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Interinstitutional Comparison of Vancomycin Area Under the Concentration–Time Curve Estimation in Korea: Need for Standardized Operational Protocols for Therapeutic Drug Monitoring Consultation

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Vancomycin, a vital antibiotic for treating gram-positive bacterial infections, requires therapeutic drug monitoring (TDM) because of its substantial pharmacokinetic variability. While traditional TDM relies on steady-state trough concentrations, recent guidelines advocate the area under the concentration–time curve (AUC) as the target index. However, detailed protocols for AUC estimation are lacking, leading to potential discrepancies among institutions. We surveyed medical institutions in Korea regarding vancomycin TDM, including AUC estimation. Nineteen participants responded to the TDM case challenge under three patient scenarios. For an ordinary patient in Case 1, the overall CV for AUC values was 0.4% when both trough and peak concentrations were included in the AUC calculation and 1.9% when utilizing only the trough concentration. For Case 2, an older patient with obesity, the corresponding CV was 6.6%. For Case 3 with multiple trough concentrations, the CV was 15.6%, reflecting variations in the selective use of data. Although the agreements in Case 1 were good, significant variability in AUC estimation was noted in cases involving atypical patient characteristics or old TDM data. Our study provides insight into the current status of vancomycin TDM in Korea and underscores the need for standardized operational protocols for AUC estimation.

Key Words: Area under the concentration–time curve, Therapeutic drug monitoring, Vancomycin

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Vancomycin, an essential antibiotic for treating gram-positive bacterial infections, requires therapeutic drug monitoring (TDM) owing to substantial interindividual pharmacokinetic variability [1]. Traditionally, monitoring relies on measuring steady-state trough concentrations [2]. However, recent guidelines from the United States and Japan recommend the area under the concentration–time curve (AUC) as the target index [3, 4], recommending Bayesian software for AUC estimation. However, the lack of standardized operational protocols may lead to significant differences in estimated AUC values across medical institutions. We investigated the current agreement in AUC values among institutions and analyzed the impact of patient charac-

teristics and TDM data utilization.

From August to September 2023, we emailed a questionnaire survey to 170 clinical pathologists, each representing a medical institution, who were certified members of the Korean Society of Clinical Chemistry. Respondents reporting vancomycin AUC values in their TDM consultation reports were invited to participate in TDM case challenges. When the TDM consultation service operated outside the laboratory medicine department where clinical pathologists work, we requested that the survey be forwarded to that department. The challenge involved three patients receiving regular vancomycin dosing, with five questions regarding AUC estimates (Supplemental Data).

Briefly, Case 1 involved a 50-year-old man of normal weight (body mass index [BMI] = 22.5 kg/m^2) with one peak and one trough concentration available. Three AUC estimates were requested: 1) the AUC of the dose cycle at TDM using peak and trough concentrations (Q1-A), 2) the 24 hr-normalized AUC (AUC24) at steady state using peak and trough concentrations (Q1-B), and 3) the AUC24 at steady state using only the trough concentration (Q1-C). Case 2 was an 80-year-old woman with obesity (BMI = 29.1 kg/m^2) with only one trough concentration available. Case 3 involved a 50-year-old man with normal weight (BMI = 22.5 kg/m^2) and five trough concentrations available, simulating a clinical scenario with old TDM data, with respondents required to select TDM data for Bayesian estimation. For Cases 2 and 3, AUC24s at steady state were requested (Q2 and Q3). Q1-A was designed for users of the Bayesian method and first-order equations, whereas the remaining questions were specifically for respondents utilizing the Bayesian method. We calculated summary statistics for central tendency and dispersion of AUC values, including mean, SD, CV, median, median absolute deviation (MAD), and MAD divided by the median (MADM). Outliers with an AUC value of < (Q1−1.5×interquartile range [IQR]) or > (Q3+1.5×IQR) were excluded from the mean, SD, and CV calculations. The Institutional Review Board (IRB) of Eunpyeong St. Mary's Hospital, The Catholic University of Korea, approved this study (IRB No. PC23QISI0207).

Among the 54 institutions that responded, 40 provided vancomycin TDM consultation services, and 21 used the AUC value as the target index. Nineteen institutions, including 11 tertiary and eight general hospitals, responded to the case challenge. Among the respondents, 17 were clinical pathologists in the laboratory medicine department, and two were pharmacists in the hospital pharmacy. For the AUC calculation, 18 respondents used Bayesian software, including the Abbottbase Pharmacokinetic System (PKS; Abbott Laboratories, Chicago, IL, USA), MwPharm++ (Mediware a.s., Prague, Czech Republic), and Continuous Assessment of Pharmaceutical Care to Improve Life (CAPCIL; Simkin Inc., Gainesville, FL, USA). One respondent used the two-point first-order pharmacokinetic equation (Table 1). Q1-A was aimed at comparing AUC values regardless of the estimation method by requesting the AUC of the dose cycle at TDM, which could also be calculated using the first-order equation. Only one respondent used the first-order equation; two respondents

Table 1. AUC estimation method of participating institutions for vancomycin TDM

AUC estimation method	TDM software	Population model*	eGFR equation	N (%)
All				19 (100)
Bayesian modeling				18 (94.7)
	MwPharm++	#vancomycin_adult_k_C2	Cockcroft–Gault	4 (21.1)
			CKD-EPI (2009)	4 (21.1)
			MDRD (IDMS-traceable)	2 (10.5)
			Jelliffe	2 (10.5)
		#vancomycin_adult_C2	CKD-EPI (2009)	1 (5.3)†
	PKS	Vancomycin Adult (18–65)	Cockcroft–Gault	1 (5.3)
			CKD-EPI (2009)	3 (15.8)
	CAPCIL	Not specified	Cockcroft–Gault	1 (5.3)
First-order equation	NA	NA	NA	1 (5.3)

*Names of built-in population models in the programs.
†One institution responded with "vancomycin_C1" in Case #1 and "#vancomycin_adult_C2" in Cases #2 and #3.
Abbreviations: AUC, area under the concentration–time curve; CAPCIL, continuous assessment of pharmaceutical care to improve life; CKD-EPI, chronic kidney disease epidemiology collaboration; IDMS, isotope dilution mass spectrometry; MDRD, modification of diet in renal disease; NA, not applicable; PKS, abbottbase pharmacokinetic system; TDM, therapeutic drug monitoring; eGFR, estimated glomerular filtration rate.

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Table 2. Summary statistics of reported vancomycin AUC24 values

Question	Bayesian software	N	AUC24					
			Mean, mg·hr/L	SD, mg·hr/L	CV, %	Median, mg·hr/L	MAD, mg·hr/L	MADM, %
Q1-B	All	18	445.7	1.8	0.4	446.0	1.5	0.3
	MwPharm++	13	446.1	1.4	0.3	446.0	1.0	0.2
	PKS	4	445.7	2.3	0.5	445.0	2.0	0.4
	CAPCIL	1	-	-	-	442.0	-	-
Q1-C	All	18	474.4	9.2	1.9	477.0	4.0	0.8
	MwPharm++	13	478.8	1.8	0.4	478.0	2.0	0.4
	PKS	4	463.3	11.3	2.4	467.5	3.5	0.7
	CAPCIL	1	-	-	-	513.0	-	-
Q2	All	18	618.3	40.8	6.6	627.5	25.5	4.1
	MwPharm++	13	642.7	15.2	2.4	646.0	11.0	1.7
	PKS	4	560.0	20.8	3.7	567.0	8.0	1.4
	CAPCIL	1	-	-	-	583.0	-	-
Q3	All	18	479.8	74.8	15.6	485.5	53.0	10.9
	MwPharm++	13	470.4	78.0	16.6	499.0	65.0	13.0
	PKS	4	481.0	49.0	10.2	465.5	15.5	3.3
	CAPCIL	1	-	-	-	597.0	-	-

Abbreviations: AUC24, 24 hr-normalized area under the concentration–time curve; CAPCIL, continuous assessment of pharmaceutical care to improve life; MAD, median absolute deviation; MADM, median absolute deviation divided by the median; PKS, abbottbase pharmacokinetic system; Q, question.

stated that the calculation was impossible, and nine respondents provided inappropriate values. The value of Q1-A should be less than half the value of Q1-B. Consequently, Q1-A was not analyzed. Summary statistics for each question and the distribution of reported AUC values are provided in Table 2 and Fig. 1, respectively.

For Q1-B, the AUC24 values showed a narrow distribution, with an overall CV and MADM of 0.4% and 0.3%, respectively. Differences among TDM software programs were minimal. In Q1-C, the CV and MADM increased slightly, suggesting that additional peak concentration data may improve the agreement among institutions. The US and Japanese guidelines recommend obtaining trough and peak samples (two-point measurement) to estimate the AUC [3, 4]. Peak concentrations may improve the accuracy of individual AUC estimates [5, 6]. However, the effect of additional peak measurements on improving Bayesian forecasting performance for the AUC at subsequent TDM or steady state appears to be minimal or modest [7, 8]. Moreover, evidence that additional peak measurements improve clinical outcomes is limited [9]. As measuring peak concentrations incurs additional costs, further research is required to assess the cost-effectiveness of a two-point measurement strategy for vancomycin TDM [10].

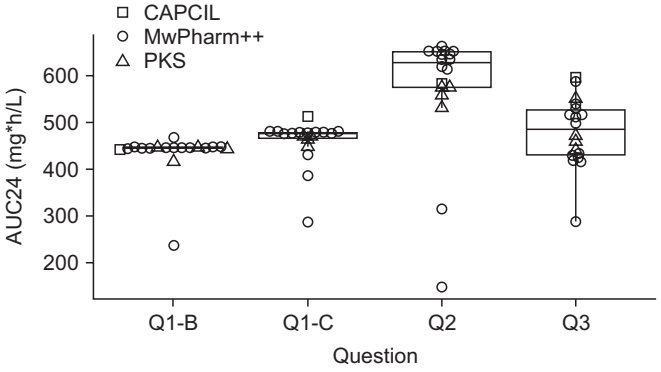

Fig. 1. Boxplot showing the distribution of the reported AUC24 values. Each data point represents a value reported by an institution. The data points are shaped according to the Bayesian program used for the calculation.
Abbreviations: AUC24, 24 hr-normalized area under the concentration–time curve; CAPCIL, continuous assessment of pharmaceutical care to improve life; PKS, abbottbase pharmacokinetic system.

The accuracy of AUC estimation using only trough data depends on the validity of the population model as a Bayesian prior [11]. The built-in population model of MwPharm++, the most commonly used by respondents, originates from a mono-

graph by the Vrije Universiteit Amsterdam Hospital (Amsterdam, Netherlands) and the Dutch Association for Quality Assessment in TDM and Clinical Toxicology [12]. However, detailed information about its development and evaluation remains unavailable, and its validity and performance in AUC estimation are unclear. Research is necessary to confirm the suitability of this model for the general inpatient population in Korea.

The CV and MADM for Q2 exceeded those for Q1-C, suggesting that patient characteristics likely influenced the agreement. Although all respondents used a general adult population model, significant variability persisted among those employing the same program. Differences in eGFR equations might contribute to this variability. Typically, renal function estimates, based on serum creatinine concentrations, act as covariates associated with clearance and can impact estimated AUC values [13, 14]. For example, the patient in Case 2, with a serum creatinine concentration of 0.45 mg/dL (39.8 μmol/L), would have an estimated glomerular filtration rate (eGFR) of 95 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and 134 mL/min/1.73 m^2 via the Modification of Diet in Renal Disease (MDRD) equation, whereas eGFR difference between the two equations was not significant in Case 1 (101 vs. 94 mL/min/1.73 m^2). Individuals with greater differences in renal function estimates would have higher variability in AUC estimates.

Older eGFR equations, such as the Cockcroft–Gault and Jelliffe equations, permit variations, including converting creatinine values from isotope dilution mass spectrometry (IDMS)-traceable to non-IDMS-traceable assay values (to compensate for differences in creatinine concentrations between when the equation was developed and the present) and body weight adjustments for obesity [15, 16]. However, the difference in AUC values according to the eGFR equation used does not seem substantial enough to deem eGFR equation differences as the primary factor for AUC variation (Supplemental Data Table S1). Even with consistent application of the same program, population pharmacokinetic model, and eGFR equation, discrepancies in reported AUC values persisted, likely owing to variations in options (including assay error, body weight type, fitting algorithm, and weighting method) not included in the survey or owing to clerical errors.

Responses to Q3 showed the highest variability, even among respondents using the same program. Case 3 included multiple old TDM data points, available for respondent discretion. Six respondents used all five given TDM data, whereas the other six used only the most recent data. No correct answer exists for the use of old TDM data. Broeker, *et al*. [17] and Guo, *et al*. [18] reported that the predictive performance of Bayesian forecasting improves marginally or deteriorates when multiple old TDM data are included. However, uniformly applying the TDM data utilization rule is impractical. In practice, interpreters evaluate each case individually, considering factors such as the patient's clinical course, data validity, and time intervals between TDM. The findings from Q3 highlight the diversity in practices and variation in estimated AUC values across institutions, even when using the same program. Moreover, preanalytical and analytical errors in vancomycin concentration measurements, along with documentation errors in dosing and sampling time, remained unaddressed in our study [19]. Such errors propagate and likely exacerbate AUC estimation inaccuracies and interinstitutional discrepancies in real-world clinical settings.

This study has limitations. First, concerns regarding the representativeness of respondents from institutions offering AUC-based TDM may arise. We administered the survey to clinical pathologists, although TDM consultation services are also provided by laboratory medicine departments, hospital pharmacies, and clinical pharmacology departments in Korea [20]. We requested that email recipients forward the survey to the relevant department providing TDM consultation. Nevertheless, of the 19 respondents who participated, only two were pharmacists in the hospital pharmacy; the remaining were clinical pathologists in the laboratory medicine department. Another limitation is the small number of respondents, which could lead to significant variability in dispersion estimates. For a comprehensive summary, we described both general and robust statistics. Additionally, the challenge cases were virtual, lacking true AUC values derived from rich, sampled concentration data. Consequently, evaluating the error in AUC estimates was infeasible; thus, we assessed the degree of agreement. However, these cases were created by emulating actual patient cases and were not completely different from reality.

In conclusion, we revealed the current status of AUC estimation for vancomycin TDM in Korea, mainly among clinical pathologists. Although AUC agreement was optimal in typical adults, discrepancies increased in patients with atypical characteristics (older and obese) and in cases that selectively used older TDM data. Standardized operational protocols for vancomycin AUC estimation should be comprehensively investigated.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.

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AUTHOR CONTRIBUTIONS

Conceptualization: HKK, TDJ, MSJ. Methodology: HKK, MP, JDS. Funding acquisition: MSJ. Supervision: TDJ, MSJ. Writing – original draft: HKK. Writing – review & editing: MP, JDS, TDJ, MSJ.

CONFLICTS OF INTEREST

None declared.

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