Augmented Renal Clearance Using Vancomycin Population-Based Pharmacokinetic Modeling With Bayesian Estimation in Critically-ill Pediatric Patients

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ABSTRACT

Background: Our study objectives were to: 1) derive the pharmacokinetic (PK) model that best describes vancomycin clearance (CL_{VANCO}) in critically-ill pediatric patients; and 2) evaluate the incidence of augmented renal clearance (ARC) in critically-ill pediatric patients using CL_{VANCO}.

Methods: A retrospective, opportunistic cohort study was conducted at two pediatric hospitals in patients receiving vancomycin from 2003 to 2015. ARC was defined as a CL_{VANCO} of ≥ 130 mL/min/1.73m^2. Using NONMEM 7.2, a one-compartmental model with first-order kinetics and Bayesian analysis was used to estimate CL_{VANCO}. Internal model validation was performed using the bootstrap technique.

Results: ARC was identified in 29 of 250 (12%) total subjects with 658 vancomycin serum concentrations. Male gender and weight were similar between these groups, at 49% and 30 (interquartile range [IQR] 15-50) kg, respectively. Median age and baseline serum creatinine (SCr) were different between those with and without ARC (11.3 [IQR 8.7-13.8]) vs 9.0 [3.0-14.2] yr, p=0.037 and 0.33 [0.30-0.40] vs 0.40 [0.30-0.60] mg/dL, p=0.013, respectively). The final model for CL_{VANCO} (L/hr) was 0.118 * Weight ($e^{(-1.13*(SCr-0.40))}$). Mean CL_{VANCO} in those with vs without ARC were 144 and 90 mL/min/1.73m^2 (p < 0.001). The CL was similar to the median bootstrap analysis values, and was within the 95% confidence intervals. CL_{VANCO} was weakly correlated to the glomerular filtration rate estimated by the Modified Schwartz method (Spearman R^2 = 0.083).

OBJECTIVES

- Derive the PK model that best describes CL_{VANCO} in critically-ill pediatric patients.
- Evaluate the incidence of ARC in critically-ill pediatric patients using CL_{VANCO}.

METHODS

Study Design: Retrospective, opportunistic cohort study

- Pediatric patients hospitalized from Sept 2003 to Feb 2016 at Miller Children's Hospital Long Beach or Rady Children's Hospital of San Diego
- Inclusion criteria: Age 1-21 years and received vancomycin for ≥48 hours while in the PICU with ≥1 serum vancomycin concentration within 96 hours of drug initiation and normal baseline serum creatinine (SCr) as defined by age at start of therapy
- Exclusions criteria: (1) Renal impairment (as measured by baseline SCr by age group), or (2) Pregnant

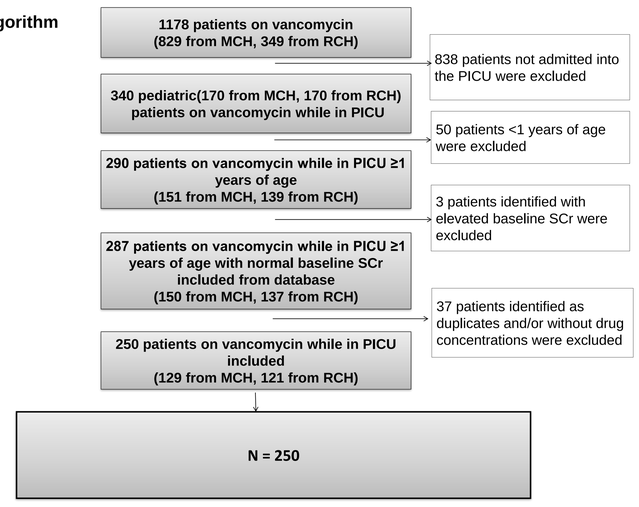
Population-based Pharmacokinetic Modeling:

- Using the first-order conditional estimation (FOCE) subroutine and the interaction option in NONMEM 7.2, a one-compartment model with first-order kinetics was used to estimate Bayesian post-hoc values for Vd, CL and Cmin.
- The AUC (mg-hr/L) was calculated by 24-hr dose (mg/day) ÷ CL (L/hr); and Steady-state Cmin determined by the intermittent short infusion model with a 1-hr infusion time (Dose = $[(Cmin)(CL)(tin)(1-e^{-k\tau})]/[(1-e^{-ktin})(e^{-ktmin})]$ where tin = infusion time, τ = dosing interval, k = elimination rate constant, and tmin = time to Cmin as calculated from the end of infusion).

Definitions:

ARC as a CL_{VANCO} of ≥ 130 mL/min/1.73m^2
Wt= Total Body Weight in kg
CL_{VANCO}= Estimation of creatinine clearance made using vancomycin drug clearance
$CL_{(MS\ or\ CG)}$= Estimation of creatinine clearance made using either Modified Schwartz or Cockcroft-Gault depending on patient's age
MOF= A reduction in minimum objective function significantly improves model fit, indicating an association that is statistically stronger (a decrease of at least 4 corresponds to a p-value ≤ 0.05)

Figure 1. Exclusion algorithm



RESULTS

Table 1. Demographics

Variable	Overall N = 250	With ARC n = 29	Without ARC n = 221	P-value
Median age (IQR), years	9.8 (3.2-14.0)	11.3 (8.7-13.8)	9.0 (3.0-14.2)	0.037
1 to < 2 yr, no. (%)	36 (14.4)	1 (3.4)	35 (15.8)	NS
2 to < 12 yr, no. (%)	117 (46.8)	14 (48.3)	103 (46.6)	NS
≥ 12 yr, no. (%)	97 (38.8)	14 (48.3)	83 (37.6)	NS
Median weight (IQR), kg	30.0 (15.0-50.0)	41.8 (25.8-53.9)	26.4 (14.6-50.0)	NS
Median height (IQR), cm	128.2 (97-156.7)	137.0 (113.5-156.3)	126 (95.0-157.0)	NS
Median ideal body weight (IQR), kg	27.0 (15.5-41.0)	30.9 (21.3-40.3)	26 (14.9-41.2)	NS
Median body surface area (IQR), m^2	1.03 (0.63-1.50)	1.26 (0.96-1.54)	0.97 (0.62-1.50)	NS
Median body mass index (IQR), kg/m^2	18.4 (16.0-21.8)	20.6 (17.9-24.6)	18.0 (16.0-21.1)	0.015
Male gender, no. (%)	122 (48.8)	15 (51.7)	107 (48.4)	NS
Median baseline SCr (IQR), mg/dL	0.4 (0.30-0.54)	0.33 (0.30-0.40)	0.4 (0.30-0.60)	0.013

Table 2. Evaluation of models to predict vancomycin pharmacokinetics

Covariates for Clearance (L/hr)	Minimum Objective Function	Change in Minimum Objective Function (MOF) from Base Model*
Base model with weight	3204.62	-
Concurrent nephrotoxic medications	3203.23	-1.39
Sex	3199.37	-5.25
Age (days)	3181.49	-23.142
SCr (mg/dL)	3027.32	-177.30

Covariates for Volume (L)	Minimum Objective Function	Change in Minimum Objective Function (MOF) from Base Model*
Base model with weight	3204.62	-
Age (days)	3204.55	-0.07
SCr (mg/dL)	3204.38	-0.24
Sex	3199.02	-5.6

Table 3. Vancomycin final pharmacokinetic model

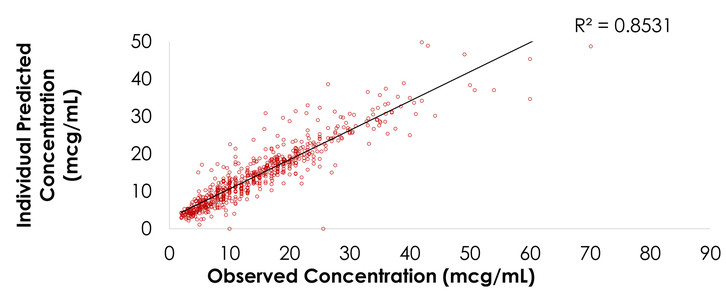
Parameter Estimates	Intersubject Variability	Residual Error	Additive Error
CL (L/hr) = 0.118 *Wt ($e^{(-1.13\ *(SCr-0.40))}$)	38.7%	21%	2.96
Vd (L) = 0.624 * Wt	34.9%		

Table 4. Median baseline post-hoc Bayesian estimates of pharmacokinetic parameters

Age (years)	Overall (N = 250)	With ARC (n = 29)	Without ARC (n = 221)	P-value
Median volume of distribution (IQR), L/kg	0.62 (0.58-0.66)	0.66 (0.63-0.72)	0.62 (0.57-0.65)	0.001
Median half-life (IQR), hr-1	3.62 (3.06-4.51)	2.89 (2.67-3.3)	3.79 (3.19-4.64)	<0.001
Median clearance (IQR), mL/min/1.73m2	97.34 (76.1-115.2)	141.3 (132.7-148.9)	91.7 (74.8-106.6)	<0.001

Figure 2. Goodness-of-fit plot for individual (A) and population (B) predicted to observed concentrations

A).



B).

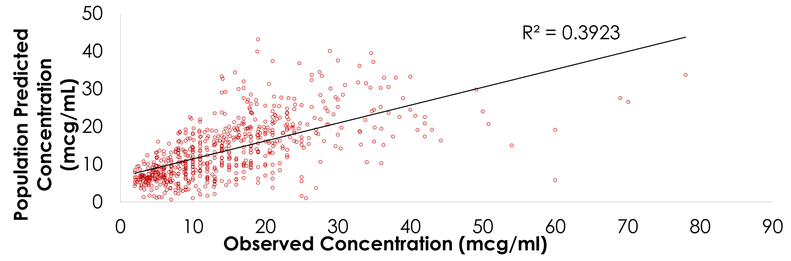
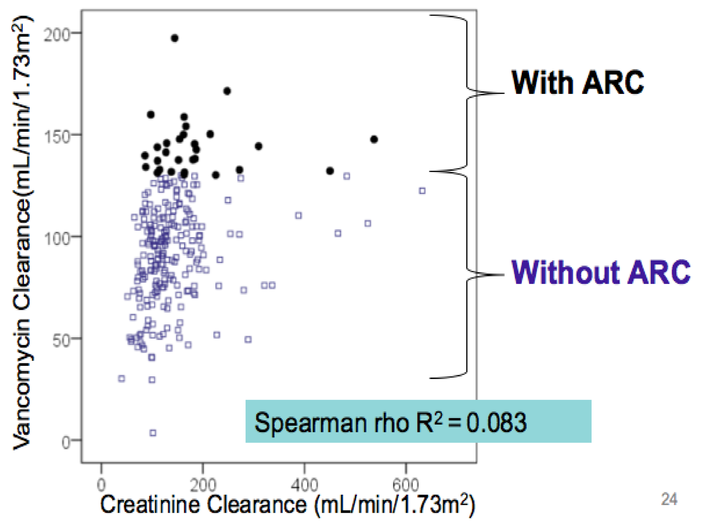


Figure 3. Spearman's rank correlation for CL_{VANCO} and $CL_{(MS\ or\ CG)}$



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CONCLUSIONS

- The incidence of ARC using CL_{VANCO} at 12% observed in this pediatric study was less than adult studies at 36% to 65%.
- The median CL_{VANCO} for ARC vs. non-ARC were 141.3 and 91.7 mL/min/1.73m^2.
- Weight and serum creatinine were independent covariates for CL in the final model, whereas age, sex, or concurrent nephrotoxic agents did contribute significantly.
- Serum creatinine was significantly lower in the group with ARC vs non-ARC.
- CL_{Vanco} and CL_{MS} were weakly correlated.

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ACKNOWLEDGMENTS

We would like to acknowledge the following groups or individuals who contributed to this research: Pharmacy staff at Rady Children's Hospital and Miller Children's Hospital for providing the pharmacokinetic information.