราน
Population Pharmacokinetics of Voriconazole in Thai Children Patients with Invasive Aspergillosis

นิพนธ์ต้นฉบับ

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Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินเภสัชจลนศาสตร์ประชากรและปัจจัยที่เกี่ยวข้องของยาวอริโคนาโซลในผู้ป่วยเด็กที่ติดเชื้อราแอสเปอร์จิลลัสชนิดรุกราน **วิธีการศึกษา:** การศึกษานี้เก็บข้อมูลย้อนหลังจากโรงพยาบาล 2 แห่ง ในผู้ป่วยเด็กที่อายุน้อยกว่า 12 ปีที่ได้รับการวินิจฉัยเป็นโรคราแอสเปอร์จิลลัสชนิดรุกราน และได้รับการรักษาด้วยยาวอริโคนาโซล ตั้งแต่เดือนมกราคม 2557 ถึงเดือนธันวาคม 2561 วิเคราะห์เภสัชจลนศาสตร์ประชากรจากข้อมูลการตรวจติดตามระดับยาในเลือด โดยวิธี non-linear mixed-effect model ประเมินความถูกต้องเหมาะสมของแบบจำลองสุดท้ายด้วยวิธี bootstrap และ prediction corrected visual predictive check (pcVPC) **ผลการศึกษา:** จากข้อมูลระดับยาวอริโคนาโซลทั้งหมด 337 ตัวอย่าง จากผู้ป่วย 79 คน พบว่าแบบจำลอง one-compartment model with first-order absorption, linear elimination, and allometric scaling มีความเหมาะสมกับข้อมูลของการศึกษา ค่าเฉลี่ยของค่าการขจัดยาเท่ากับ 11.3 ลิตรต่อชั่วโมงต่อ 70 กิโลกรัม ค่าการกระจายตัวเท่ากับ 273 ลิตรต่อ 70 กิโลกรัม ค่าคงที่การดูดซึมยา 1.19 ต่อชั่วโมง และค่าชีวประสิทธิผลของยารับประทาน เท่ากับ 0.796 ปัจจัยที่มีผลต่อค่าพารามิเตอร์คือ น้ำหนักโดยใช้สมการแอลโลเมตรี (allometric equation) และ aspartate aminotransferase (AST) ต่อค่าการขจัดยา (*P*-value < 0.001) **สรุป:** แบบจำลองทางเภสัชจลนศาสตร์ประชากรสามารถนำมาช่วยประเมินพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาวอริโคนาโซลและเป็นแนวทางในการกำหนดขนาดยาโดยคำนึงถึงปัจจัยที่เกี่ยวข้อง ได้แก่ น้ำหนักและ AST

คำสำคัญ: เภสัชจลนศาสตร์ประชากร, ยาวอริโคนาโซล, เด็ก, ไทย, การติดเชื้อแอสเปอร์จิลลัสชนิดรุกราน

Abstract

Objective: To estimate the population pharmacokinetics of voriconazole, to identify factors influencing voriconazole pharmacokinetics in Thai children patients with invasive aspergillosis. **Methods:** This study was a two-center, retrospective study in children (<12 years) with invasive aspergillosis treated with voriconazole between January 2014 and December 2018. A population pharmacokinetics was conducted from routine voriconazole therapeutic drug monitoring data and was analyzed by a non-linear mixed-effect modeling approach. Bootstrap and prediction corrected visual predictive check (pcVPC) were used to validate the final models. **Results:** A total of 337 voriconazole plasma concentrations from 79 patients were collected in this study. The data were appropriately fitted by a one-compartment model with first-order absorption, linear elimination, and allometric scaling. The mean of clearance was 11.3 L/h/70 kg, volume of distribution was 273 L/70 kg, absorption rate constant was 1.19 h^{-1}, and oral bioavailability was 0.796. Covariate analysis identified that body weight with allometric scaling improved the model, and aspartate aminotransferase (AST) presented a significant impact on clearance (*P*-value < 0.001). **Conclusion:** Final population pharmacokinetic model can be useful to assess the pharmacokinetic parameters of voriconazole and guide dosing strategies base on factors including body weight and AST.

Keywords: population pharmacokinetics, voriconazole, pediatric, Thai, invasive aspergillosis

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Introduction

Invasive aspergillosis (IA), caused by an *Aspergillus* species, leads to morbidity and mortality in immunocompromised children patients. The success rate of treatment is only 40-50%, while the mortality rate is 23 - 58%. Voriconazole is the drug of choice for the treatment of invasive aspergillosis.[1-4] The dosage regimens are approved with a loading dose of 6 mg/kg iv q 12 h for day 1, followed by a maintenance dose of 4 mg/kg iv q 12 h, then switching to 200 mg orally q 12 h for aged ≥ 12 years (aged 12 to <18 years, including 12 to 14 years weighing ≥ 50 kg). Safety and efficacy not established for age < 12 years. However, the European Medicines Agency (EMA) recommended a dosage regimen with a loading dose of 9 mg/kg iv every 12 hours (q 12 h) for day 1, followed by a maintenance dose of 8 mg/kg iv q 12 h,

then switching to 9 mg/kg orally q 12 h for children (aged 2 to < 12 years) and young adolescents (aged 12 to 14 years weighing < 50 kg).[5,6]

Voriconazole is metabolized mainly via cytochrome P450 (CYP) 2C19 and to a lesser extent by CYP2C9 and CYP3A4 enzymes. The CYP2C19 phenotypes are classified as follows. Extensive metabolizer (EM) is the wild-type allele with normal enzyme activity. Ultrarapid metabolizer (UM) is associated with increased enzyme activity. Intermediate metabolizer (IM) and poor metabolizers (PM) are 1 and 2 non-functional alleles with decreased enzyme activity.[7] UM had lower dose-corrected trough concentrations than EM. While IM and PM had higher dose-corrected trough concentrations than EM. The CYP2C19 phenotype appears to influence drug metabolizer. There are highly polymorphic pharmacogenetic, and genetic variants which may alter metabolism resulting in interindividual phenotypic variability.[8] Frequency of these phenotypes differs between the ethnic groups which differently affects the metabolism of drugs. The prevalence of PM is 3 - 5% in Caucasians and African Americans, 15 - 20% in Asian.[9] The PM found in 15.7% of Thais which is lower than other Asians including Chinese, Japanese, Philippines, and Vietnam (19.8%, 18.8%, 23%, and 20%, respectively).[10] A study of CYP2C19 polymorphisms and voriconazole plasma level in Thais found that PM had significantly higher concentrations than EM (*P*-value = 0.039).[11] Moreover, many factors influence voriconazole pharmacokinetics including age, weight, hepatic function, CYP2C19/CYP3A-interacting comedication, etc.[2,9] As a consequence, the influence of covariates on a pharmacokinetic parameter for children should be studied. To our knowledge, a few studies including the data from groups of Caucasians and African Americans have reported the children population pharmacokinetic models of voriconazole in children patients[5,6,12-15] which may differ from Asians. The population pharmacokinetics of voriconazole were rare in Asian populations.[15]

Thus, we conducted a population pharmacokinetic study of voriconazole in Thai children patients. The present study aimed to identify factors influencing voriconazole pharmacokinetics in Thai children patients with invasive aspergillosis.

Methods

The study was a two-center, retrospective study. Data from routinely performed voriconazole therapeutic drug monitoring (TDM) at two university hospitals in Bangkok, Thailand between January 2014 and December 2018 were collected. TDM was conducted as a standard of care, but the frequency of sampling was dependent on individual decisions made for each patient. Blood samples at steady state were normally taken for at least 5 days or 2 days if there was a loading dose after initiation therapy. Plasma voriconazole concentrations were measured with different methods of each hospital, i.e., high-performance liquid chromatography (HPLC) or liquid chromatography tandem-mass spectrometry (LC-MS/MS). The lower limits of quantification (LLOQ) of HPLC and LC-MS/MS were 0.2 and 0.05 mg/liter, respectively. For model building, concentrations below the LLOQ were elided. Patients aged less than 12 years with invasive aspergillosis, who received voriconazole intravenously and orally, were included if voriconazole was determined. The subject was excluded if the serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level was > 5 times the upper limit of normal (ULN), or if they were pregnant or noncompliant to the drug regimen. The initial dosage regimen of voriconazole for median intravenous (IV) loading dose was 8.89 (5.68 - 11.54) mg/kg and median IV and oral maintenance dose was 7.81 (4.35 - 9.62) and 8.31 (4.41 - 13.16) mg/lg, respectively. The dosage regimen was approximately the same as the recommended dose. The voriconazole adaptive doses administered ranged from 2.92 to 17.86 mg/kg. Patient data were collected from patients' medical records, including voriconazole dosage regimens, demographic factors (age, sex, and body weight), biochemistry (AST, ALT, alkaline phosphatase [ALP], direct bilirubin [DB], total bilirubin [TB], and albumin [ALB]), CYP2C19 phenotype (EM, IM, PM, and UM), coadministration of CYP2C19 inhibitors and inducers, and analysis method of drug levels

Population pharmacokinetic modeling

Population pharmacokinetic analysis of voriconazole was conducted using non-linear mixed-effect modeling with NONMEM version 7.4.3 (Icon Development Solutions, Ellicott City, MD, USA), ADVAN 6 (for modeling one- or two-compartment models with non-linear or mixed linear and nonlinear elimination), ADVAN 2 (for modeling one-

compartment models with linear elimination) and ADVAN 4 subroutine (for modeling two-compartment models with linear elimination). The NONMEM runs were executed with PDx-Pop version 5.2.1 (Icon Development Solutions, Ellicott City, MD). The first-order conditional estimation with the interaction method was applied throughout the model-building procedure. The search for the best structural model was performed by comparing one- or two-compartment models with first-order absorption linear, non-linear or mixed linear and nonlinear elimination after intravenous or oral administration. Data from both intravenous and oral were sequentially modeled into central and gut compartment models. Pharmacokinetic parameters including clearance terms (clearance [CL], intercompartmental clearance [Q], maximum velocity of metabolism [Vmax]), volume term (central volume of distribution [Vc], peripheral volume of distribution [Vp], volume of distribution [Vd]), absorption rate constant (Ka), Michaelis-Menten constant (Km), and oral bioavailability (F) were tested. The interindividual variability in the pharmacokinetic parameters was evaluated using additive, proportional, and exponential error models. Additive, proportional, exponential, and combined proportional and additive error models were used to access the residual variability. In comparing models, parameters estimation based on minimizing an objective function value (OFV) and Akaike information criterion (AIC). The OFV and AIC were used to compare and improve model fit, with smaller numbers indicating goodness of fit.

Covariate analysis was performed after selection of the base model. For covariate screening, potential covariates were selected based on the physiological plausibility and prior knowledge. Continuous covariates included demographic factors (body weight and age) and laboratory tests (AST, ALT, ALP, DB, TB, and ALB) were first screened using scatterplot of parameter versus covariates. Subsequently, direct covariate testing was conducted using the stepwise method to establish the full model and final model. The continuous covariates (such as age, body weight, AST, ALT, ALP, DB, TB and ALB levels) were centered at their median values and were tested via linear, power, and exponential models. The categorical covariates (such as route of administration, analysis method of drug levels, CYP2C19 phenotypes, and CYP2C19 inducer or inhibitor) were also examined with linear, proportional, power, and exponential models. A significant covariate was retained in the final model when the following criteria were met: (i) a decrease in the OFV of > 3.84 (*P*-value < 0.05) for forward inclusion steps and an increase in OFV of > 10.83 (*P*-value < 0.001) for backward elimination steps and (ii) a 95% confidence interval (CI) of parameter estimates that did not include zero.[16,17]

Model evaluation

Visual evaluation methods (goodness of fit plots) were applied to evaluate the performance of both the base model and final model. The stability and predictive performance of the final model were tested by both the bootstrap resampling method and prediction corrected visual predictive check (pcVPC). One thousand bootstrap data sets were generated by resampling from the original data set. Median parameter values and their 95% CI from bootstrap estimates were compared with the estimates of the final model. pcVPC was used to graphically assess the appropriateness of the final model. The concentration profiles were simulated by 1,000 data sets and compared with observed data to evaluate the predictive performance of the model.

Ethics approval

The study protocol was approved by the Institutional Ethics Committee of King Chulalongkorn Memorial Hospital (COA No.306/2019, date of approval, 12/3/2019) and Ramathibodi Hospital (COA No. MURA2019/50, date of approval, 8/2/2019).

Results

A total of 337 voriconazole concentrations from 79 patients were included in this study. A total of 275 concentrations were steady-state trough concentrations, while 62 of the concentrations were sparse concentrations. The time after the last dose covered a wide range of 2 to 17 h with a median of 11.5 h. The median of trough concentrations was 1.67 mg/L (min - max = 0.06 - 10.17 mg/L), and only 50.54% concentrations were maintained within the therapeutic range (1.0 - 5.5 mg/L). The subjects were divided into three groups according to their CYP2C19 phenotype (EM, IM, and PM). No UM patients were found (Table 1).

Population pharmacokinetic model development

In the model building process, the structural model was conducted by one- or two-compartment models with first-order absorption linear, non-linear or mixed linear and nonlinear

Table 1 Patient demographic and clinical data (N = 79).

Characteristics	N (%)
	number (%) or median (range)
Gender: male: female	42 (53.16): 37 (46.84)
Age (year)†	5.11 (0.04 - 11.95)
Weight (kg)†	16 (2.8 - 66.0)
CYP2C19 phenotype[a]	
EM: IM: PM	18 (56.25): 10 (31.25): 4 (12.5)
Liver function†	
AST (U/L)	38.0 (8.0 - 200.0)
ALT (U/L)	39.0 (5.0 - 200.0)
ALP (U/L)	190 (22.0 - 941.0)
DB (mg/dL)	0.3 (0.08 - 11.0)
TB (mg/dL)	0.6 (0.1 - 14.1)
ALB (g/L)	33.0 (15.6 - 48.0)
Route of administration	
IV	19 (24.05)
Oral	34 (43.04)
Route of administration switching	
Switch from IV to oral	15 (18.99)
Switch from Oral to IV	11 (13.92)
Co-medication drugs	
Total[b]	54 (68.35)
Prednisolone	12 (15.19)
Methylprednisolone	6 (7.6)
Hydrocortisone	4 (5.06)
Dexamethasone	7 (8.86)
Omeprazole	39 (49.37)
Pantoprazole	0 (0.0)
Lansoprazole	4 (5.06)
Analysis method of drug levels	
HPLC	16 (20.25)
LC/MS/MS	63 (79.75)

† Median (min-max).

[a] 32 patients had CYP2C19 phenotype.

[b] The number of patients who had co-medication drugs with voriconazole at least one; CYP2C19 inducers: steroids (prednisolone, methylprednisolone, hydrocortisone, dexamethasone; CYP2C19 inhibitors: proton pump inhibitors (omeprazole, pantoprazole, lansoprazole).

elimination. Mixed linear and non-linear models failed because of overparameterization of model. Comparisons of the one- or two-compartment models with first-order absorption linear or non-linear elimination showed that AIC values for linear models were 827 and 843.938 for one- and two- compartment, respectively, and those for non-linear were 1001.99 and 1007.13 for one- and two- compartment, respectively. As a consequence, a one-compartment model with first-order absorption, linear elimination, and allometric scaling demonstrated the best fit to the observed data. The interindividual and residual variability models were best described by an exponential model and a proportional error model, respectively. Patient body weight was added in the model with allometric scaling to improve model stability. In allometric scaling, it was found that using a standardized to 70 kg body weight resulted in more model improvement than the median weight. Linear clearance (CL) was scaled allometrically using a weight to a power of 1. The parameter Ka was fixed to values of 1.19 h^{-1}, as reported in the literature.[6] It was not possible to obtain reasonable estimates of these parameters due to the complex model with sparse data to inform the parameters. Besides, most concentrations in this study were steady trough concentration measurements, which could not fully reflect the characteristics of the absorption phase.

The impact of each covariate on parameters was evaluated using a stepwise approach. Incorporation of the above covariates into the final model led to 15.68 decreases of the OFV indicating impact of significant covariate on AST. A summary of the covariate models development shown in Table 2. The pharmacokinetic equations 1 - 4 of the final model are presented as follows.

$$V\ (L/70\ kg) = 273 \times (WT/70) \quad (1)$$

$$CL\ (L/h/70\ kg) = 11.3 \times (WT/70)^{0.75} \times e^{(-0.00441 \times (AST-38))} \quad (2)$$

$$Ka\ (h^{-1}) = 1.19 \quad (3)$$

$$F = 0.796 \quad (4)$$

The population parameter estimates (including V, CL, Ka, F and the interindividual variability and residual variability) of the basic model and final model are presented in Table 3.

Table 2 A Summary of the covariate models development (N = 337).

Stepwise approach	Covariate	OFV	Δ OFV	*P*-value
Base model	WT	811.000	-	-
Forward addition				
V	AGE	810.702[a]	-0.298	NS
	FORM	808.067[a]	-2.933	NS
	METH	807.477	-3.523	NS
CL	AGE	804.601[b]	-6.399	< 0.05
	AST	795.323	-15.677	< 0.05
	ALT	808.082[a]	-2.918	NS
	ALP	788.102[a]	-22.898	NS
	DB	810.776	-0.224	NS
	TB	810.701[a]	-0.299	NS
	ALB	810.634	-0.366	NS
	FORM	811.000	0.000	NS
	METH	811.000	0.000	NS
	CYP2C19 phenotype	807.196[a]	-3.804	NS
	CYP2C19 inducers	811.000	0.000	NS
	CYP2C19 inhibitors	811.000	0.000	NS
Full model	AST	795.323	-15.677	< 0.05
Backward elimination	AST	811.000	+15.677	< 0.01

Note: OFV, objective function value; ΔOFV, change in objective function value; V, volume of distribution; CL, clearance; WT, weight; AGE, age; FORM, Formulation; METH, Analysis method of drug levels; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alkaline phosphatase; DB, Direct bilirubin; TB, Total bilirubin; ALB, albumin; CYP2C19 inducers: steroids (prednisolone, methylprednisolone, hydrocortisone, dexamethasone; CYP2C19 inhibitors: proton pump inhibitors (omeprazole, pantoprazole, lansoprazole); NS, not significant.

[a] 95% CI including zero.

[b] collinearity with weight.

Table 3 A summary of population parameter estimates of base model, final model and bootstrap analysis (N = 337).

Parameter	Estimate (% RSE), 95% CI		Median (95% CI)[a] of Bootstrap (n = 1,000)	Bias (%)
	Base model	Final model		
V	271 (29.0), 117-425	273 (27.8), 124-422	282 (130-470)	3.3
CL	10.40 (16.9), 6.95-13.8	11.30 (17.3), 7.46-15.1	11.37 (7.6-15.5)	0.62
Ka	1.19 FIX	1.19 FIX	1.19 FIX	-
F	0.75 (19.6), 0.46-1.04	0.80 (19.1), 0.5-1.09	0.82 (0.53-1.15)	2.5
AST on CL	-	-0.00441 (45.1), -0.0083 to -0.00051	-0.00440 (-0.0085 to -0.00054)	-0.23
IIV_V	66.80 (44.6), 23.66-91.43	56.90 (46.0), 17.89-78.48	51.90 (0.71-82.34)	-8.79
IIV_{CL}	60.90 (27.2), 41.59-75.43	61.90 (22.5), 46.26-74.30	61.74 (46.37-76.55)	-0.26
RUV	76.70 (9.85), 68.92-83.84	75.50 (9.91), 67.75-82.52	74.89 (67.08- 82.34)	-0.81

Note:

V, Volume of distribution (L/70 kg); CL, clearance (L/h/70 kg); Ka, absorption rate constant (h^{-1}); F, oral bioavailability; AST on CL, Aspartate aminotransferase effect on CL (exponential relationship); IIV_V Inter-individual variability of V (%CV); IIV_{CL} Inter-individual variability of CL (%CV); RUV, Residual unexplained variability, proportional error (%CV).

% CV: % coefficient of variation = sqrt (estimate parameter) x 100.

% RSE: % relative standard error = (standard error/estimate parameter) x 100.

95% CI: 95% confident interval = parameter estimate ± (1.96 x standard error).

Bias % = (Estimate $_{Bootstrap}$ – Estimate $_{Final\ model}$)/Estimate $_{Final\ model}$ X 100 %.

[a] 95% CI (2.5th -97th percentiles) of 1,000 bootstrap.

Model evaluation

The goodness of fit plots for final model are demonstrated in Figure 1. Coordinates of population predictive (PRED) and individual predictive (IPRED) versus observed concentration are around the identity line (Figure 1A and B). Besides, the scatterplot of PRED and time after dose versus conditional weighted residual errors (CWRES) demonstrated a good distribution of the point around the zero lines, and most of the points were within the range of -3 and 3, indicating the model was well fit (Figure 1C and D).

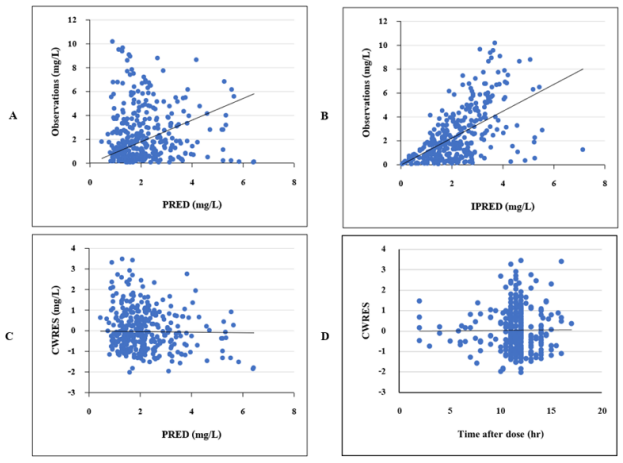

Figure 1 Goodness of fit plot for the final model.

Observations vs PRED (A), Observations vs IPRED (B), CWRES vs PRED (C), CWRES vs Time after dose (D).

The bootstrap analysis showed that for the final model, 997 out of 1,000 runs converged successfully. The point population estimates of all parameters were similar to the mean values obtained from bootstrapping and fell within the 95% confidence interval (CI) (Table 3), suggesting precise and stable parameter estimation in the final model. The pcVPC shows adequately predictive performance of the final model in Figure 2 and observations outside 90% CI were only 2.37%.

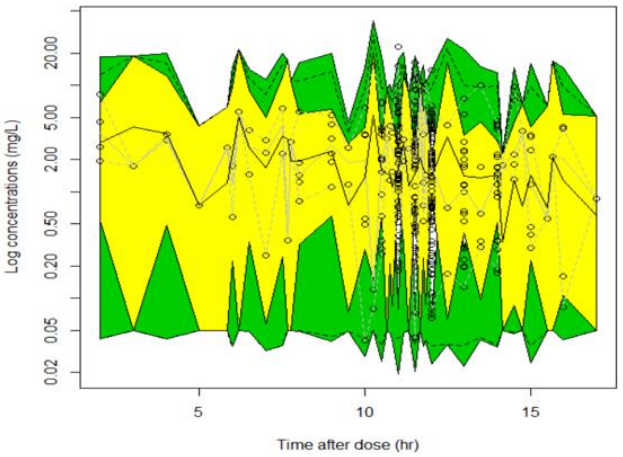

Figure 2 pcVPC for the final model.

The green and yellow lines represent 2.5th, 97.5th percentiles and median of the simulated data. The grey dashed and solid lines represent 2.5th, 97.5th percentiles and median of observed data. The black line represents the comparable quantile line of the simulated data. The opened circles represent prediction-corrected observed data.

Discussions and Conclusion

The pharmacokinetic behavior of voriconazole is complex and differs in children, adolescents, and adults, depending on age and administered dose. Pharmacokinetics of voriconazole in children are complex and still incompletely understood.[5,18] In this study, both one- or two-compartment models, and linear, nonlinear or mixed were evaluated. We found that a one-compartment model with first-order absorption, linear elimination, and allometric scaling appropriately described the concentration-time data of voriconazole at steady state in Thai children patients with invasive aspergillosis. The structure of the model is similar to that of the model reported by Martin et al.[12] In our model, demographic information, biological factors, and clinical conditions were investigated as potential covariates. Body weight with allometric scaling and AST levels were found to have a significant effect on CL. In the present study, the typical population value of voriconazole CL in children was estimated to be 11.3 L/h/70 kg. Previous pharmacokinetic studies of voriconazole that reported CL values of 7.79 L/h/70 kg in children aged 2 to 18 years[12], and 6.16 L/h/70 kg in both children and adults aged 2 to 55 years.[6] It was notable that the CL value in this study was higher than these studies. The results above imply that body weight is vitally important factors related to voriconazole clearance. The

children patient has a much higher ability for elimination of the drug per kilogram of body weight than adults, due to a greater liver mass to body mass ratio than adults.[5,18] The oral bioavailability of voriconazole in adults was 96%, while children bioavailability was lower.[19] The estimated F of voriconazole in the present study was 80%, which was similar to the value of 73%, as reported in Japanese children study.[15] With different ethnic groups, our estimated oral bioavailability was higher than previously reported values of 45 – 66% in Caucasians and African Americans.[5,6,15,19]

After stepwise processes, body weight and AST levels were identified as significant factors influencing voriconazole pharmacokinetics in our study. Indeed, the inclusion of body weight as a covariate significantly improved the model fit. The significant effects of body weight as a surrogate of size on voriconazole pharmacokinetics have been reported in most child studies.[5-6,12-15] A significant effect of AST on voriconazole clearance is consistent with the result of Li et al[20], which showed that higher AST values were significantly associated with a reduction in CL. Not surprisingly, AST had effect on CL. AST was an indicator of liver function in which voriconazole is metabolized primarily through the liver.

Previous studies confirmed that voriconazole undergoes extensive hepatic metabolism, which is mainly mediated by CYP2C19 phenotypes.[13,21] CYP2C19 distribution varies among different ethnic groups. This study explored the influence of CYP2C19 genetic polymorphism on the pharmacokinetic parameters of voriconazole; unfortunately, this covariate was not retained in the final model. The absence of any significant effect of these covariates on the population parameters of voriconazole could have resulted from the small sample size, which could hamper the detection of any significant effects. In addition to the CYP2C19 phenotype, coadministration of CYP2C19 inhibitors and inducers were tested and also had no significant effect on voriconazole pharmacokinetics.

There are some limitations to the current study. Most of the samples were trough concentrations, which did not sufficiently reflect the absorption characteristics of voriconazole. The sample size was relatively small, making it difficult to examine the influence of several covariates, such as CYP2C19 gene phenotype and co-medications, on the pharmacokinetics of voriconazole. Evaluation of the CYP phenotyping, which has been demonstrated to have a significant impact on the CL of voriconazole, is warranted in the future. Finally, we did not perform external validation of the final model due to insufficient data.

To our knowledge, there were six studies on children population pharmacokinetic models for voriconazole.[5,6,12-15] However, most of these studies focus on Caucasian patients, one study was conducted in Japanese patients[15] whereas children population pharmacokinetic in Thai children patients has not been investigated. This study is the first to perform population pharmacokinetic analysis of voriconazole in this patient population. Further work needs to focus on the optimization of voriconazole dose regimens for the treatment of different infections with pharmacokinetic/pharmacodynamic analysis. Moreover, further studies are needed to confirm the improvement of clinical outcomes in model-guided treatment.

In summary, a one-compartment model with first-order absorption, linear elimination, and allometric scaling adequately described the voriconazole concentration data from Thai children subjects with invasive aspergillosis. Body weight and AST levels were significant covariates for CL. The final model can provide helpful information to facilitate individualized voriconazole dosage regimens with similar patient population characteristics, achieving steady-state concentration within the therapeutic range.

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