TITLE PAGE

Title of project:

Vancomycin Therapeutic Drug Monitoring in Pediatrics: Trough Monitoring vs. Area Under the Curve

Course title: PHPR 898B, Research Project II, Spring 2021

Date: April 11, 2021

Faculty advisor(s): Christopher A. Thomas and Christian Armstrong

Student(s): Robert Cortez and Elizabeth Vadasz

ABSTRACT

Specific Aims: To determine the intrapatient difference in vancomycin dosing requirements (in mg/kg/day) when comparing area under the curve (AUC) against trough level monitoring goals in pediatric patients at Phoenix Children's Hospital. To determine number of dose changes, correlation of an AUC of 400 mg h/L to trough levels, correlation of trough levels to vancomycin doses, rates of nephrotoxicity, and clinical treatment failure requiring escalation to a more broad-spectrum anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agent when using trough monitoring compared to AUC dosing.

Methods: Retrospective chart review of patients less than 19 years old who received vancomycin therapy for at least 48 hours at PCH between January 1st, 2018 and October 31st, 2020 and had at least one vancomycin peak and trough level measured at steady state within the hospital admission.

Main Results: One-hundred pediatric patient charts were reviewed (mean age = 7 years; SD = 5.1; mean weight = 27.1 kg; SD = 19.4; 47% Caucasian). Daily vancomycin exposure was 12.5% lower with AUC monitoring when compared to trough monitoring. An average of two dose changes were required to reach therapeutic steady state. When trough monitoring was utilized, an average trough of 10.5 mg/L was observed as compared to a trough of 8.4 mg/L correlated to an AUC target > 400 mg h/L There were no observed differences in rates of nephrotoxicity and no patients required escalation in anti-MRSA therapy.

Conclusions: Vancomycin dosing requirements in these pediatric patients appear to be lower when comparing AUC against trough level monitoring methods.

Vancomycin Therapeutic Drug Monitoring in Pediatrics: Trough Monitoring vs. Area Under the Curve

INTRODUCTION

Therapeutic drug monitoring of vancomycin has seen a recent shift from utilizing trough levels to area under the curve to minimum inhibitory concentration ratios (AUC/MIC) to guide dosing modifications. Recently published consensus guidelines recommend an AUC/MIC ratio of $\geq$ 400 (assuming a vancomycin MIC of 1 mg/L) as the preferred pharmacokinetics/pharmacodynamics (PK/PD) vancomycin therapeutic drug monitoring parameter in both pediatric and adult patients.[1] Additionally, data suggests that the risk of acute kidney injury (AKI) increases in a direct relationship with trough concentration, especially above 15-20 mg/L and when the daily AUC exceeds 650-1300 mg h /L.[1] These guidelines suggest that use of AUC/MIC guided vancomycin dosing is beneficial in order to achieve therapy goals, minimize adverse effects such as nephrotoxicity, and reduce risk of MRSA resistance.

The need to target trough levels > 15 mg/L to achieve AUC/MIC > 400 in pediatric patients is controversial. At PCH, current practice utilizes a hybrid model of trough and AUC dosing, beginning with trough monitoring with a goal range of 10-20 mg/L depending on diagnosis, disease severity, and location of infection. Dosing is switched to AUC monitoring when patients require 20 mg/kg/dose on trough monitoring. The results of this study may help demonstrate the applicability and impact of recent guideline changes in the pediatric patient population. We also aim to evaluate the differences in nephrotoxicity rates between trough monitoring and AUC monitoring methods. The results of this study may be compared with the new and previous monitoring guidelines to help determine which method best reduces incidences of nephrotoxicity. Therefore, the purpose of this study is to examine the differences in intrapatient vancomycin dosing requirements when comparing trough monitoring against AUC monitoring methods in pediatric patients at Phoenix Children's Hospital.

METHODS

Design This study used a retrospective chart review to compare vancomycin exposure, and the frequency and severity of nephrotoxicity in patients on trough monitoring compared to AUC monitoring. This study was approved by the University of Arizona/Phoenix Children's Hospital Human Subjects Protection Program.

Subjects Patients were included in the study if they were less than 19 years old at the time of vancomycin therapy, received vancomycin for at least 48 hours at PCH between January 1st, 2018 and October 31st, 2020, and had at least one vancomycin trough level measured at steady state (after the third dose). Each patient in the study served as their own comparator and also had at least one peak and one trough level at steady state for AUC calculation within the same hospital admission. Patients with renal dysfunction (calculated CrCl < 50 mL/min/1.73 m^2 by Modified Schwartz in patients aged < 18 years or Cockcroft-Gault in patients aged 18 to < 19 years), receiving renal replacement therapy or on extracorporeal membrane oxygenation, and neonates (defined as post-menstrual age < 37 weeks at time of birth and/or corrected age < 4 weeks) were excluded from the study.

Treatment Independent variables were trough monitoring and AUC monitoring.

Measures Data were collected using an electronic data collection form via Microsoft Excel. The primary outcome variable was the intrapatient difference in daily vancomycin dosing requirements (mg/kg/day), within 24 hours of reaching steady state at a target AUC > 400 mg h/L in comparison to steady state dosing requirements over the 24 hours prior to switching from trough monitoring. The secondary outcome variable was serum creatinine while receiving vancomycin therapy, measured in mg/dL over the 24 hours before switching to AUC monitoring and measured at least 24 hours after switching from trough monitoring to AUC. Additional secondary outcome variables included number of dose changes required to reach a therapeutic level at steady state, occurrence of change in therapy to a broader anti-MRSA agent, AUC level measured at steady state in mg h/L in correlation with trough levels in mg/L measured at steady state within 24 hours before switching to AUC, and trough levels in mg/L correlated with a vancomycin dose in mg/kg/day.

Descriptive variables included in data collection were comorbid conditions such as renal dysfunction, congenital heart disease, and/or cystic fibrosis, and concomitant nephrotoxic medication use. Demographic data were collected on age, gender, height, weight, race, and baseline kidney function (defined by serum creatinine (SCr) in mg/dL).

Data Collection Data were collected by retrieving patient charts at Phoenix Children's hospital from the electronic medical record [Sunrise Clinical Manager (SCM)]. Patients were de-identified and stored using Excel with an assigned unique study identification number.

Data analysis

The descriptive and demographic variables were analyzed by calculating summary means and standard deviations to compare groups.

RESULTS

A total of 100 pediatric patient charts were analyzed. The demographic characteristics of the patients are shown in table 1**.** Differences in daily vancomycin dosing requirements are shown in table 2**.** On average, 69.3 mg/kg/day vancomycin was required when utilizing trough monitoring compared to 60.6 mg/kg/day when targeting AUC > 400 mg h/L. This correlates to an intrapatient reduction in vancomycin exposure of 12.5% when using AUC monitoring. Secondary outcome variables, includi**ng**, number of dose changes required to reach a therapeutic steady state level, correlation of AUC to trough levels, rates of nephrotoxicity and occurrence of change in therapy by switching to a broader anti-MRSA agent are shown in table 3. Of the 100 patient charts reviewed, an average of two dose changes were required to reach therapeutic steady state prior to switching from trough to AUC monitoring. When monitoring trough levels, the average trough of 10.5 mg/L correlated to a dose of 17.7 mg/kg/dose compared to 15.5 mg/kg/dose when targeting AUC > 400, which correlated to an average trough of 8.4 mg/L. No patients demonstrated an increase in SCr by $\geq$ 0.5 mg/dL or a $\geq$ 50% increase in baseline on at least two consecutive days and no escalations of therapy were observed.

DISCUSSION

The primary finding of this study is that pediatric patients appeared to require lower daily vancomycin doses when utilizing AUC monitoring compared to trough monitoring. The average dose and corelated trough when reaching AUC target goals > 400 mg h/L was within the therapeutic range as reported in current literature. Similar results have been reported by Le et al., who demonstrated in a retrospective study that trough levels between 8-9 mg/L in pediatric patients correlated to patients achieving the therapeutic goal AUC/MIC > 400, with a total daily dose of 60-70 mg/kg/day.[2]

Compared to AUC monitoring, which requires one initial trough and peak level to be drawn, when utilizing trough-guided dosing, an average of two dose changes per patient was required to reach a therapeutic steady state. Given the cost to obtain each trough level, these findings suggest approximately $530 in increased costs per patient associated with trough monitoring. Overall, this suggests potential cost savings over $17,000 per year if AUC monitoring was utilized.

Patient's reached an average of 17.7 mg/kg/dose while utilizing trough monitoring prior to switching to AUC monitoring. This is lower than the standard practice at PCH, which is to switch from trough monitoring to AUC monitoring once patients reach requirements of 20 mg/kg/dose. This may explain why the observed intrapatient difference in daily dosing requirements was lower than expected. These results further support previous studies that indicate trough levels between 15-20 mg/L are unnecessary for serious infections.

Implications for practice: These findings have several implications for establishing best practices for vancomycin dosing and monitoring methods. First, these results exemplify the potential impact to optimize vancomycin dosing strategies and improve time in therapeutic range. Additionally, since fewer trough levels and dose changes per patient are required, these findings suggest that AUC monitoring minimizes cost related to vancomycin therapy.

Limitations: This study was limited by the small study population in a single center. These results could limit the generalizability to other pediatric patients receiving vancomycin therapy.

CONCLUSIONS

Vancomycin dosing requirements in the pediatric patients included in this study were 12.5% lower when targeting AUC/MIC compared to trough monitoring goals. Rates of nephrotoxicity were no different when using AUC/MIC monitoring compared to trough monitoring.

REFERENCES

1. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society by America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 2020; 77: 835–64.
2. Le J, Bradley JS, Murray W, et al. Improved vancomycin dosing in children using area under the curve exposure. *Pediatr Infect Dis J*. 2013;32(4):e155-e163. doi:10.1097/INF.0b013e318286378e.

TABLES AND FIGURES

TABLE 1. CHARACTERISTICS OF STUDY SUBJECTS

AGE (MEAN; SD)	7 years; 5.1 years
GENDER (%)	
FEMALE	47%
MALE	53%
HEIGHT (MEAN; SD)	117 cm; 34.4 cm
WEIGHT (MEAN; SD)	27.15 kg; 19.4 kg
BMI (MEAN; SD)	17.5 kg/m^2; 3.3 kg/m^2
ETHNICITY (MEAN; SD)	
WHITE	47%
BLACK	2%
HISPANIC	36%
ASIAN	4%
AMERICAN INDIAN OR ALASKA NATIVE	10%
OTHER	1%
BASELINE KIDNEY FUNCTION (MEAN; SD)	Scr = 0.32 mg/dL; SD = 0.14 mg/dL
COMORBID CONDITIONS (%)	
CONGENITAL HEART DISEASE	9%
CYSTIC FIBROSIS	6%
URINARY PROBLEM	13%
COVID-19	2%
CONCOMITANT-NEPHROTOXIC MEDICATION USE (%)	
NSAIDS	24%
AMINOGLYCOSIDES	11%
OTHER ANTI-INFECTIVE AGENTS	12%
ANTI-FUNGAL AGENTS	6%
ANTI-REJECTION AGENTS	4%

SD = Standard Deviation; BMI = Body Mass Index; COVID-19 = Coronavirus Disease of 2019; NSAIDS = Non-steroidal anti-inflammatory drugs

TABLE 2. PRIMARY OUTCOME VARIABLE RESULTS

	Targeting steady state trough goal	Targeting steady state goal AUC 400-600 mg h/L	Intrapatient difference
VANCOMYCIN TOTAL DAILY DOSING REQUIREMENTS (MG/KG/DAY)	69.3	60.6	12.5%

TABLE 3. SECONDARY OUTCOME VARIABLE RESULTS

REDUCTION IN NEPHROTOXICITY RATES (%)	0%
DOSE CHANGES REQUIRED (MEAN; RANGE)	2 (0 – 22)
CHANGE IN THERAPY (%)	0%
CORRELATION OF AUC/MIC TO TROUGH LEVELS (MG/L)	
TROUGH MONITORING (MEAN; RANGE)	10.5 (3.6 – 32)
AUC MONITORING (MEAN; RANGE)	8.4 (2.9 – 14.9)

APPENDICES

Appendix A: Data Collection Form

CODEBOOK

Column	Item No.	Variable Name	Code
A	1	ID Number	assigned unique number
B	2	Age	years
C	3	Weight	kg
D	4	Height	cm
E	5	BMI	kg/m2
F	6	Gender	female = 1, male = 2
G	7	Race	White = 1, Black = 2, Asian = 3, American Indian or Alaska Native = 4, Native Hawaiian or Pacific Islander = 5, **Hispanic/Latino = 6**
H	8	Ethnicity	Hispanic or Latino = 1, not Hispanic or Latino = 2
I	9	Comorbid conditions	none = 1 renal dysfunction = 2, congenital heart disease = 3, cystic fibrosis = 4, other = 5 (must define)
J	10	Concomitant nephrotoxic medication use	Yes = 1 (define), No = 2
K	11	Vancomycin regimen flat dose - trough monitoring	mg
L	12	Vancomycin dose - trough monitoring	mg/kg
M	13	Vancomycin frequency (# doses in 24 hours) - trough monitoring	Q6H = 4, Q8H = 3, Q12H = 2, etc.
N	14	Vancomycin total daily dose - trough monitoring	mg/kg/day
O	15	Vanco Trough	ug/mL
P	16	Vanco Peak	ug/mL
Q	17	AUC	ug h/L
R	18	Est. flat dose (AUC target 400)	mg
S	19	Est. weight based dose (AUC target 400)	mg/kg
T	20	Est. dose frequency (# doses in 24 hours) - AUC target 400	Q6H = 4, Q8H = 3, Q12H = 2, etc.
U	21	Est. total daily dose - AUC target 400	mg/kg/day
V	22	Est. vanco trough - AUC target 400	
W	23	Change in intrapatient dosing requirement (trough monitoring vs. esti	%
X	24	SCr (baseline)	mg/dL
Y	25	SCr increase by 0.5 mg/dL or 50%	Yes = 1, No = 2
Z	26	# of dose changes prior to AUC monitoring	#

DATA ENTRY SHEET

Age (2)	Weight (3)	Height (4)	BMI (5)	Gender (6)	Race (7)	Ethnicity (8)	Comorbid Condt. (9)	Nephr. Med (10)	Vanco regimen flat dose - T (11)	Vanco weight based dose - T (12)	Vanco dose frequency - T (13)	Vancomycin TDD - T (14)	Trough (15)	Vanco peak (16)	AUC (17)	Est. flat dose - AUC 400 target (18)	Est. wt based dose - AUC target 400 (19)	Est. frequency - AUC 400 target (20)	Est. TDD - AUC 400 target (21)	Est. vanco trough - AUC target 400	Est. intrapatient Diff. (23)	SCr (24)	SCr inc (25)	# dose changes (26