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Evaluation of the Effectiveness of a Vancomycin Nomogram at Predicting Trough Levels within a Therapeutic Range

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Abstract: Objectives: The aim of this study was to assess the ability of a vancomycin nomogram to effectively predict vancomycin serum trough concentrations within the desired 15-20 mg/L therapeutic range. Methods: A retrospective chart review was performed on a randomized sample of trough concentrations from adult patients at HVMC (Holston Valley Medical Center) receiving intravenous vancomycin dosing regimens determined by the vancomycin nomogram over an eight-month span. Key findings: 102 patients were included in the study. Trough concentrations ranged from 3.5 mg/L to 40.8 mg/L with 36 (35.2%) patients having trough levels within the desired range of 15-20 mg/L. In addition, 75 (73.5%) patients had trough levels within the range of 10-25 mg/L. Conclusion: This study demonstrated that the vancomycin nomogram at HVMC is an effective dosing tool that provides consistency among multiple pharmacists and predictable serum trough concentrations.

Key words: Vancomycin, pharmacokinetic, nomogram, trough.

1. Introduction

Vancomycin, a glycopeptide antibiotic commonly used to treat serious infections associated with gram-positive organisms, specifically MRSA (methicillin-resistant *Staphylococcus aureus*), is a narrow therapeutic index drug [1, 2]. Individualized dosing and attention to specific patient factors are important to achieve optimal outcomes from vancomycin therapy and to prevent toxicity [1, 3, 4]. Based upon clinical data that patients were less likely to be successfully treated with vancomycin if the *S. aureus* MIC was ≥ 4 mg/L, in 2006 the CLSI (Clinical and Laboratory Standards Institute) lowered the susceptibility and resistance breakpoints for the MIC (minimum inhibitory concentration) of vancomycin to ≤ 2 mg/L for "susceptible," 4-8 mg/L for "intermediate," and ≥ 16 mg/L for "resistant."[3, 5-7]. More recently, several studies have discerned worse clinical outcomes for patients infected by MRSA isolates with a vancomycin MIC ≥ 1 mg/L [5-9]. The pharmacokinetic parameter that best predicts the efficacy of vancomycin is the area under the curve (AUC) to MIC ratio (AUC:MIC) [6, 8, 9]. Specifically, studies have shown that an AUC:MIC ≥ 400 is associated with clinical success of vancomycin therapy [6, 8, 9].

In the clinical setting, however, time and financial resources can limit the ability to obtain multiple serum vancomycin concentrations necessary to determine the AUC and subsequently calculate the AUC:MIC. Therefore, vancomycin serum trough concentrations are used as the conventional method for monitoring vancomycin effectiveness [5, 8, 9]. To obtain the most accurate results, trough concentrations should be drawn just prior to the next dose once the patient has reached steady-state [8]. According to the most recent IDSA (Infectious Diseases Society of America)/ASHP (American Society of Health System Pharmacists') guidelines on the therapeutic monitoring of vancomycin in adult patients, vancomycin serum trough concentrations should be maintained above 10

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mg/L to avoid development of resistance, and ideally between 15 mg/L and 20 mg/L for complicated infections such as osteomyelitis, endocarditis, meningitis, bacteremia, and hospital-acquired pneumonia caused by *S. aureus* to improve penetration, increase probability of obtaining optimal target serum concentrations, decrease the incidence of nephrotoxicity, and improve clinical outcomes [8, 9]. Trough serum vancomycin concentrations of 15-20 mg/L correlate to an AUC:MIC ≥ 400 in most patients if the MIC is ≤ 1 mg/L [6, 8, 9].

HVMC (Holston Valley Medical Center) is a 505-bed, acute-care, teaching hospital located in Kingsport, Tennessee. The HVMC inpatient pharmacy has an ASHP-accredited postgraduate year one (PGY1) pharmacy residency program and provides extensive clinical and dosing services, including a vancomycin dosing service for all adult inpatients. The average number of patients requiring vancomycin dosing and monitoring at HVMC is approximately 35 to 40 per day. Traditionally, dosing of vancomycin entailed giving a 25 mg/kg loading dose followed by a maintenance dose of 15-20 mg/kg at a frequency of 1.5-2 times the estimated vancomycin half-life, based on the patient's CrCl (creatinine clearance) estimated using the Cockcroft-Gault equation. A maximum dose of 3 g was set for any vancomycin dose. Multiple pharmacists completed dosing, which allowed for great variability in dosing and often resulted in sub-optimal dosing.

A nomogram targeting a vancomycin serum trough concentration of 15-20 mg/L was originally developed by the University of Texas, College of Pharmacy at Austin and Valley Baptist Medical Center in Harlingen, Texas, and a poster evaluating the nomogram was made available on the University of Texas website [10]. The nomogram, with a few revisions, was adopted for use at HVMC in November 2012 and is currently still in use (Table 1). The nomogram provides a dosing

Table 1 Vancomycin dosing nomogram.

	Modified CrCl (ml/min)									
Patient weight (kg)	30	40	50	60	70	80	90	100	110	120
40	500mg q24h	500mg q18h	750mg q18h	500mg q12h	500mg q12h	750mg q12h	750mg q12h	500mg q8h	500mg q8h	500mg q6h
45	500mg q24h	500mg q18h	750mg q18h	500mg q12h	750mg q12h	750mg q12h	500mg q8h	500mg q8h	750mg q8h	750mg q8h
50	500mg q24h	500mg q18h	500mg q12h	500mg q12h	750mg q12h	500mg q8h	500mg q8h	750mg q8h	750mg q8h	750mg q8h
55	750mg q24h	750mg q18h	500mg q12h	750mg q12h	750mg q12h	1g q12h	1g q12h	750mg q8h	750mg q8h	750mg q8h
60	750mg q24h	750mg q18h	1g q18h	750mg q12h	750mg q12h	1g q12h	1g q12h	750mg q8h	750mg q8h	1g q8h
65	750mg q24h	750mg q18h	1g q18h	750mg q12h	1g q12h	1g q12h	750mg q8h	750mg q8h	1g q8h	1g q8h
70	1g q24h	750mg q18h	750mg q12h	750mg q12h	1g q12h	750mg q8h	750mg q8h	750mg q8h	1g q8h	1g q8h
75	1g q24h	1g q18h	750mg q12h	750mg q12h	1g q12h	750mg q8h	750mg q8h	1g q8h	1g q8h	1g q8h
80	1g q24h	1g q18h	750mg q12h	1g q12h	1g q12h	750mg q8h	750mg q8h	1g q8h	1g q8h	1.2g q8h
85	1g q24h	1g q18h	750mg q12h	1g q12h	1.2g q12h	1.2g q12h	1g q8h	1g q8h	1g q8h	1.2g q8h
90	1.2g q24h	1g q18h	750mg q12h	1g q12h	1.2g q12h	1.2g q12h	1g q8h	1g q8h	1.2g q8h	1g q6h
95	1.2g q24h	1g q18h	1g q12h	1g q12h	1.2g q12h	1g q8h	1g q8h	1.2g q8h	1.2g q8h	1g q6h
100	1.2g q24h	1.2g q18h	1g q12h	1g q12h	1.2g q12h	1g q8h	1g q8h	1.2g q8h	1g q6h	1g q6h
105	1g q18h	1.2g q18h	1g q12h	1.2g q12h	1.2g q12h	1g q8h	1g q8h	1.2g q8h	1g q6h	1g q6h
110	1g q18h	1.2g q18h	1g q12h	1.2g q12h	1.2g q12h	1g q8h	1.2g q8h	1g q6h	1g q6h	1.2g q6h
115	1g q18h	1.2g q18h	1g q12h	1.2g q12h	1g q8h	1g q8h	1.2g q8h	1g q6h	1.5g q8h	1.2g q6h
120+	1g q18h	1.2g q18h	1g q12h	1.2g q12h	1g q8h	1g q8h	1.2g q8h	1g q6h	1.5g q8h	1.2g q6h

Modified CrCl = (140 – age) {x 0.85 for females}/Serum creatinine*
***For Serum Creatinine < 0.8, round to 0.8 (age less than 65) or round to 1 (age 65 or older)**

Fig. 1 Modified Creatinine Clearance Equation.

regimen of a 20 mg/kg loading dose followed by a 10-15 mg/kg maintenance dose at a frequency of 1-1.5 times the estimated half-life, based on the patient's renal function calculated as a modified CrCl (Fig. 1). A maximum of 2.5 g is used for any vancomycin dose. The nomogram caps patient weight at 120 kg and uses the modified CrCl (maximum 120 mL/min) to ensure patients who are obese, elderly, or have low muscle mass and are not dosed too frequently.

The objective of this study was to assess the ability of a vancomycin dosing nomogram to effectively predict vancomycin serum trough concentrations within the desired 15-20 mg/L therapeutic range.

2. Methods

2.1 Patient Selection

We conducted a single-center, IRB-approved, retrospective chart review on a randomized sample from approximately 2,000 vancomycin serum trough concentrations for patients at HVMC receiving intravenous vancomycin dosing regimens according to the vancomycin nomogram. The enrollment period extended from July 12, 2013 through February 28, 2014, and evaluable trough concentrations were identified by alerts set up through TheraDoc™, a clinical surveillance system. To obtain the randomized sample, we evaluated every fourth trough concentration identified for inclusion or exclusion into the study.

2.2 Study Population

For inclusion into the study, each trough concentration had to correspond with a unique patient (not already included) 18 years of age or older who received at least 3 appropriately administered doses of intravenous vancomycin prior to collection of a trough concentration. We considered trough concentrations drawn within one hour of the scheduled fourth or later dose and vancomycin doses administered within 1.5 hours of the scheduled time appropriate for inclusion. Trough concentrations corresponding with patients who were less than 18 years of age, who had an estimated creatinine clearance < 30 mL/min, who were receiving dialysis, or who were pregnant were excluded from the study.

2.3 Data Collection

We collected data for each patient which included age, gender, weight, height, diagnoses, vancomycin regimen, vancomycin serum trough concentration, serum creatinine, and modified creatinine clearance.

2.4 Endpoints

The primary endpoint of the study was to assess the achievement of the nomogram to provide trough concentrations within the target range of 15-20 mg/L at least 33.3% of the time. The secondary endpoint was to assess the achievement of the nomogram to provide trough concentrations within a broader range of 10-25 mg/L at least 75% of the time. We determined the broader range of 10-25 mg/L to be significant as it neither corresponds with the development of resistance nor vancomycin toxicity. We chose the desired percentages for each trough concentration range based on dosing history at HVMC and the initial study at Valley Baptist Medical Center.

3. Results

During the enrollment period, we identified and randomized 1,576 vancomycin serum trough concentrations, resulting in 394 trough concentrations evaluated for inclusion. We excluded 292 concentrations, leaving 102 troughs, correlating with 102 patients, included in the study (Fig. 2). The majority of patients were excluded due to administration times or trough collection times that fell outside of our window for inclusion.

Fig. 2 Randomization.

Table 2 Patient characteristics.

Gender	Number
Male	46 (45)
Female	56 (55)
Average age (yrs)	60.7 (20-98)
Average SCr (mg/dL)	0.86 (0.4-1.81)
Average modified CrCl (mL/min)	75.7 (31-139)
Average weight (kg)	79.3 (36.1-151.5)
Diagnosis (%)	
Pneumonia	32
Skin & soft tissue infection	30
Bacteremia/sepsis	18
Urinary tract infection	7
Osteomyelitis	5
Other	8

Male patients made up 45% of the study population, and the average age for all study participants was 61 years. The average modified CrCl was 76 mL/min, and the average weight of patients was 79 kg (Table 2). The majority of patients were receiving intravenous vancomycin for pneumonia or skin and soft tissue infections, 32% and 30%, respectively.

Trough concentrations ranged from 3.5 to 40.8 mg/L. Of the 102 included patients, 36 (35.2%) had a trough concentration with the target range of 15-20 mg/L, which met the primary endpoint. A total of 75 patients (73.5%) had a trough concentration within the broader range of 10-25 mg/L, which was just short of reaching the secondary endpoint.

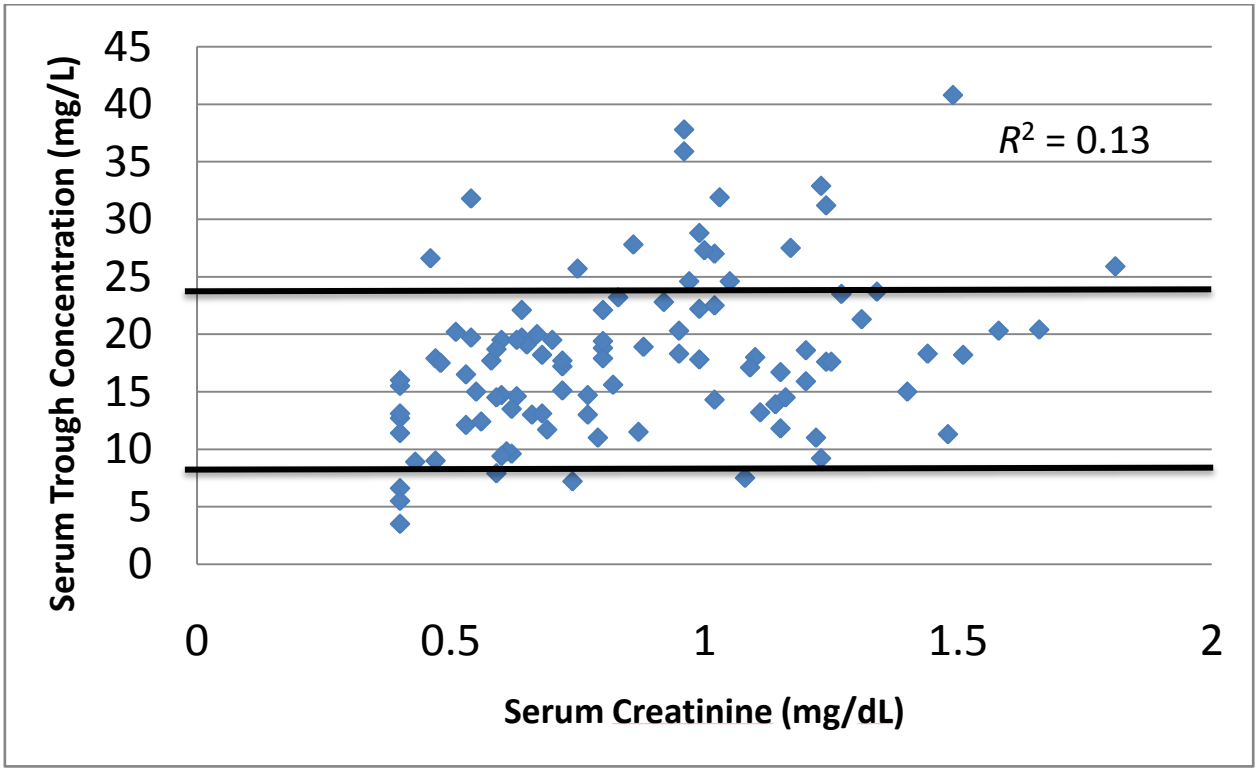
All the trough concentrations were plotted against various patient demographics to determine if any correlation existed betw2een the concentrations and those criteria (Figs. 3a-3d). No correlation was found between the trough concentration and serum creatinine, modified CrCl, age, or weight.

4. Discussion

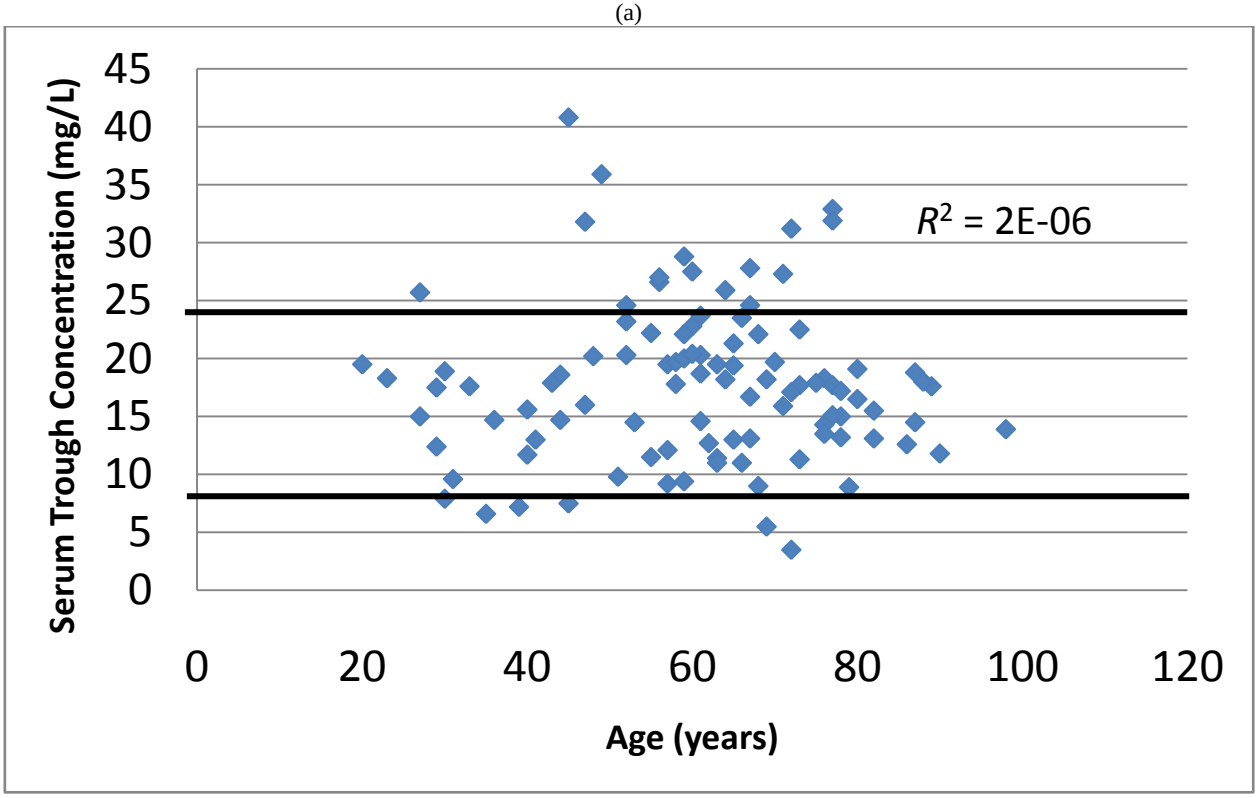
Pharmacists at HVMC are responsible for dosing all adult inpatient vancomycin orders. Initially, one "kinetics pharmacist" dosed all orders, with several pharmacists rotating through this assigned role throughout the month. In 2011, HVMC established a pharmacy residency program and focused on expanding clinical services, which allowed pharmacists to become more decentralized. Therefore, several pharmacists with varying education and experience became responsible for pharmacokinetic dosing services each day, often resulting in inconsistent dosing. Vancomycin doses (both loading and maintenance doses) were rounded to the nearest 100 mg, resulting in more work for our IV sterile compounding room and more drug waste when these unique doses were changed or discontinued. In addition, patients whose weight dictated loading doses over 2.5 g or maintenance doses over 2 g were mostly likely to be the patients to develop vancomycin toxicity with trough levels > 30 mg/L.

Previously published vancomycin dosing strategies, including various equations and nomograms, have mostly targeted and/or resulted in lower vancomycin trough level ranges, more specifically levels in the ranges of 5-10 mg/L or 10-15 mg/L [1, 11, 12]. A few recently published nomograms have targeted vancomycin trough concentrations between 15 and 20 mg/L with varying success [10, 13, 14].

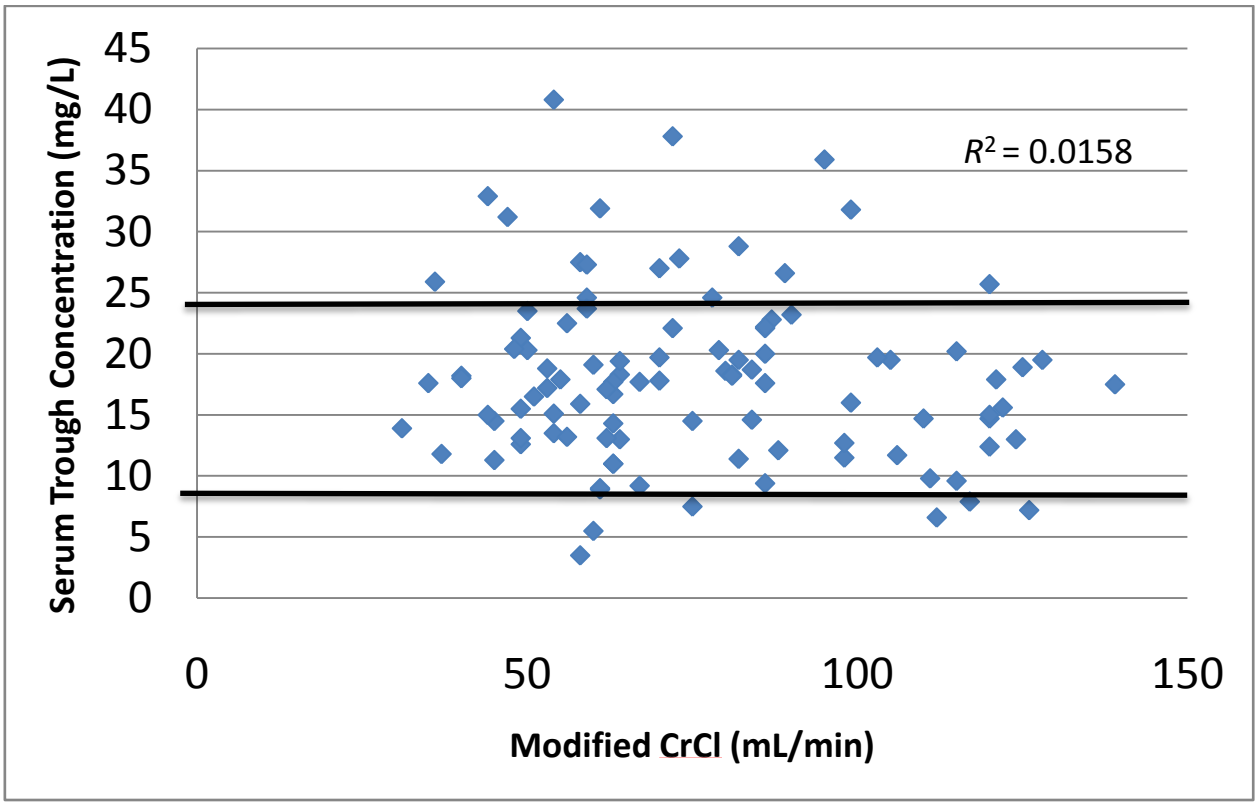
HVMC chose to implement a vancomycin dosing nomogram to optimize dosing, reduce variability in dosing between pharmacists, and minimize toxicity of vancomycin. Additional reasons for implementing a


Serum Trough Concentration (mg/L)
45
40
35
30
25
20
15
10
5
0
R^2 = 0.13
0
0.5
1
1.5
2
Serum Creatinine (mg/dL)

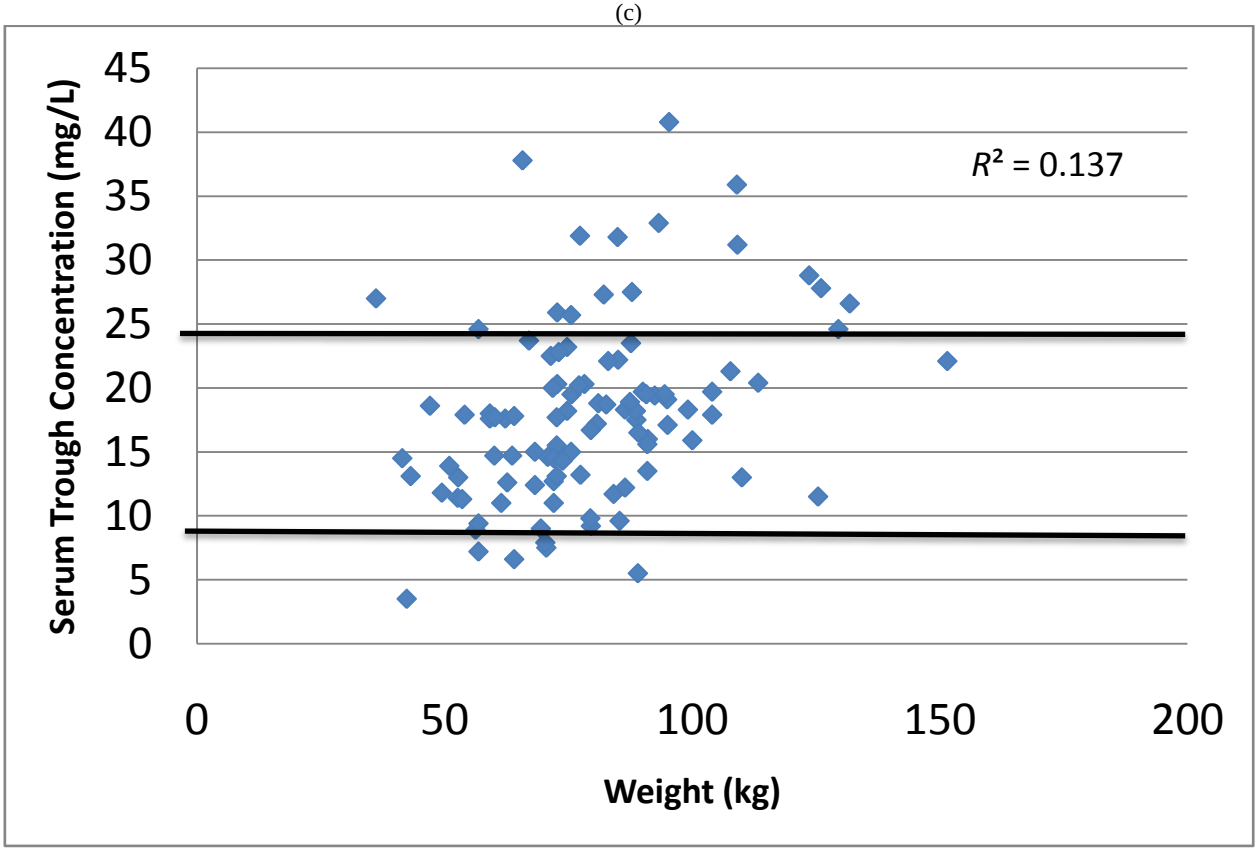
(a)


Serum Trough Concentration (mg/L)
45
40
35
30
25
20
15
10
5
0
R^2 = 2E-06
0
20
40
60
80
100
120
Age (years)

(b)



(c)



(d)

Fig. 3 Trough concentration vs. (a) serum creatinine; (b) age; (c) modified creatinine clearance and (d) weight.

nomogram included a desire to standardize vancomycin doses in an effort to streamline the IV compounding process and reduce drug waste. Furthermore, the vancomycin nomogram uses daily vancomycin doses that are the same or often less than the daily doses required previously to get the same level, providing an additional cost-savings. The vancomycin nomogram from Valley Baptist Medical Center was adopted, revised and employed at HVMC in November 2012. Evaluation of the nomogram began in July 2013 allowing an eight-month period for pharmacists to adjust to the new dosing method.

Our study showed that more than one-third of the adult patients at HVMC dosed with the new nomogram achieved therapeutic levels; three-fourths of the same patients achieved levels considered both safe and efficacious. More importantly, therapeutic levels were achieved on day 2 or 3 of therapy, ensuring patients were receiving optimal dosing early in their course of therapy and reducing the number of adjustments and repeat levels required.

The vancomycin dosing nomogram met the primary endpoint and nearly met the secondary endpoint of our study, providing trough concentrations within the desired therapeutic range of 15-20 mg/L, as set forth by both IDSA and ASHP [8, 9]. HVMC now has less variability in vancomycin dosing and trough concentrations achieved. In addition, the ease of use of the nomogram affords HVMC with a high degree of pharmacist satisfaction when dosing vancomycin.

In addition to our primary and secondary endpoints, we were interested to determine if the nomogram included any outlying areas that strayed from optimal dosing or provided opportunity for adjustment. When evaluating the trough concentrations versus multiple patient demographics, there was surprisingly no correlation between any comparisons; therefore, it demonstrated that the nomogram appropriately doses patients of varying weights, ages, and renal functions and is not specific to any particular patient population.

Several limitations to our study are evident. The principal limitation to the study is the lack of a comparator group. Due to limitations of the TheraDoc™ software, it was not feasible to collect data on vancomycin dosing outcomes prior to implementation of the nomogram. The original study by Valley Baptist Medical Center, however, showed no difference in trough concentrations between the nomogram and vancomycin dosing using first-order pharmacokinetics [10].

Another limitation to our study includes the relatively small sample size, especially when compared to the number of troughs evaluated for inclusion. The small number of included patients was primarily due to vancomycin administration times outside of the 1.5-hour window allowed or trough concentrations collected outside of the one-hour allowable window. Other reasons for exclusion included missed vancomycin doses, cessation of vancomycin therapy prior to collection of trough concentrations, alterations in vancomycin dosing prior to collection of trough concentrations secondary to changes in renal function, and dosing not based on the nomogram. Dosing not based on the nomogram was due to known dosing history of patients, misinterpretation of the nomogram, and hesitancy of a few pharmacists to fully adopt the nomogram, especially in the first year after implementation. Lastly, time constraints prohibited evaluation of a larger population for inclusion.

A third limitation to this study is the reliance on nursing documentation and charting of vancomycin administration times. It was not feasible to ensure the doses were given exactly as documented.

Some potential for bias is possible, as the goals of the study were set after implementation of the nomogram at HVMC. Therefore, preformed expectations of the nomogram influenced the selection of endpoints. This knowledge, however, allowed us to set more realistic goals for the study.

HVMC will continue to use the nomogram for all adult inpatients that require intravenous vancomycin dosing. We have and will also continue to evaluate

individual trough concentrations that fall outside the 10-25 mg/L range to determine the reasons for such levels. If a trend is detected, adjustments to the nomogram can be made. In our opinion, other hospitals, especially those who need to optimize vancomycin dosing or those who have resident pharmacists, may benefit from validating the use of this nomogram in their patient populations as well.

5. Conclusion

Dosing intravenous vancomycin can be a daunting task, especially for a pharmacist with little or no pharmacokinetic experience. Many factors may contribute to variability in vancomycin pharmacokinetics in individual patient, with age, weight, and renal function being the main factors. When adding in consideration for the needed pharmacodynamic optimization of vancomycin to treat MRSA or serious, deep-seated infections, dosing can become even more challenging. Pharmacists who are responsible for dosing vancomycin may have differing methods based on their education and professional experience. Dose optimization, dosing consistency, and pharmacist efficiency are key components to a successful pharmacokinetic dosing service. The vancomycin nomogram is an effective tool that provides consistent dosing and predictable serum trough concentrations and has allowed HVMC to provide a more successful pharmacokinetic service.

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