Individualized Vancomycin Dosing Using Bayesian Modeling in Pediatric Patients with Lymphomas and Leukemias

Paulina Okuńska[1], Anna Małecka[2], Joanna Renke[2], Ninela Irga-Jaworska[2], Paweł Wiczling[1]

[1] Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdansk, Gdansk, Poland

[2] Department of Paediatrics, Haemathology & Oncology, Medical University of Gdansk, Gdansk, Poland

www.mug.edu.pl

BACKGROUND

Profound myelosuppression in children with acute leukemia or lymphoma frequently leads to severe infections requiring vancomycin therapy. In these patients, polypharmacy and drug interactions often cause suboptimal vancomycin concentrations, increasing the risk of nephrotoxicity at high levels and treatment failure with antibiotic resistance at low levels.

AIM

The study aimed to analyze historical clinical and laboratory data on serum vancomycin and creatinine concentrations in pediatric hematology patients. The objective was to develop an integrated pharmacokinetic model to optimize vancomycin dosing strategies and support therapeutic drug monitoring (TDM).

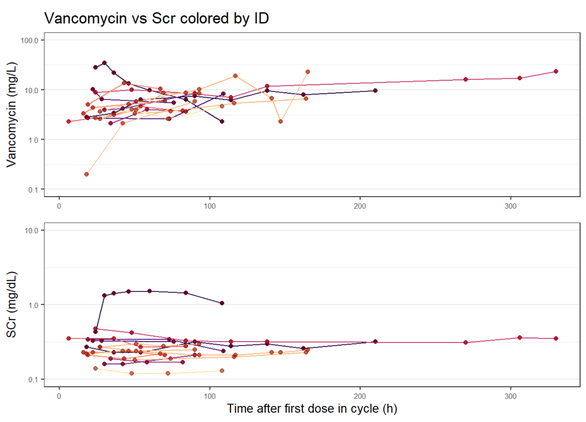


Figure 1. *Individual profiles of vancomycin and serum creatinine concentrations on a semi-log scale, colored by individual patient.*

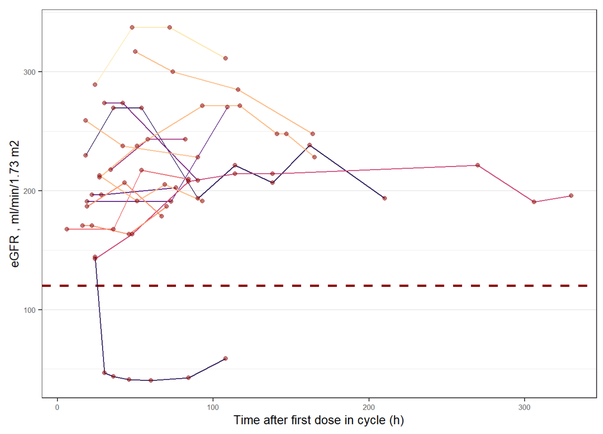


Figure 2*. Estimated glomerular filtration rate (eGFR), calculated using the „Bedside Schwartz" equation, is given by the following formula:* $GFR = 0.413 \cdot \frac{Height\ [cm]}{S_{CR}[mg/dL]}$. The vertical line indicates the reference value.

METHOD

Data were collected from 15 treatment cycles in **9 pediatric hematology patients** (3 boys and 6 girls, aged 3.66-16.8 years) treated for leukemia or lymphoma at the University Clinical Centre in Gdańsk. All patients received individualized dosing at 6-hour intervals. Serum vancomycin and creatinine concentrations were measured alongside demographic and clinical covariates.

In this work we model Vancomycin and SCr data simultaneously. It allows to properly handle measurement errors. We start with a simple one-compartment model as is often done in literature:

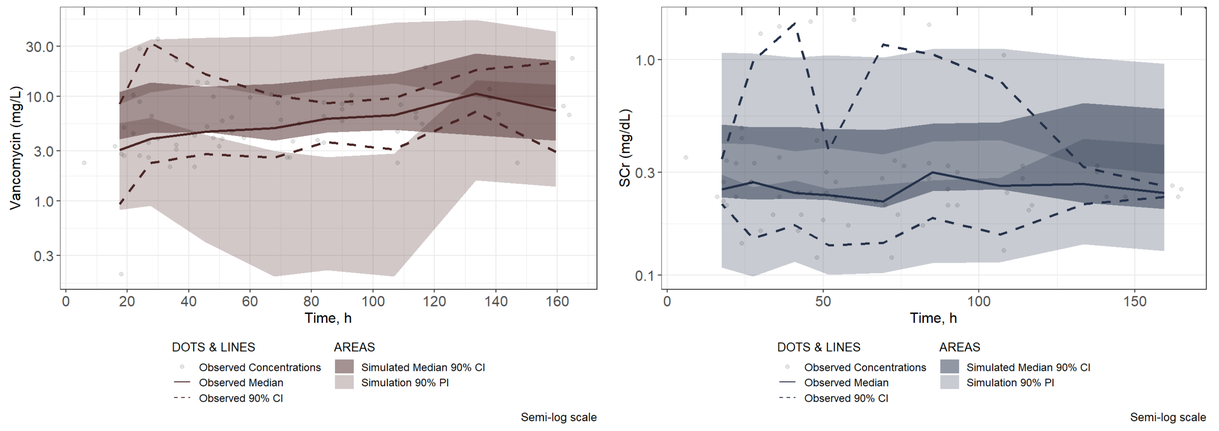
$$V_d \cdot \frac{dC}{dt} = Rate(t) - \frac{CL}{V_d} \cdot C$$
$$\frac{dSCr}{dt} = CRP - CL \cdot SCr$$

where C and SCr represent vancomycin and creatinine concentrations. $Rate(t)$ denotes the patient-specific vancomycin dosing rate, and CRP denotes the creatinine production rate.

A hierarchical Bayesian framework with informative literature-based priors was applied to capture both inter-individual and population-level variability. Model parameters were allometrically scaled to body size, enabling integration of prior knowledge with observed pediatric data and quantification of predictive uncertainty.

$$logC_{Obs_{i,j}} \sim student_t\left(\nu_1, f_1\left(P_i, t_{i,j}\right), \sigma_1\right)$$
$$logSCr_{Obs_{i,j}} \sim student_t\left(\nu_2, f_2\left(P_i, t_{i,j}\right), \sigma_2\right)$$
$$logP_i \sim MST\left(\nu_{eta}, log\theta_P + logfr_P + allo_P \cdot log\left(\frac{BW_i}{70}\right), \Omega\right)$$

where $P_i = (CL_i, Vd_i, CRP_i)$ is a vector of subject-specific parameters at each measurement occasion, $\nu_{1,2}$ denotes degrees of freedom, $f_{1,2}(.)$ are functions corresponding to the above ODE functions, MST denotes the multivariate Student-(t) distribution, θ_P is a vector of typical values of P_i, $allo_P$ is a vector of allometric exponents describing the relationship between P_i and BW_i. In turn, $\sigma_{1,2}$ represents the residual error scale, whereas Ω is the scale matrix describing unexplained between-subject variability and correlations between random effects. fr_P represents the difference between the healthy reference population and the studied population.



Figures 3 and 4. *Posterior predictive checks (PPC) comparing posterior simulated predictions with observed vancomycin and creatinine concentrations over time. Points represent observed concentrations, solid lines indicate observed trends, and shaded ribbons show 50% and 90% posterior predictive intervals, with darker and lighter areas corresponding to inner and outer quantiles of the predictive distribution, respectively. The left panels present vancomycin concentrations, whereas the right panels show creatinine concentrations.*

RESULTS

The joint one-compartment model adequately described vancomycin and creatinine kinetics, with posterior parameter estimates remaining consistent with literature-based priors. Typical pharmacokinetic parameter estimates (posterior mean vs. prior mean) were: θ_{CL} = 7.56 L/h vs 7.21 L/h; θ_{CRP} = 7.07 vs. 7.22; θ_{V1} =44.9 L vs. 44.8 L. Inter-individual variability estimates (posterior mean vs. prior mean) were: ω_{CL} = 0.375 vs. 0.305; ω_{CRP} = 0.314 vs. 0.306; ω_{V1} = 0.179 vs. 0.205. Prior allometric exponents were centered at 0.75 for CL and 1 for both CRP and V1, while posterior estimates were 0.7 for CL, 1.4 for CRP, and 1 for V1. The model reliably reproduced observed concentration–time profiles and enabled individualized dose prediction, with serum creatinine identified as a key covariate supporting dose optimization.

CONCLUSION

This study presents an integrated Bayesian model describing both vancomycin and creatinine kinetics in pediatric hematology patients, providing a framework for individualized therapy and uncertainty quantification in small populations. The approach may improve therapeutic drug monitoring, support dose optimization and reduce toxicity risk in pediatric oncology patients.

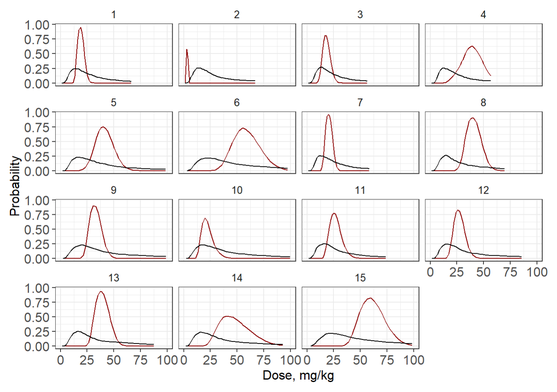
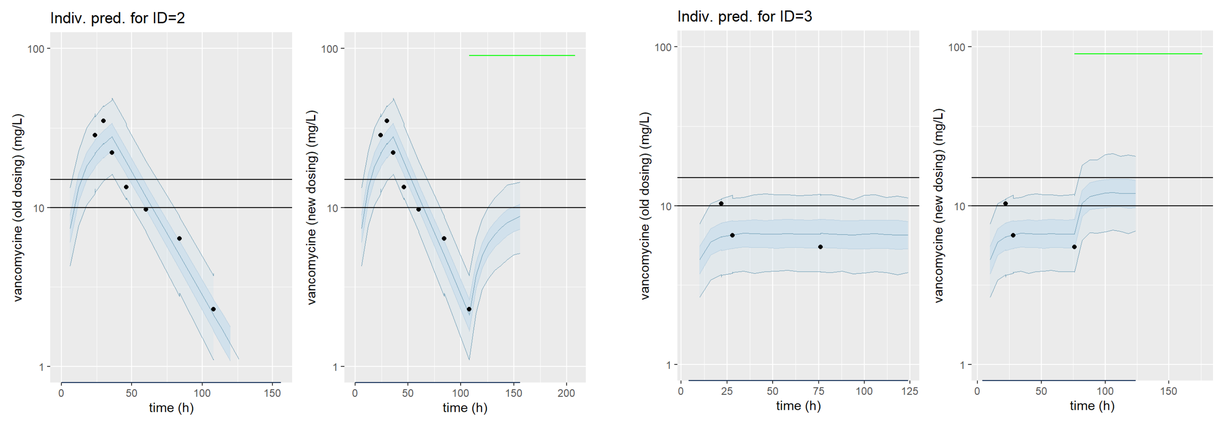


Figure 5. *PTA for the therapeutic target defined as* $C_{trough} < 15\ mg/L$ *and* $C_{trough} > 10\ mg/L$. *Red lines represent individual predictions, whereas black lines correspond to population-based predictions after q6h dosing. The results are faceted by individual subject-occasion.*

CLINICAL APPLICATION

The model's clinical applicability was demonstrated by individualized dose predictions under varying levels of prior information, ranging from no measurements to single or combined vancomycin and creatinine values.



Figures 6 and 7. *Predictions derived from the latest measurements for two representative patients: ID = 2, presenting impaired kidney function confirmed by a reduced eGFR value, and ID = 3. The future evolution was simulated using all available observations within the PTA framework. Black lines represent the PTA, points correspond to observed observations, and blue shaded areas indicate model-based predictive distributions, the green line represents projected observations under the new dosing regimen.*

References: [1] Aljutayli A, El-Haffaf I, Marsot A, Nekka F. An Update on Population Pharmacokinetic Analyses of Vancomycin, Part II: In Pediatric Patients. Clin Pharmacokinet 61, 47–70 (2022). https://doi.org/10.1007/s40262-021-01050-w PMID: 34671937. [2] Schwartz GJ and Work DF. Measurement and estimation of GFR in children and adolescents. J Am Soc Nephrol. 2009; Nov; 4(11): 1832-643. [3] . Huang GM, Qiu Y, Liu TT, Lu JJ. Comparison of vancomycin clearance between augmented renal clearance and normal renal function in critically ill infants: A population pharmacokinetics study. J Clin Pharmacol. 2022 Jan 20. doi: 10.1002/jcph.2029. Epub ahead of print. PMID: 35049078.

For correspondence: Paulina Okuńska; Division of Biopharmacy and Pharmacokinetics; Faculty of Pharmacy; Medical University of Gdansk
okunskapaul@gmail.com or paulinaokunska@gumed.edu.pl