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Optimization of Vancomycin Dosing in Very Low-Birth-Weight Preterm Neonates

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Abstract

Objective—To compare vancomycin serum trough concentrations and 24-hour area under the serum concentration-versus-time curve (AUC₂₄) among very low-birth-weight (VLBW) premature infants before and after implementation of an institution-wide increase in neonatal vancomycin dosing.

Study Design—We performed a retrospective analysis of vancomycin concentrations among preterm VLBW neonates before (2007–2010) and after (2010–2013) implementation of a new vancomycin dosing protocol consisting of increased vancomycin daily dose and frequency of administration.

Results—Neonates weighing < 1,500 g and receiving the new vancomycin dosing regimen had lower rates of undetectable trough concentrations (24 vs. 50%, $p = 0.04$), higher median trough concentrations (10.8 vs. 5.9 µg/mL, $p = 0.003$), a higher proportion of goal trough concentrations of 10 to 20 µg/mL (35 vs. 4%, $p = 0.005$), and a significantly higher vancomycin AUC₂₄ (438 vs. 320 mg·h/L, $p = 0.004$) compared with historical controls.

Conclusion—Increasing the vancomycin daily dose and dosing frequency led to an increase in vancomycin trough concentrations and AUC₂₄, and a decrease in the proportion of undetectable (< 5.0 µg/mL) troughs, without an increase in toxicity among VLBW premature neonates.

Keywords

vancomycin; neonates; preterm; VLBW; AUC₂₄

Very low-birth-weight (VLBW) (< 1,500 g) and preterm infants are at high risk for sepsis.¹ Vancomycin is commonly used as empiric therapy for neonatal late-onset sepsis and is considered the treatment of choice for Gram-positive organisms including coagulase-negative staphylococci (CoNS) and methicillin-resistant *Staphylococcus aureus* (MRSA). Despite its widespread use, there is no consensus regarding neonatal vancomycin dosing and great variability in vancomycin dosing regimens across institutions.^{2,3} We observed that a large proportion of VLBW neonates receiving vancomycin at our institution had undetectable vancomycin troughs. Therefore, we adopted a new dosing protocol to standardize and increase vancomycin daily dose and frequency of administration. The goal of this study was to compare vancomycin trough concentrations and 24-hour area under the serum concentration-versus-time curve (AUC₂₄) among VLBW infants before and after implementation of the new vancomycin dosing protocol.

Methods

We performed a retrospective analysis of preterm VLBW infants receiving vancomycin in the Neonatal Intensive Care Unit (NICU) at Mayo Clinic, Rochester, MN, from January 2007 to March 2013. The new vancomycin dosing protocol was implemented in September 2010 by establishing a standard electronic order entry form for prescribers. Infants in the intervention group (September 2010–March 2013) were dosed according to the new institutional dosing protocol (Table 1). Infants in the control group (January 2007–August 2010) received a variety of dosing regimens, most commonly 15 mg/kg every 18 or 24 hours.

Infants were included if they were treated with vancomycin, had a steady state vancomycin trough concentration obtained within 1 hour before the fourth or any subsequent dose, weighed < 1,500 g at the time of vancomycin administration, and provided MN state research authorization (MN Statute 144.335). The first vancomycin course per patient was included. Patients were excluded if they did not have vancomycin concentrations measured, received vancomycin in the prior 7 days, had renal insufficiency (defined as urine output < 1 mL/kg/hour), indomethacin administration within 24 hours of a vancomycin dose, or extracorporeal membrane oxygenation (ECMO). Demographic and clinical information was collected through medical record review. Ototoxicity was defined as failure of the Automated Auditory Brainstem Response (AABR) test. Definite nephrotoxicity was defined as a 2-fold increase in serum creatinine or a serum creatinine increase above 1 mg/dL with a concurrent decrease in urine output to less than 1 mL/kg/hour over a minimum of 48 hours. Probable nephrotoxicity was defined as a rise in serum creatinine as specified above without concomitant decrease in urine output.

Vancomycin trough concentrations were measured using the enzyme-multiplied immunoassay technique (EMIT). The goal vancomycin trough range was 10 to 20 µg/mL. Trough concentrations > 20 µg/mL were considered supratherapeutic while troughs < 5 µg/mL were considered undetectable. Vancomycin minimal inhibitory concentration (MIC) was determined by the clinical microbiology laboratory using the agar dilution method and interpreted according to Clinical Laboratory and Standards Institute (CLSI) guidelines.

Predicted AUC_{24} was calculated for all patients using the following equation: $AUC_{24} = \text{vancomycin daily dose} / \text{vancomycin clearance}$. Vancomycin clearance (CL_{vanc}) was calculated using the neonatal predictor model by Capparelli⁴ based on the following equation: $CL_{vanc} (L/h) = WT \times (0.028/CR + 0.000127 \times AGE + 0.0123 \times GA28) + 0.06$ (WT, weight in kg; CR, serum creatinine (mg/dL); AGE, postnatal age (days) if CR < 0.7; GA28 is 1 if gestational age > 28 weeks and 0 if gestational age ≤ 28 weeks). The model by Capparelli was chosen because it was derived from a broad population including neonates similar to our study population and used a vancomycin trough analysis method similar to the one used at our institution. Furthermore, we compared CL_{vanc} calculated using models by Capparelli,⁴ Grimsley,⁵ and Silva⁶ and found no significant differences (data not shown).

Data were analyzed using Wilcoxon rank sum test, chi-squared test or Fisher exact test, as appropriate, and Spearman rank correlation. A *p*-value < 0.05 was considered statistically significant. This study was approved by the Mayo Clinic Institutional Review Board.

Results

Demographic Information

Fifty-seven infants were included in the study, 29 in the intervention group and 28 in the control group. There were no statistically significant differences between groups in terms of gender, gestational age, weight, baseline creatinine, or CL_{vanc} (Table 2). In the intervention group, indications for vancomycin were most commonly empiric therapy followed by bacteremia and necrotizing enterocolitis (NEC). In contrast, in the control group, indications for vancomycin were most commonly bacteremia followed by empiric therapy and NEC (Table 2).

Microbiology

CoNS was the most commonly identified pathogen from blood, respiratory, or intra-abdominal sources in both intervention and control groups. Among patients with positive cultures from any source, a higher proportion of virulent organisms including methicillin-susceptible *S. aureus* (MSSA), MRSA, and Enterococcus were identified in the intervention group compared with the control group (46 vs. 21%, *p* = 0.13) (Table 1). Vancomycin minimum inhibitory concentrations (MICs) were greater among isolates in the intervention group. Among CoNS isolates, the vancomycin MIC was ≥ 2 µg/mL in 8 of 15 control patients and in 7 of 7 intervention patients. Among *S. aureus* isolates, the vancomycin MIC was 2 µg/mL in 2 of 5 patients in the intervention group and in 1 of 2 patients in the control group.

Vancomycin Trough Concentrations and Predicted AUC_{24}

The mean daily dose of vancomycin was significantly higher in the intervention versus control group (30 vs. 19 mg/kg/day, *p* < 0.001) (Table 2). Patients in the intervention group had a lower frequency of undetectable initial troughs (24 vs. 50%, *p* = 0.04), higher median troughs (10.8 vs. 5.9 µg/mL, *p* = 0.003), and a higher proportion of goal troughs (10–20 µg/mL) (35 vs. 4%, *p* = 0.005) than patients in the control group (Table 2). There was no significant difference in the proportion of infants with initial trough concentrations > 20

µg/mL between groups. Median predicted AUC₂₄ was significantly higher in the intervention versus control group (438 vs. 320 mg·h/L, $p = 0.004$). Vancomycin trough concentration correlated moderately with predicted AUC₂₄ (Spearman rho = 0.482, $p = 0.0001$).

Toxicity

Two patients in the intervention group had probable vancomycin-associated nephrotoxicity. No patients in the control group experienced nephrotoxicity ($p = 0.49$). Among patients who underwent AABR hearing screens, failures occurred in 3 of 24 (13%) in the intervention group and 3 of 22 (14%) patients in the control group ($p = 1.00$). These failures could not be attributed solely to vancomycin, as 5 of 6 infants who failed the AABR had also received gentamicin.

Discussion

We observed significant differences in vancomycin trough concentrations in VLBW neonates before and after implementation of a standardized neonatal dosing regimen. Specifically, we found that increasing vancomycin daily dose and dosing frequency among VLBW neonates led to a significant reduction in the proportion of patients with undetectable vancomycin trough concentrations, an increase in median trough concentrations, and an increase in predicted vancomycin AUC₂₄.

It remains unclear what optimal vancomycin trough concentrations are in neonates, as pharmacokinetic and pharmacodynamic data are lacking. Goal vancomycin trough concentrations of 15 to 20 µg/mL⁷ and an AUC/MIC ratio 400⁸ have been proposed for adults and children for optimal treatment of invasive MRSA infections. A recent pediatric study found that trough concentrations of 7 to 10 µg/mL correspond to an AUC/MIC > 400 if the MIC of MRSA is 1 µg/mL.⁹ However, it is not clear if similar parameters are required for optimal vancomycin activity in neonates or against CoNS, the predominant pathogen in the neonatal population. A small study in eight neonates observed vancomycin AUC₂₄ 400 mg·h/L with trough concentrations of 5 to 10 µg/mL.¹⁰ Regardless of how one defines target vancomycin trough concentrations, undetectable vancomycin troughs reflecting subtherapeutic serum drug levels were significantly less common following our intervention with 69% of neonates in the intervention group reaching trough concentrations of 5 to 20 µg/mL. In addition, our study determines that AUC₂₄ > 400 mg·h/L is achievable with higher daily doses of vancomycin and demonstrates that there is moderate correlation between vancomycin trough concentration and AUC₂₄ in neonates.

It is notable that one-fourth of patients in the intervention group had undetectable initial vancomycin trough levels. This suggests that our new dosing protocol underdoses some infants. The appropriate vancomycin dose is particularly challenging to identify in this heterogeneous population in which weight, gestational age and postnatal age, renal function, and coadministered medications all affect drug clearance.¹¹ Continuous vancomycin infusion in neonates^{12,13} could be an alternative to conventional interval-based dosing, potentially avoiding unwanted low troughs and high peaks, but requires further study.

We observed no difference in the frequency of vancomycin-associated toxicities between the intervention and control groups, although our study was not powered to detect these. While we did observe a similar number of AABR failures in both groups, it is currently unclear whether vancomycin is truly ototoxic in neonates.^{14,15} Two patients in the intervention group had reversible nephrotoxicity compared with none in the control group. This nephrotoxicity may have been due to overall severity of illness, which appeared to be greater in patients in the intervention group who had more infections with *S. aureus* than did the control group.

This study has several limitations. It was a single-center retrospective analysis with a small sample size. We did not classify severity of illness or distinguish between positive blood cultures that were contaminants versus true pathogens, and, therefore, did not attempt to correlate vancomycin concentrations with clinical cure or mortality. Despite these limitations, our study adds to the paucity of data on vancomycin dosing in the neonatal patient population.

In conclusion, at our institution, standardizing and optimizing vancomycin dosing increased vancomycin trough concentrations, raised the vancomycin AUC₂₄ to > 400 mg·h/L, and decreased the frequency of undetectable (< 5.0 µg/mL) troughs. Given the lack of standardized neonatal vancomycin dosing guidelines, institutions should assess the frequency of therapeutic vancomycin concentrations in preterm infants and adjust their neonatal vancomycin dosing regimens as needed. Studies correlating vancomycin serum concentrations and clinical outcomes in neonates are needed.

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Table 1

Vancomycin dosing protocol for neonates implemented in the Neonatal Intensive Care Unit at Mayo Clinic Children's Hospital in September 2010

Postnatal age	Weight < 1,300 g	Weight ≥ 1,300 g
< 7 d	15 mg/kg every 24 h	15 mg/kg every 18 h
≥ 7 d	15 mg/kg every 12 h	15 mg/kg every 8 h

Table 2

Characteristics and pharmacokinetic parameters among neonates receiving vancomycin at Mayo Clinic Children's Hospital from January 2007 to August 2010 (control group) and September 2010 to March 2013 (intervention group)

Characteristics	Control (N = 28)	Intervention (N = 29)	p Value
Male gender, no. (%)	12 (42.9)	9 (31.0)	0.35
Gestational age (GA) at birth, median in weeks (range)	26 (24.0–30.1)	25.9 (22.9–31.6)	0.52
Corrected GA at study entry, median in weeks (range)	29.1 (25–32.6)	28.1 (24–37.3)	0.45
Birth weight, median in kg (range)	0.80 (0.48–1.46)	0.75 (0.45–1.58)	0.26
Weight at study entry, median in kg (range)	0.94 (0.47–1.47)	0.91 (0.49–1.49)	0.88
Indication for vancomycin, no. (%)			0.51
Empiric	9 (32.1)	14 (48.3)	
Bacteremia	15 (53.6)	10 (34.5)	
NEC	3 (10.7)	3 (10.3)	
Other	1 (3.6)	2 (6.9)	
Positive culture from any source ^a	19 (67.9)	13 (44.8)	0.08
Identified organism ^b			0.37
CoNS	15 (79.0)	7 (53.9)	
MSSA	1 (5.3)	2 (15.4)	
MRSA	1 (5.3)	3 (23.1)	
Enterococcus	1 (5.3)	1 (7.7)	
Viridans group <i>Streptococcus</i>	1 (5.3)	0 (0)	
Baseline creatinine, median in mg/dL (range)	0.65 (0.2–1.4)	0.50 (0.2–1.3)	0.07
Median vancomycin clearance ^c in L/h/kg (range)	0.057 (0.03–0.15)	0.065 (0.03–0.16)	0.10
Median daily vancomycin dose (mg/kg/d)	19.6 (13.3–40.8)	29.8 (14.0–46.5)	< 0.001
Vancomycin trough concentrations			
< 5.0 µg/mL, no. (%)	14 (50)	7 (24)	0.04
5–10 µg/mL, no. (%)	13 (46)	10 (34)	0.36
10–20 µg/mL, no. (%)	1 (4)	10 (34)	0.005
> 20 µg/mL, no. (%)	0 (0)	2 (7)	0.16
Median vancomycin trough concentration ^d in µg/mL (range)	5.85 (5.1–10.0)	10.75 (5.0–25.7)	0.003
Median vancomycin AUC ₂₄ in mg·h/L (range)	320 (194–769)	438 (130–776)	0.004

Abbreviations: AUC₂₄, 24-hour area under the serum concentration-versus-time curve; CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NEC, necrotizing enterocolitis.

^aIncludes blood, respiratory, or intra-abdominal source.

^bAmong patients with positive cultures from any source.

^cCalculated as described in “Methods” section and by Capparelli et al.⁴

^dAmong patients with detectable initial vancomycin trough concentrations.