1566. Population Pharmacokinetics of Voriconazole: Serum Albumin Status as a Novel Marker of Clearance and Dosage Optimization

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Background. Voriconazole (VRCZ) is a first-line agent for the treatment of invasive aspergillosis. In this study, we report the first study on population pharmacokinetics (PPK) of VRCZ in Thai patients.

Methods. A PPK study was performed by combining blood VRCZ data from intensive pharmacokinetic (PK) sampling and trough concentration. A non-linear mixed-effect model with FOCE ELS optimization by Phoenix NLME was used. Validity of the model was confirmed by bootstrap, visual predictive check (VPC) and goodness-of-fit (GOF) plot. Recommended dosage regimens based on albumin level of patient were simulated.

Results. One hundred and six patients using oral VRCZ were included. Eighty-eight patients had the phenotype results which were 43, 37, and 8 of extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM), respectively. The linear one-compartment model with first-order absorption and elimination by fixing Ka value at 1.0 well described the data. CYP2C19 phenotypes did not influence any PK parameter during the covariate model building, then all 106 patients were included in the model construction. The final model was V (Liter) = θ_V × (Actual body weight/55) $^{\theta 1}$ × exp (η_V), CL (L/hr) = θ_{CL} × (albumin/28) $^{\theta 2}$ × (logGGT/2.4)$^{\theta 3}$ × exp (η_{CL}), Table 1. Estimated clearance (CL) and volume of distribution (V) values were 7.33 L hour^{-1}and 439.69 L, respectively. VPC (Figure 1) and 96% of 1000 succeeded bootstrap results (Table1) showed a good consistency to the observed data. Serum albumin had more impact correlation across all patients with CL, R^2 = 0.18, $P \leq 0.001$. Patient with serum albumin 30 g/L had CL lower than patient having serum albumin > 30 g/L, P = 0.0007, irrespective of PM status because of there were all phenotypes which distributed across two groups; %EM: %IM: %PM for 55: 38.3: 6.6 and 48:36:16, respectively. Dosing simulation (Table 2) found that patient having albumin 30 g/L required a lower daily maintenance dose to achieve any trough level.

Conclusion. Serum albumin is a novel marker influencing VRCZ CL. Therapeutic drug monitoring with this dosing regimen could be another practical option for more specialized patient condition.

Table 1 Final population pharmacokinetic parameters and its bootstrap results

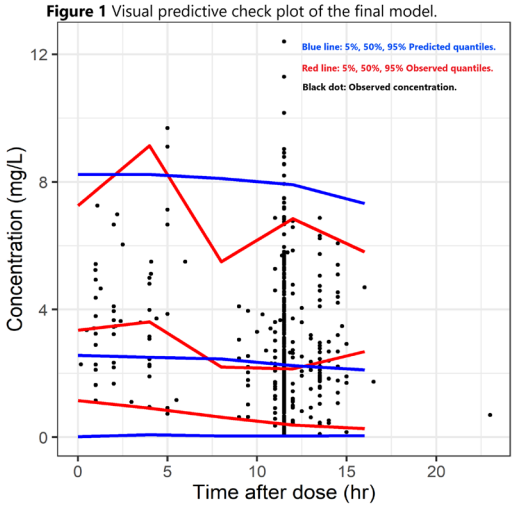
	Final model			Bootstrap		
	Estimate value	95% CI	%CV	Estimate value (median)	95%CI	%CV
θ_{CL} (L/h)	7.33	6.78,7.89	3.83	7.27	6.26,8.22	6.78
θ_V (L)	439.69	430.62, 448.77	1.05	436.26	150.35, 947.82	45.52
Ka (fixed)	1	NA	-	1	NA	-
θ1 (fixed)	1	NA	-	1	NA	-
θ2	0.93	0.75, 1.12	10.18	0.93	0.57, 1.31	18.93
θ3	-0.58	-0.67, -0.49	-7.95	-0.57	-0.97, -0.22	-31.17
Interindividual variability ω^2_{CL} (ω_{CL} x 100)	0.190 (43.58)	0.147, 0.234	11.58	0.181 (42.650)	0.120, 0.253 (34.760, 50.310)	20.183
$\eta_{shrinkage}$	0.19	-	-	-	-	-
ω^2_V (ω_V x 100)	0.080 (28.28)	0.063, 0.098	11.083	0.080 (28.28)	0.002, 0.503 (5.216, 70.961)	171.89
$\eta_{shrinkage}$	0.92	-	-	-	-	-
Residual variability(σ)	0.59	0.54, 0.64	4.21	0.58	0.51, 0.66	6.09

Table 2 Maintenance dose regimen simulation and the probability of trough achievement of a patient having serum albumin ≤ 30 g/l and albumin > 30 g/l.

		Probability	of	trough	achievement	
Trough level (mg/l)	**< 2**	**2-2.99**	**3 – 3.99**	**4 – 4.99**	**5-5.99**	**6-6.99**
Regimen						
200 mg po q.12 h.						
Albumin ≤ 30 g/l	38%	30%	17%	8%	4%	2%
Albumin > 30 g/l	66%	24%	8%	2%	0	0
225 mg po q. 12 h.						
Albumin ≤ 30 g/l	29%	30%	19%	11%	5%	2%
Albumin > 30 g/l	57%	27%	10%	4%	1.3%	0.7%
250 mg po q. 12 h.						
Albumin ≤ 30 g/l	23%	28%	21%	13%	7%	4%
Albumin > 30 g/l	49%	29%	13%	5%	2.1%	0.8
275 mg po q. 12 h.						
Albumin ≤ 30 g/l	18%	26%	22%	14%	9%	5%
Albumin > 30 g/l	41%	30%	16%	7%	3%	1%
300 mg po q. 12 h.						
Albumin ≤ 30 g/l	14%	24%	22%	16%	9%	6%
Albumin > 30 g/l	35%	30%	19%	9%	4%	2%

The target concentration range is 2.0-5.0 mg/l.

Figure 1 Visual predictive check plot of the final model.



Disclosures. **All authors:** No reported disclosures.

1567. Pharmacokinetic/Pharmacodynamic Target Attainment in Adult and Pediatric Patients following Administration of Ceftaroline Fosamil as a 5-Minute Infusion

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Background. Ceftaroline fosamil is approved in the United States for treating patients ≥2 months old with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, and for similar indications in Europe. The active metabolite, ceftaroline, has in vitro activity against common Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*. Population pharmacokinetic (popPK) modeling and simulation were used to assess systemic exposure and PK/pharmacodynamic (PK/PD) target attainment for *S. aureus* and *S pneumoniae* for 5- and 60-minute infusions.

Methods. A simultaneous popPK model, including 2 compartments each, for ceftaroline fosamil and ceftaroline was previously developed using an extensive database of adult and pediatric data. An effect of renal function maturation as a function of postmenstrual age was included on ceftaroline clearance for children <2 years. This model was used to conduct simulations for-approved ceftaroline doses administered as 5- and 60-min infusions to adult and pediatric patients with normal renal function and mild renal impairment. For adults, 100 simulations of 300 patients each were performed for each dose regimen, and covariates were generated from a multivariate normal distribution using covariate correlations from observed data. For pediatric patients, 100 simulations were performed for each dose regimen with 600 patients in each 1-month age group. Weights for pediatric age groups were based on CDC growth charts.

Results. The median proportion of simulated patients with normal renal function achieving %*f*T>MIC targets of 35% and 44% (associated with 1-log kill of *S. aureus* and *S pneumoniae*, respectively), are shown for 5- and 60-min infusions (figure). PK/PD target attainment was similar for both infusion times and was >99% at an MIC of 1 mg/L for *S. aureus* and an MIC of 0.5 mg/L for *S pneumoniae*. Ceftaroline AUC was similar for both infusion times, and C_{max} was approximately 30%–40% higher for the 5-min infusion.

Conclusion. Ceftaroline fosamil gave as a 5-min infusion to adult and pediatric patients ≥2 months of age achieved similar PK/PD target attainment as a 60-min infusion for *S. aureus* and *S pneumoniae* for MICs up to 1 mg/L and 0.5 mg/L, respectively.

Figure. Median proportion of simulated patients with normal renal function achieving %fT>MIC targets of 35% and 44% (1-log kill of *S aureus* and *S pneumoniae*, respectively) for 5- and 60-min infusions

Age Group	Dose	% of Patients achieving %*f*T>MIC of 35% (*S. aureus*)		% of Patients achieving %*f*T>MIC of 44% (*S. pneumoniae*)	
		MIC of 1 mg/L		MIC of 0.5 mg/L	
		60-min	5-min	60-min	5-min
≥18 years	600 mg q12h	99.7	99.0	100	99.7
12 to <18 years	12 mg/kg q8h*	100	100	100	100
6 to <12 years	12 mg/kg q8h*	100	100	100	100
2 to <6 years	12 mg/kg q8h*	100	100	100	100
18 to <24 months	8 mg/kg q8h	100	99.8	100	100
12 to <18 months	8 mg/kg q8h	100	100	100	100
6 to <12 months	8 mg/kg q8h	100	100	100	100
2 to <6 months	8 mg/kg q8h	100	100	100	100

%fT>MIC, % time of the dosing interval free drug concentration are >MIC; MIC, minimum inhibitory concentration; q8h, every 8 hours; q12h, every 12 hours.
*Maximum dose of 400 mg.

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