Population pharmacokinetic modelling for vancomycin using Bayesian model averaging approach

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Introduction

- Vancomycin (VCM) has been used as a first-line standard treatment against methicillin-resistant *Staphylococcus aureus* for over 60 years [1].
- More than 60 studies of population pharmacokinetic (PK) modelling for VCM have been reported, but model structures and selected covariates were different from study to study [2,3].
- It is known that model selection based on statistical criteria is dependent on data richness and may lead to models with incorrect inference.
- Some Bayesian dose-optimizing software for estimation of VCM exposure are available, but the accuracy of the prediction is dependent on one population PK model selected [4].
- Bayesian model averaging (BMA) framework [5] could obtain posterior distribution of parameter estimation and posterior selection probability for each of multi-models, and the inference with averaging multi-models based on posterior distributions and probabilities is generally more reliable [6].
- The objective of this study was to apply BMA approach to the population PK analysis of VCM and develop averaged model for population PK of VCM.

Methods

Data

- Data were collected from adult patients who measured at least one plasma VCM concentration in Kyorin University Hospital (Tokyo, Japan) from January 2018 to December 2019.

Bayesian Model Averaging (BMA)

- BMA was performed by Markov chain Monte Carlo (MCMC) Bayesian estimation algorithm implemented in NONMEM ver.7.4.4 [7].
  - ✓ A switch parameter (***I***), a variable (0 or 1) following a Bernoulli distribution, was adapted to each model structure and each covariate.
  - ✓ 10,000 samples from two MCMC chains (burn-in: 5,000, iteration: 5,000, two chains) were obtained to make an inference about posterior distributions, and if ***I*** was estimated as 1 in each sample, the model or covariate were selected in this sample.
  - ✓ The posterior selection probability of model structure or covariate was calculated from the posterior distribution of ***I***.
  - ✓ Candidate model structures: One- and two-compartment model
  - ✓ Candidate covariates for each PK parameters as follows
    - ➢ Clearance (***CL***): Age, sex, body weight (WT), albumin (ALB), aspartate aminotransferase (AST), and creatinine clearance (CLcr)
    - ➢ Volume of distribution in central compartment (***Vc***): Age, sex, serum creatine (SCr), and WT
    - ➢ Inter-compartmental clearance (***Q***): WT
    - ➢ Volume of distribution in peripheral compartment (***Vp***): WT

$$CL = CL_{pop} \times (Age_i/65)^{\theta_1 \cdot I_1} \times \theta_{2(female)}{}^{Sex_i \cdot I_2} \times (WT_i/70)^{\theta_3 \cdot I_3} \times (ALB_i/4)^{\theta_4 \cdot I_4} \times (AST_i/20)^{\theta_5 \cdot I_5} \times (CLcr_i/100)^{\theta_6 \cdot I_6}$$

$$Vc = Vc_{pop} \times (Age_i/65)^{\theta_7 \cdot I_7} \times \theta_{8(female)}{}^{Sex_i \cdot I_8} \times (SCr_i/0.8)^{\theta_9 \cdot I_9} \times (WT_i/70)^{\theta_{10} \cdot I_{10}}$$

$$Q = I_{2comp} \times Q_{pop} \times (WT_i/70)^{\theta_{11} \cdot I_{11}} \qquad Vp = I_{2comp} \times Vp_{pop} \times (WT_i/70)^{\theta_{12} \cdot I_{12}}$$

I_{2comp}: Switch parameter for model structure. XX_{pop} : Population mean for XX.

- Prior information of ***I*** for these model structures and covariate selections were set from 43 models reported for population PK modelling of VCM.
  - ✓ Model structure: One- and two-compartment models were 0.5 in each.
  - ✓ Covariate selection in each PK parameter: Shown in Table 1

Table 1 Prior information of *I* for covariate selections.

PK	Covariate	N*	Prior value of *I*	PK	Covariate	N*	Prior value of *I*
CL	Age	4	0.1	***Vc***	Age	5	0.1
	Sex	1	0.025		Sex	1	0.025
	WT	7	0.2		SCr	2	0.05
	ALB	1	0.025		WT	22	0.5
	AST	1	0.025	***Q***	WT	1	0.05
	CLcr	29	0.7	***Vp***	WT	7	0.4

* The number of models in which each covariate was selected as a covariate.

- The convergence and autocorrelation of MCMC chains were confirmed by visual diagnosis and statistical methods [8,9].
  - ✓ The potential scale reduction factors ($\hat{R}$) for all parameters were calculated using Gelman-Rubin method to evaluate the convergence.
  - ✓ The effective sample size (N_{eff}) and N_{eff}/N (N: the number of MCMC samples) were calculated to evaluate the autocorrelation.

Reference

[1] Rybak MJ et al. Pharmacotherapy. (2020) 40, 363-367.
[2] Aljutayli A et al. Clin Pharmacokinet. (2020) 59, 671-698.
[3] Chung E et al. Clin Pharmacokinet. (2021) 60, 985-1001.
[4] Turner RB et al. Pharmacotherapy. (2018) 38, 1174-1183.
[5] Hoeting JA et al. Stat Sci. (1999) 14, 382–417.
[6] Longford NT. J R Statist Soc A. (2005) 168, 469–472.
[7] Beal SL et al. 1989-2011. NONMEM Users Guides. Icon Development Solutions, Ellicott City, Maryland, USA.
[8] Gelman A et al. Statistical Science. (1992) 7, 457–472.
[9] Gelman A et al. Bayesian Data Analysis, Third Edition. Chapman and Hall/CRC. (2013)

Results

Data

- Total 1626 observed plasma VCM concentrations from 453 patients were available (Figure 1), and patients' background was shown in Table 2.

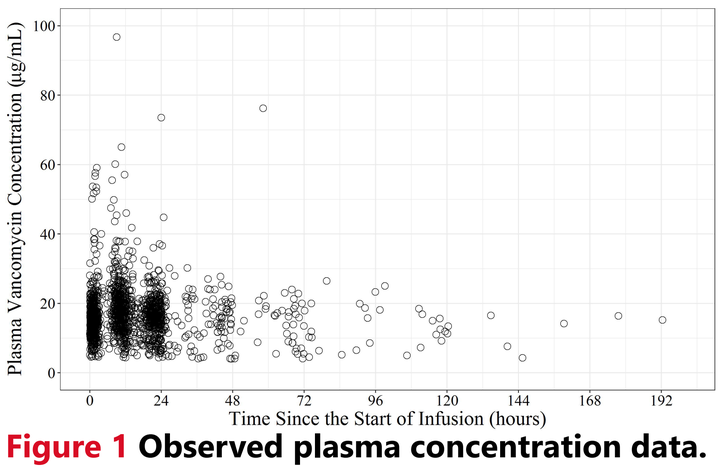

Figure 1 Observed plasma concentration data.

Table 2 Patients' background.

Number of patients	**453**
Sex (Male : Female)	273 : 180
Characteristics	**Median (range)**
Age (years)	74 (20 – 103)
WT (kg)	57.0 (20.4 – 120.0)
ALB (g/dL)	2.5 (1.1 – 4.6)
AST (IU/L)	28 (6 - 1808)
SCr (mg/dL)	0.71 (0.17 – 10.51)
CLcr* (mL/min)	69.2 (6.2 – 341.6)

$$* \; CLcr = \frac{WT \times (140 - Age)}{72 \times SCr} (\times 0.85 \; if \; female)$$

BMA

- Model structure was selected as two-compartment model with first order elimination from all samples (posterior selection probability = 100%).
- The population mean values of averaged population PK models for VCM were calculated as mean values from all samples and the values were shown in Table 3.
  - ✓ The estimated values were roughly similar to reported values in other studies.
- The summary of covariate selection was shown in Table 4.
  - ✓ CLcr was selected as a covariate for CL in all samples (100%) and the power value was estimated as 1.00.
  - ✓ There was one reported model in which ALB was identified as a significant covariate for CL, however ALB was selected as a covariate for CL with high probability (97.7%).

Table 3 Estimated model values.

Parameter	Value (RSE)
CL (L/hr)	3.51 (7.2%)
Vc (L)	110 (5.7%)
Q (L/hr)	0.680 (27.8%)
Vp (L)	274 (36.5%)
BSV_CL (%)	58.9 (11.9%)
BSV_Vc (%)	57.8 (12.8%)
BSV_Q (%)	77.5 (38.9%)
BSV_Vp (%)	211.2 (92.7%)
RUV_prop (%)	23.7 (4.9%)

RSE: Relative standard error.
BSV: Between subject variability.
RUV: Residual unidentified variability.

Table 4 Summary of covariate selection.

Parameter	Covariate	Probability (%)*	Value (RSE)
CL	Age	8.9	0.0431 (169.7%)
	Sex	0.6	0.935 (3.5%)
	WT	19.0	0.111 (99.7%)
	ALB	97.7	0.307 (31.5%)
	AST	3.5	0.00159 (412.4%)
	CLcr	100	1.00 (6.4%)
Vc	Age	7.0	0.0104 (326.8%)
	Sex	2.6	0.835 (8.4%)
	SCr	4.7	0.000101 (29.0%)
	WT	56.1	0.259 (66.6%)
Q	WT	33.7	0.728 (65.7%)
Vp	WT	37.1	1.55 (112.7%)

*Posterior selection probability calculated form all samples (the ratio of ***I***=1).

- The MCMC chains and the number of samples were appropriate.
  - ✓ The trace plots for all estimated parameters are shown in Figure 2.
  - ✓ $\hat{R}$ value was lower than 1.05 for all parameters.
  - ✓ N_{eff}/N was lower than 1 for all parameters.

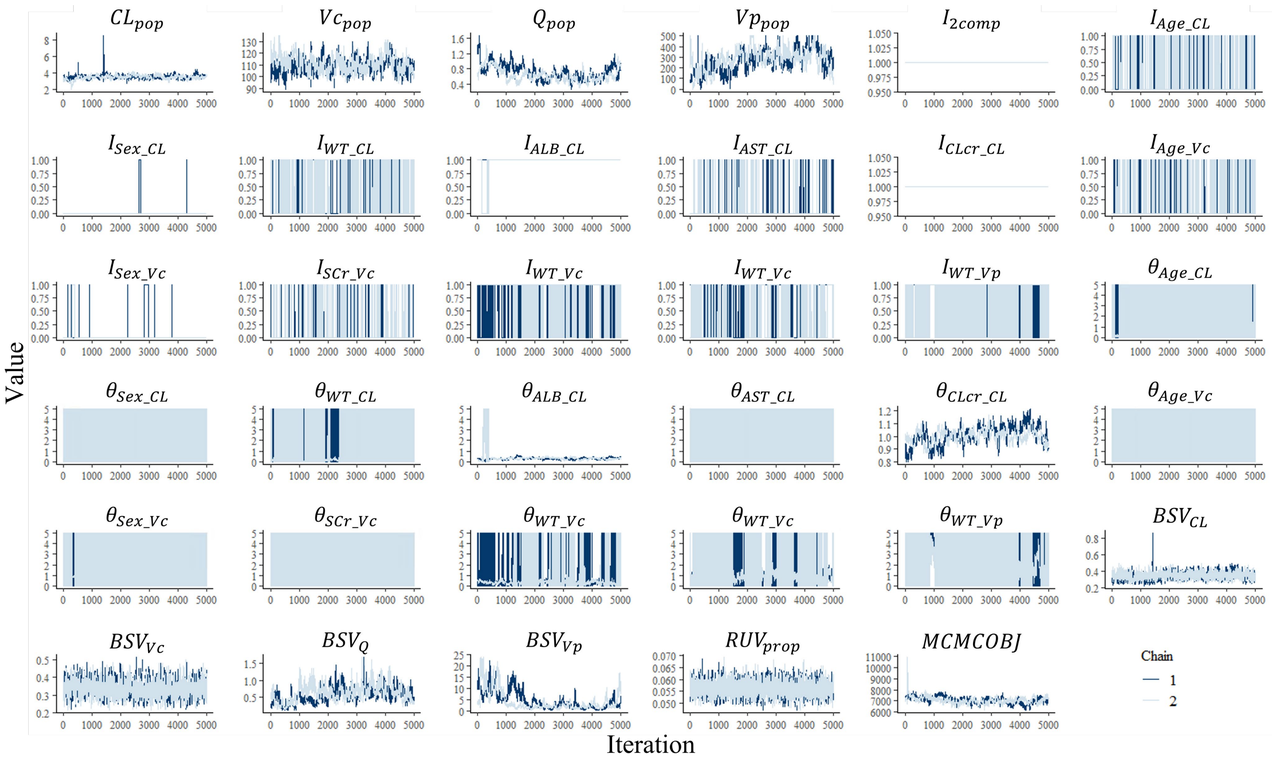

Figure 2 Trace plots for all parameters.

Conclusion

- We performed population PK analysis using BMA approach and developed the averaged model of VCM.
- Based on our averaged model, the influence of each covariate on PK parameters could be evaluated and VCM exposures could be estimated based on various covariate models but not one model.
- This model-averaging method may be applicable to other population PK analyses.

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