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CLINICAL LABORATORY PHARMACY ASPECTS OF PRECISION VANCOMYCIN THERAPY

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INTRODUCTION

Interest in the individualization of intravenous vancomycin therapy is increasing. A key technical component of individualized treatment is pharmacokinetic modeling performed using pharmacokinetic software based on vancomycin concentrations [1]. Vancomycin therapy should be initiated targeting an AUC_{24} range of 400–600 mg · h/L [1]. In addition to drug concentration data, the availability of the results of various laboratory tests is essential for the appropriate interpretation of modeling results. In certain cases, these results are technically required inputs of the pharmacokinetic models.

Our aim is to provide a structured overview of the laboratory parameters relevant to individualized vancomycin therapy based on Bayesian pharmacokinetic modeling, and to investigate their practical relevance.

METHODS

Based on a literature review, we identified and systematically classified laboratory parameters that support clinical decision-making in vancomycin therapy guided by TDM [1-4]. We evaluated the ongoing clinical laboratory practice at Semmelweis University, the availability of relevant assays, and the significance of the identified laboratory parameters in terms of the interpretation of pharmacokinetic modeling results and the assessment of clinical status.

Vancomycin therapy was performed at the Department of Internal Medicine and Hematology, Semmelweis University (Budapest, Hungary), where individualized treatment was supported by a multidisciplinary team involving the treating physician, an infectologist, a resident physician, a pharmacist, and a clinical laboratory pharmacist. Vancomycin concentrations were determined using a particle-enhanced turbidimetric inhibition immunoassay, serum creatinine using the enzymatic method, C-reactive protein using immunoturbidimetry, albumin by the bromocresol green method, and urea by an enzymatic urease–glutamate dehydrogenase assay on a Siemens Atellica® CH platform (Diagnosticum Zrt., Budapest, Hungary). Procalcitonin was assayed using electrochemiluminescence immunoassay on a Roche Cobas® e411 analyzer (Roche Magyarország Kft., Budapest, Hungary). Creatinine clearance was calculated using the Cockcroft–Gault equation [5]. Minimal inhibitory concentrations (MIC) were assessed at the Clinical Microbiology Laboratory of our Department using the broth microdilution method.

The online calculators used for the pharmacokinetic analyses are listed in Table 1, while key characteristics of patients are summarized in Table 2.

RESULTS AND DISCUSSION

The laboratory parameter groups relevant to vancomycin therapy are summarized in Table 3. With the exception of markers of vancomycin flushing syndrome, monitoring all parameters is recommended from the start of therapy. Among renal function markers, serum creatinine is currently the preferred first-line test as creatinine clearance is used as a covariate in pharmacokinetic models, and the assay is available as an urgent test. However, the limitations of the relationship between serum creatinine levels and renal function are well recognized [6]. Urea levels, in addition to albumin, are covariates in a single model [4]. Changes in these latter parameters do not result in clinically relevant differences in the modeled 24-hour area under the concentration–time curve (AUC_{24}, Figure 2). Serum cystatin C levels are influenced by considerably fewer physiological variables and thus show a stronger correlation with renal function [7]. However, higher costs and longer turnaround times limit their applicability for monitoring acute clinical conditions. Changes in clinical status are best characterized by C-reactive protein levels, whereas variations in procalcitonin concentrations are primarily associated with the presence of the pathogen (Figure 1). The limited availability and long turn-around time of tryptase prevents it from being a practically relevant test in vancomycin flushing syndrome.

Successful microbiological investigation may have critical impact on therapeutic outcomes. Therefore, the method used for MIC determination should always be reported along with known differences from results obtained with broth microdilution [1].

Table 3. Laboratory parameters to be monitored during vancomycin therapy.

Parameter group	Laboratory parameter	Available as an urgent test	Turnaround time
Parameters characterizing renal function	Serum creatinine	✓	1 hour
	Serum cystatin C	X	1-7 days
Acute-phase parameters	C-reactive protein	✓	1 hour
	Procalcitonin	✓	1 hour
Microbiological parameters	Pathogen identification	X	1 day
	Minimum inhibitory concentration	X	1 day
Markers of vancomycin flushing syndrome [2,3]	Tryptase	X	2-7 days
	Lactate	✓	Point-of-Care Test
Additional laboratory parameters required for pharmacokinetic modeling [4]	Serum albumin	✓	1 hour
	Serum urea	✓	1 hour

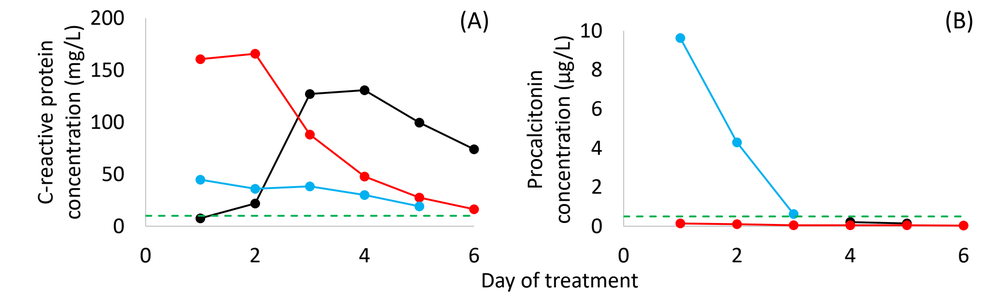

Figure 1. Acute-phase laboratory parameters. (A) C-reactive protein, (B) procalcitonin. Data series shown in different colors correspond to individual patients. The dashed green line indicates the upper limit of the reference range

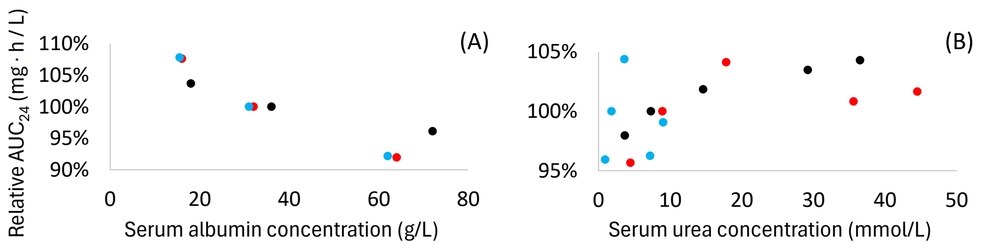

Figure 2. Effect of changes in (A) serum albumin and (B) serum urea levels on the calculated 24-hour vancomycin area under the concentration–time curve when applying the population pharmacokinetic model of Revilla et al[2]

An increase in serum creatinine concentration or a decrease in creatinine clearance beyond patient-specific thresholds results in a progressively steeper rise in the calculated AUC_{24}. However, the characteristics of this relationship vary among individuals, and exceeding the threshold of 600 mg · h/L does not coincide with surpassing the upper limit of the laboratory reference range (Figure 3).

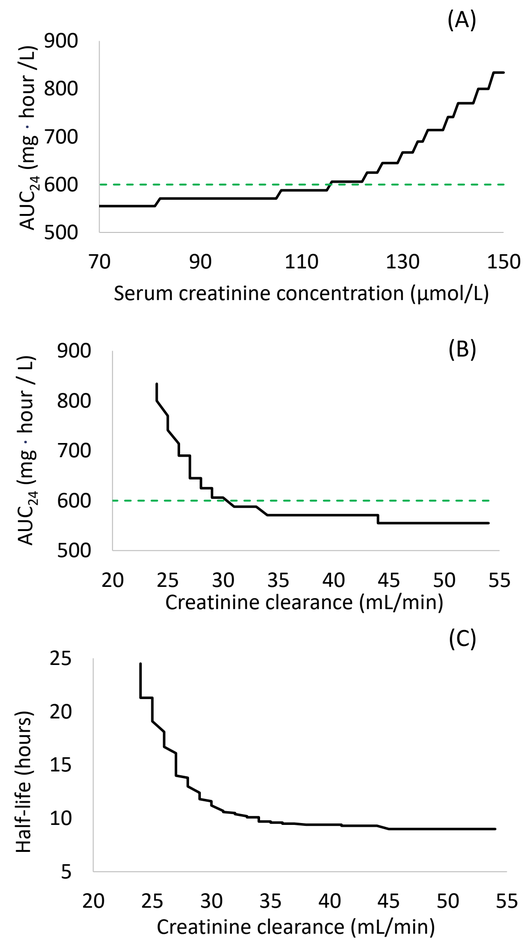

Figure 3. Relationship between serum creatinine concentration and creatinine clearance with the calculated 24-hour vancomycin area under the concentration–time curve (AUC_{24}). The dashed green line indicates the upper limit of the reference range.

In contrast to the limited association observed between covariate laboratory parameter values and the calculated AUC_{24}, a marked difference was observed in AUC_{24} values and calculated half-lives estimated by one- or two-compartment models (analytical equation–based approaches rely inherently on one-compartment models [1]). Failure to account for this difference may lead to inappropriate clinical decisions (Figure 4).

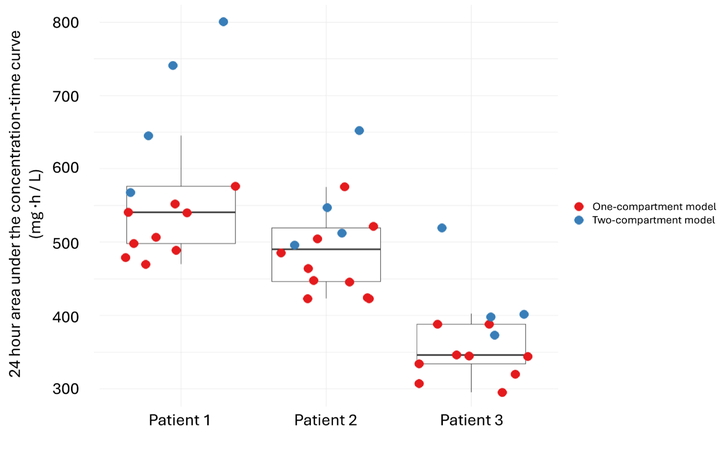

Figure 4. Calculated 24-hour vancomycin areas under the concentration–time curve according to the number of compartments included in the applied population pharmacokinetic model.

Based on the results of vancomycin drug monitoring and pharmacokinetic evaluation, our laboratory reports the calculated AUC_{24}, the dosing regimens predicted by the pharmacokinetic software to achieve the target steady-state AUC_{24} range (e.g. 400–600 mg · h/L), and the demographic, pharmaceutical and clinical information related to the assessment. Laboratory test results and the relationship between these and the calculated AUC_{24} are also reported. The information is communicated to the clinical pharmacist and the treating physician in the form of an interpretative laboratory report.

CONCLUSION

For clinically effective pharmacokinetic analyses based on vancomycin drug concentration measurements, assessment of the presented laboratory parameters and the integrated interpretation of pharmacokinetic results and laboratory data are essential. This process is facilitated by consultation with the laboratory from the initiation of therapy. Laboratory turnaround time has a fundamental impact on the clinical utility of the results. Familiarity with the key characteristics of the applied population pharmacokinetic model is also important. Determination of the MIC is required for efficient therapeutic decision-making. The appropriate interpretation of microbiological results requires sharing information on the assay method.

Table 1. Key characteristics of the online calculators used for pharmacokinetic analyses.

Pharmacokinetic calculator	Modeling algorithm	Population pharmacokinetic model	Pharmacokinetic compartments	Input laboratory parameters
VancoPK (https://vancopk.com/)	Analytical (explicit equations)	None	Central	Serum creatinine
UCSF calculator (https://ucsf.app.box.com/s/c0ojmqmqmpinp7snrn4ifce1h8cg5d0q/file/1625867051579)	Analytical (explicit equations)	None	Central	Serum creatinine
VancoCalc (https://www.vancocalc.com/)	Bayesian, parametric	Buelga DS et al. Antimicrob Agents Chemother 2005;49:4934.	Central	Serum creatinine
TDMx (https://tdmx.eu/)	Bayesian, parametric	Goti V et al. Ther Drug Monit 2018;40:212.	Central, peripheral	Serum creatinine
		Mangin O et al. Clin Pharmacokinet 2014;53:849.	Central	Serum creatinine
		Roberts JA et al. Antimicrob Agents Chemother 2011;55:2704.	Central	Serum creatinine
		Adane ED et al. Pharmacotherapy 2015;35:127.	Central	Serum creatinine
		Revilla N et al. Br J Clin Pharmacol 2010;70:201.	Central	Serum creatinine, albumin, urea
		Thomson AH et al. J Antimicrob Chemother 2009;63:1050.	Central, peripheral	Serum creatinine
BestDose (https://bestdoserx.com/)	Bayesian, nonparametric	Unpublished model	Central, peripheral	Serum creatinine

Table 2. Key characteristics of the patients included in the presented clinical cases. MIC, minimum inhibitory concentration.

	Patient 1	Patient 2	Patient 3
Sex	Female	Male	Female
Age (years)	66	45	50
Weight (kg)	46	70	54
BMI (kg/m^2)	19.3	25.7	22.5
Last serum creatinine level prior to drug level measurement (µmol/L)	65	62	38
Pathogen	Streptococcus mitis/oralis	Methicillin-resistant Staphylococcus aureus	Enterococcus faecium
Type of microbiological specimen	Central venous catheter	Urine, sputum	Urine
MIC determination method; result	MIC not determined	Broth microdilution; 1.0 mg/L	MIC not determined

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