Methodological Study of Vancomycin Dosing in Elderly Patients Using Actual Serum Creatinine Versus Rounded Serum Creatinine

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Abstract

Purpose The practice of intentional rounding up of serum creatinine (SCr) in elderly patients with low measured values can lead to an underestimation of creatinine clearance and subsequent inaccurate dosing of medications. Thus, the purpose of this study was to evaluate the accuracy of vancomycin dose calculations for patients aged ≥ 65 years using an SCr rounded up to 1 mg/dL versus actual SCr.

Methods This study compared the difference between measured steady-state vancomycin trough concentrations with predicted trough concentrations that have been calculated using rounded SCr and actual SCr. All non-obese patients ≥ 65 years of age with a baseline SCr < 1 mg/dL who received a vancomycin regimen based on a SCr rounded to 1 mg/dL, and had a steady-state trough drawn between June 2014 and December 2015, were evaluated. A total of 1709 patients were evaluated, of whom 56 met all the selection criteria.

Results The mean difference between measured vancomycin trough concentrations and predicted trough concentrations using rounded SCr was 8.84 versus 4.54 $\mu\text{g/mL}$ using actual SCr [mean difference 4.31, 95% confidence interval (CI) 3.2–5.41; $p < 0.0001$]. In female patients, the mean difference between measured concentrations and predicted concentrations using rounded SCr was 9.68 versus 3.53 $\mu\text{g/mL}$ using actual SCr (mean difference 6.15, 95% CI 4.42–7.88; $p < 0.0001$), while in male patients the mean difference between measured concentrations and

predicted concentrations using rounded SCr was 8.21 versus 5.29 $\mu\text{g/mL}$ using actual SCr (mean difference 2.92, 95% CI 1.6–4.24; $p < 0.0001$).

Conclusion Using actual SCr to perform vancomycin dosing calculations more accurately predicted measured vancomycin troughs than using an SCr rounded to 1 mg/dL. In our sex-specific analysis, using actual SCr resulted in more accurate trough projections for both males and females than using a rounded SCr.

Key Points

This study compared the measured vancomycin trough concentrations with predicted vancomycin trough concentrations using serum creatinine (SCr) rounded to 1 mg/dL versus actual SCr.

Using rounded SCr may underestimate renal vancomycin clearance, which may lead to underdosing of vancomycin in non-obese patients aged ≥ 65 years.

The use of rounded SCr resulted in subtherapeutic vancomycin troughs in 92.9% of patients.

1 Introduction

Vancomycin is a tricyclic glycopeptide antibiotic that exhibits bactericidal activity via inhibition of cell-wall biosynthesis. It is used to treat infections caused by susceptible gram-positive bacteria such as enterococci and methicillin-resistant *Staphylococcus aureus* [1]. Vancomycin concentrations require close monitoring due to

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risks for adverse events and the impact of age and renal function [1–4]. Studies have shown that there is an age-related decrease in renal function [5, 6] which can be measured using creatinine clearance (CrCl). Lindeman et al. [7] concluded that the mean decrease in CrCl was 0.75 mL/min/year.

A 24-h urine collection is the gold standard for measuring CrCl; however, the Cockcroft–Gault equation is normally used due to difficulty meeting urine collection requirements of specific temperature conditions, patient participation, and the time required [8, 9]. The estimation of CrCl via the Cockcroft–Gault equation includes sex, age, weight, and serum creatinine (SCr) [10]. A decrease in SCr in elderly patients can be attributed to both reduced protein intake and muscle mass [9, 11, 12]. For elderly patients with an SCr <1 mg/dL, correction of decreased SCr can lead to the practice of rounding SCr up to 1 mg/dL to prevent overestimation of CrCl [13–17].

Smythe et al. [17] analyzed the accuracy of CrCl and daily aminoglycoside dosing based on both a rounded SCr value of 1 mg/dL and actual SCr. By using the 24-h urine collection method, the difference between CrCl for rounded SCr was 28.8 mL/min (19.1–38.4), compared with actual SCr at 2.3 mL/min (–10.3 to 14.8). The difference between actual aminoglycoside dose required, as determined by concentration measurements and predicted dose using rounded SCr and actual SCr, was -89 ± 67 mg and 14 ± 120 mg, respectively. The authors concluded that rounding SCr to 1 mg/dL significantly underestimated both CrCl and the correct aminoglycoside dosage.

The practice of rounding up SCr in the elderly can lead to underestimation of CrCl and underdosing of medications. The purpose of this study was to evaluate the accuracy of vancomycin dose calculations for patients aged 65 years or older using an SCr rounded up to 1 mg/dL versus actual SCr in patients admitted to a large community hospital.

2 Patients and Methods

2.1 Study Design and Setting

This single-center, retrospective, chart review study was reviewed and approved by the Institutional Review Board of the University of North Carolina (UNC). The study was conducted at UNC REX Healthcare, a large community hospital in Raleigh, NC, USA.

Data collected included patient age, weight, height, sex, amputee status, outside hospital transfer status, vancomycin dose, dosing interval, SCr, time of administration, date and time of trough draw, number of doses administered before trough was obtained, and measured

trough. The equations used to perform vancomycin pharmacokinetic calculations (Table 4 in Appendix) were determined by the UNC REX Healthcare Department of Pharmacy.

The primary outcome of this study was to compare the measured steady-state trough concentration with the predicted troughs using rounded SCr versus actual SCr. A secondary outcome of this study was to compare the measured trough concentration of patients with an SCr ≤ 0.7 mg/dL with the troughs predicted using actual SCr versus actual SCr adjusted for the laboratory-specific correction factor. The correction factor is the result of standardization of creatinine assays with the isotope dilution mass spectrometry traceable method [18]. The standardization was to compensate for the original assay and samples, which validated the Cockcroft–Gault equation, no longer being available. The UNC REX Healthcare correction factor is 1.68, based on our assay and instrument used to determine SCr.

Other secondary outcomes include the primary outcome stratified by sex, assessment of the incidence of nephrotoxicity (>0.5 mg/dL change in SCr over baseline, $\geq 50\%$ increase in SCr over baseline in consecutively obtained daily SCr values, or a CrCl decrease of 50% from baseline on two consecutive days), and percentage of vancomycin troughs that were therapeutic, subtherapeutic, and supratherapeutic. Therapeutic was defined as a vancomycin trough between 15 and 20 $\mu\text{g/mL}$.

2.2 Patient Selection

Patients who received intravenous vancomycin between 20 June 2014 and 15 December 2015 were evaluated for inclusion in this study. Patients were included if they met the following criteria: age ≥ 65 years, an SCr of <1 mg/dL, a total body weight <1.2 times their ideal body weight, an appropriately drawn steady-state vancomycin trough (during their hospital stay, within 1 h of ordered time, and after at least four half-lives have passed since beginning the regimen), and an SCr rounded to 1 mg/dL during vancomycin dose calculation with a trough goal between 15 and 20 $\mu\text{g/mL}$. Patients were excluded if they were an amputee, were transferred from another healthcare facility, or had unstable renal function detected prior to trough being drawn (as indicated by an observed change in SCr of $\geq 25\%$). A total of 1709 patients were evaluated for this study.

2.3 Data Collection

The following data were obtained: age, sex, height, weight, SCr, vancomycin regimen, infusion time, indication, and measured trough concentration.

2.4 Statistical Analysis

Baseline demographics, clinical characteristics, nephrotoxicity, and troughs were tabulated based on descriptive statistics. Paired *t* tests were performed to evaluate the relationship between our primary endpoint and secondary endpoints of actual SCr versus actual SCr plus correction factor, as well as the primary outcome stratified by sex. All statistical computations were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

Overall, 1709 patients were screened for inclusion, of whom 64 met the inclusion criteria. The most common reasons for exclusion were age <65 years (771 patients) and SCr ≥ 1 mg/dL (603 patients). Of the 64 patients who met the inclusion criteria, eight were excluded due to transfer from another healthcare facility (three patients)

Fig. 1 Screening and eligibility process of the study population

and unstable renal function prior to trough being drawn (five patients). A total of 56 patients were included in the analysis (Fig. 1). Patient demographics and clinical characteristics are summarized in Table 1.

A patient example and summary of calculations are reported in Table 4 and Fig. 4 in Appendix. The mean difference between measured vancomycin trough concentrations and predicted trough concentrations using rounded SCr was 8.84 µg/mL, compared with 4.54 µg/mL for actual SCr [mean difference 4.31, 95% confidence interval (CI) 3.2–5.41; $p < 0.0001$] (Table 2; Fig. 2). In comparing actual SCr with actual SCr plus correction factor, the mean differences were 3.2 and 3.8 µg/mL, respectively (mean difference -0.59 , 95% CI -1.99 to 0.8 ; $p = 0.38$). In females, the mean difference between measured concentrations and predicted concentrations using rounded SCr was 9.68 versus 3.53 µg/mL for actual SCr (mean difference 6.15, 95% CI 4.42–7.88; $p < 0.0001$), while the mean difference for males was 8.21 µg/mL for rounded SCr and 5.29 µg/mL for actual SCr (mean difference 2.92, 95% CI 1.6–4.24; $p < 0.0001$) (Table 2; Fig. 3). When comparing root mean squared, the SCr rounded to 1 µg/mL had a variance of 77.68 compared with actual SCr of 5.51. The variance for actual SCr plus correction factor was 4.95.

As shown in Table 3, subtherapeutic troughs occurred in 92.9% (52/56) of patients and nephrotoxicity occurred in 7% (4/56) of patients when the SCr was rounded to 1 mg/dL for vancomycin pharmacokinetic calculations with a trough goal between 15 and 20 µg/mL.

4 Discussion

Rounding SCr up to 1 mg/dL in elderly patients with an SCr <1 mg/dL is a practice used for calculating CrCl. In our trial, there was a statistically significant difference in the accuracy of population-based predictive vancomycin dosing kinetics between using rounded SCr and actual SCr. Comparing the measured vancomycin trough with that predicted using rounding SCr resulted in a mean difference of 8.84 µg/mL, while using the actual SCr resulted in a mean difference of 4.54 µg/mL. The smaller difference indicates a more accurate prediction. There was no statistically significant difference in the evaluation of actual SCr with actual SCr plus correction factor. The root mean squared for the actual SCr was 5.51, compared with 77.68 when the SCr was rounded to 1 µg/mL. The larger variance when using the SCr rounded to 1 µg/mL method shows that it provides a less accurate prediction. The difference between actual SCr (5.51) compared with actual plus correction factor (4.95) was negligible. In both male and female patients, a statistically significant difference was observed between rounded SCr and actual SCr. Based on

Table 1 Patient demographic and clinical characteristics

	Mean (range)
Age (years)	77 (65–93)
Total body weight (kg)	65.8 (43.3–94.5)
Ideal body weight (kg)	65.8 (43.2–86.8)
Observed trough concentration (µg/mL)	8.46 (2.6–19.4)
Serum creatinine (mg/dL)	0.72 (0.28–0.99)
	Frequency (%)
Sex	
Female	24 (42.9)
Male	32 (57.1)
Indication	
Pneumonia	21 (37.5)
Skin and soft tissue	19 (33.9)
Bacteremia	9 (16.1)
Other ^a	6 (10.7)
Urinary tract infection	1 (1.8)

^a Other: perforated colon, neutropenic fever, sacral decubitus ulcer, cervical discitis, pleural fluid infection, fever due to intra-abdominal or endovascular source

our results, using rounded SCr had a larger numerical effect in females compared with males.

Creatinine is mainly produced by metabolism of creatinine in the muscle, in which elderly patients typically have reduced protein intake and low muscle mass [9, 11, 12]. As seen in this study, the average difference between actual SCr and rounding SCr up to 1 mg/dL was 0.28 mg/dL; however, the difference was as large as 0.72 mg/dL. The use of actual SCr is a closer representation of a patient's true renal function compared with SCr rounded up to 1 mg/dL.

Farber and Mollering [19] concluded that older age is one of the risk factors for vancomycin-induced nephrotoxicity. In our patient population, nephrotoxicity was

Fig. 2 Primary outcome. *CI* confidence interval **Fig. 3** Secondary outcome of measured trough concentration of patients with serum creatinine ≤ 0.7 mg/dL. *CI* confidence interval**Table 3** Secondary outcomes: nephrotoxicity and troughs

Parameter (<i>n</i> = 5)	Frequency
Nephrotoxicity	4 (7.1%)
Troughs	
Sub-therapeutic	52 (92.9%)
Therapeutic	4 (7.1%)
Supra-therapeutic	0 (0%)

observed in 7.1% of patients, which is comparable with Cantu et al. [20], in which researchers determined that the frequency of nephrotoxicity due to vancomycin therapy was 5–7%. A subtherapeutic vancomycin trough was

Table 2 Trial outcomes

Outcome	Parameter	Rounded (µg/mL)	Actual (µg/mL)	Correction factor (µg/mL)	Mean difference (95% CI)	<i>p</i> Value	Standard deviation
Primary	–	8.84	4.54	–	4.31 (3.2 to 5.41)	<0.0001	4.14
Secondary	SCr < 0.7 µg/dL	–	3.2	3.8	–0.59 (–1.99 to 0.8)	0.38	3.23
	Female (<i>n</i> = 24)	9.68	3.53	–	6.15 (4.42 to 7.88)	<0.0001	4.09
	Male (<i>n</i> = 32)	8.21	5.29	–	2.92 (1.6 to 4.24)	<0.0001	3.66
Additional analysis							
Root mean squared	–	77.68	5.51	4.95	–	–	–

SCr serum creatinine, *CI* confidence interval

observed in 92.9% of patients, while the remaining 7.1% were therapeutic.

Our study limitations include the following: the small sample size may have made it difficult to find a significant relationship between actual SCr and actual SCr plus correction factor; the retrospective design required case report forms to be cross-matched with the electronic medical record; prospective dosing equations were used retrospectively; CrCl cutoffs were not used; and patients' actual CrCl was used for equations. Per institution-specific protocol, CrCl was calculated based on ideal body weight. The Devine formula [21] was used for the calculation of ideal body weight in patients under 60 inches in height, however the LBW2005 [22] equation may have been more appropriate in this clinical setting.

5 Conclusions

We observed underdosing of vancomycin in elderly patients when SCr rounded to 1 mg/dL was used to perform pharmacokinetic calculations. Based on our results, the measured trough was more accurately predicted by using actual SCr compared with utilizing an SCr rounded to 1 mg/dL in elderly patients with an SCr <1 mg/dL. In elderly patients, it may be necessary to consider using actual SCr to perform pharmacokinetic calculations. We also considered adding a maximum CrCl based on age. Our observations should ideally be confirmed by the conduction of a large randomized controlled trial. A future study may

include vancomycin dose calculations using an SCr rounded to 1 mg/dL compared with that of actual SCr in obese patients aged ≥ 65 years.

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Compliance with Ethical Standards

Ethical approval This study was approved by the Institutional Review Board of the University of North Carolina—Chapel Hill.

Conflict of interest Tramaine Young, Matt Daniel, Stephanie Baumhover, Duke Edison, and Jane Green have no conflicts of interest that may be directly relevant to the content of this article.

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Appendix

See Table 4 and Fig. 4.

Table 4 Equations used to calculate vancomycin trough [23–28]

Variable	Equation
Ideal body weight (IBW)	Female: $45 \text{ kg} + [2.3 (\text{height in inches} - 60 \text{ inches (in)})]$ Male: $50 \text{ kg} + [2.3 (\text{height in inches} - 60 \text{ in})]$
Correction factor	0.168
CrCl	Female: $[(140 - \text{Age}) \times \text{IBW}] / (72 \times \text{SCr}) \times 0.85$ Male: $\{(140 - \text{Age}) \times \text{IBW}\} / (72 \times \text{SCr})$
Ke	$(\text{CrCl} \times 0.00083) + 0.0044$
Half-life ($t_{1/2}$)	$0.693/\text{Ke}$
Volume of distribution (Vd)	0.7 L/total body weight (kg)
Ko	Vancomycin dose/infusion rate
Frequency	$[\ln (C_{\text{max,desired}}/C_{\text{min,desired}})/\text{Ke}] + \text{infusion rate}$
Maintenance dose	$(C_{\text{max,desired}})(\text{Vd})(\text{Ke})(1 - e^{-\text{Ke} (\text{frequency})})(\text{infusion rate}) / (1 - e^{-\text{Ke} (\text{infusion rate})})$
Vancomycin peak (C_{max})	$[\text{Ko} \times 1 - e^{-\text{Ke} (\text{infusion rate})}] / (\text{Ke})(\text{Vd})(1 - e^{-\text{Ke} (\text{frequency})})$
Vancomycin trough (C_{min})	$C_{\text{max}} \times e^{-\text{Ke} (\text{frequency} - \text{infusion rate})}$

Fig. 4 Vancomycin pharmacokinetics patient example

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