Spinal Cord (2011) 49, 1158–1163

www.nature.com/sc

ORIGINAL ARTICLE

Evaluation of methods to estimate glomerular filtration rate versus actual drug clearance in patients with chronic spinal cord injury

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Study design: A retrospective chart review.
Objectives: To evaluate different methods of estimating renal function compared with patient-specific vancomycin and aminoglycoside (AG) clearance (CL_{DRUG}) in patients with spinal cord injury (SCI), and to develop a new equation to more accurately estimate glomerular filtration rate (GFR) in SCI patients in order to optimize dosing for vancomycin and AG.
Setting: Veterans Affairs medical center in California, United States of America, tertiary care facility with the largest inpatient SCI center in the VA system.
Methods: Retrospective data collection from patient records. Pharmacokinetic analysis was performed to obtain actual $CL_{DRUG,}$ which is compared with different methods of estimating GFR.A total of 310 patients were initially assessed; however, only 141 patients met the inclusion criteria, had a diagnosis of chronic SCI, and received vancomycin or AG with at least one drug level at steady state from January to December of 2008.
Results: All four equations evaluated to estimate GFR significantly overestimated CL_{DRUG}: the Modification of Diet in Renal Disease equation by 141%, Cockcroft–Gault equation by 83%, Chronic Kidney Disease Epidemiology Collaboration equation by 82% and 24-h endogenous creatinine clearance by 71% ($P<0.001$). The modified Cockcroft–Gault equation (CL_M) showed improvement, however, still overestimated CL_{DRUG} by 39% ($P<0.001$). Thus, a new equation for SCI (CL_{SCI}) was developed which underestimated CL_{DRUG} by $<5\%$ ($P=0.16$).
Conclusion: Compared with different methods of estimating GFR, $CL_{SCI}=2.3\times x^{0.7}$ (x equals CL_M in $ml\,min^{-1}$) more accurately estimates CL_{DRUG} in chronic SCI patients.
Spinal Cord (2011) **49,** 1158–1163; doi:10.1038/sc.2011.82; published online 26 July 2011

Keywords: Cockcroft–Gault creatinine clearance; aminoglycosides; vancomycin; drug level; spinal cord injury; glomerular filtration rate

Introduction

It is crucial to renally adjust medications that are eliminated primarily by the kidneys in order to avoid toxicity and/or decrease incidence of adverse drug reactions. Cockcroft–Gault creatinine clearance (CL_{CG}) has been exclusively used to estimate glomerular filtration rate (GFR) based on serum creatinine (SCr) to calculate dosing regimens for renally cleared medications including vancomycin and aminoglycosides (AG). However, CL_{CG} may not extrapolate to patients with spinal cord injury (SCI) because the Cockcroft and Gault (CG) study excluded 31 patients with 24-h creatinine excretion $<10\,mg\,kg^{-1}$, and it did not reveal whether the study population included SCI patients and to what extent.[1] Furthermore, CG reported that creatinine excretion in paraplegics was as much as 40% lower than predicted.[1] Likewise, other studies have found that patients with SCI have significantly low SCr, therefore, CL_{CG} is overestimated.[2–4] Such findings may be because of reduced creatinine production caused by diffuse muscle atrophy and persistent immobility. Overestimation of GFR results in dosing renally cleared medications higher than recommended, and this could lead to supratherapeutic vancomycin and AG serum levels leading to adverse drug effects and/or toxicity.[5–7] In the nephrology arena, a more recently developed equation, the Modification of Diet in Renal Disease equation (MDRD), has been widely used to estimate GFR.[8–9] Moreover, a new equation, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), has been proposed to more accurately estimate GFR compared with MDRD.[10] However, data on the application of MDRD in pharmacokinetic dosing of vancomycin and AG are inconsistent, while there is no data to date on CKD-EPI.[11–14]

The objectives of this study are: (1) to evaluate different methods of estimating GFR compared with patient-specific

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Received 29 November 2010; revised 23 June 2011; accepted 26 June 2011; published online 26 July 2011

vancomycin and AG drug clearance (CL_{DRUG}) in SCI patients, (2) to assess whether there is a difference in the estimation of renal function between anatomical degrees of SCI when compared with CL_{DRUG} and (3) to develop a new equation to more accurately estimate GFR in SCI patients in order to optimize dosing for vancomycin and AG.

Materials and methods

This study was a retrospective chart review, and the protocol was reviewed and approved by the institution's institutional review board.

All patients with a diagnosis of chronic SCI (defined as duration of injury >1 year) at a Veterans Affairs medical center, who received tobramycin, gentamicin, amikacin, or vancomycin with at least one drug level at steady state from January 2008 to December 2008, were evaluated for enrollment in this study. Patients were excluded from the study if they had a limb amputation, received dialysis treatment, experienced changing of renal function (defined as $>20\%$ or $\geqslant 0.3\,mg\,dl^{-1}$ change in SCr concentration), had a history of SCI <1 year, had diagnosis of multiple sclerosis, their antibiotic doses had not been administered or charted, their drug levels had not been at steady state (defined as at least 4 half-lives), or if the drug levels had been reported as below the sensitivity of the assay.

Patient demographics, degree of SCI, vancomycin and AG administration records, sampling times, SCr concentrations and 24-h endogenous creatinine clearance (CL_{24H}) were obtained and recorded. Method of bladder emptying was documented, and 24-h urine was collected according to Lippincott's nursing procedures and skills.[15] The dose of vancomycin was infused over ~ 60 min and AG over 30 min. AG peak drug concentration was measured at least 30 min after the infusion was completed, and AG and vancomycin trough generally within 1 h before the end of the dosing interval. Ideal body weight (IBW) was determined by using the method of Devine.[16] Patient-specific vancomycin volume of distribution (Vd) was calculated using the Rushing and Ambrose method.[17] Empiric vancomycin clearance and AG clearance are equal to the estimated creatinine clearance (CL_{CR}), according to the method described by CG.[1] Estimation of pharmacokinetic parameters of vancomycin and AG was made using a one-compartment open model. Patient-specific Vd and CL_{DRUG} were determined from the measured serum levels using the method of Sawchuk *et al*.[18]

The formulas can be described as follows:

Adjusted body weight = IBW + 0.4 (actual weight–IBW)

Rushing and Ambrose method: Vd (L) = 0.17 (age) + 0.22 (actual body weight in kg) + 15

4-Variable MDRD = $175 \times \text{standardized SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female)

CKD-EPI = $141 \times \min(\text{SCr}/k, 1)^{\alpha} \times \max(\text{SCr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.159$ (if black), where k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

CL_{24H} (ml min^{-1}) = [urine creatinine $\times$ urine volume (ml)]/[SCr $\times$ time (h) $\times$ 60]

CL_{CG} (ml min^{-1}) = [(140–age) $\times$ IBW in kg]/(72 $\times$ SCr); (multiply 0.85 for females)

Modified CG formula (CL_M) (ml min^{-1}) = [(140–age) $\times$ IBW in kg]/(72 $\times$ SCr); (multiply 0.85 for females); (SCr rounded to 1 mg dl^{-1} for patients with SCr <1 mg dl^{-1} while using the actual SCr for patients with SCr $\geqslant 1$ mg dl^{-1}).

CL_{DRUG} is compared with each of the different methods of estimating GFR:

1. MDRD.
2. CKD-EPI.
3. CL_{24H} using standard collection techniques.
4. CL_{CG}.
5. CL_M.
6. A new equation for SCI (CL_{SCI}).

Using Microsoft Excel 2007, a best-fit line between CL_{DRUG} and the method closest to estimating GFR was obtained to determine CL_{SCI} that would better predict CL_{DRUG}. Analyses between CL_{DRUG} and each of the different methods to estimate GFR were conducted using independent two-tailed *t*-tests, with an alpha level of 0.01 and 95% power. The calculated CL_{CR} determined by CL_{SCI} was correlated with the values obtained by pharmacokinetic analysis of actual drug levels using standard linear regression analysis (Pearson product-moment correlations, *r*).

Results

The patient characteristics are presented in Table 1. There were no patients on gentamicin or tobramycin who met the inclusion criteria, as amikacin is the primary AG at the study institution. The study population almost entirely used an aid of bladder retention catheter for 24-h urine collection: 75% had indwelling catheters, 20% external condom catheters, 2% ileal conduit and 3% reflex voiding.

Table 2 presents evaluation of different methods to estimate GFR compared with CL_{DRUG}. The data demonstrates that all methods overestimate CL_{DRUG} (<0.001). The mean difference between CL_{DRUG} and MDRD is largest where overestimation by MDRD is $\sim 140\%$. Figure 1 depicts the difference between MDRD and CL_{DRUG}. A total of 32% (45 of 141 patients) had estimated clearance from MDRD within ± 30 ml min^{-1} of CL_{DRUG}. On the other hand, 67%

Table 1 Baseline characteristics

	Mean ± s.d.
Number of patients	141
Male/female, *n*	140/1
Tetraplegic/paraplegic, *n*	89/52
Vancomycin/amikacin, *n*	109/32
SCr >1 mg dl^{-1}, *n*	30
Age (years)	65.72 ± 10.54
Height (cm)	179.96 ± 7.01
Weight (kg)	80.35 ± 20.69
BMI (kg m^{-2})	24.6 ± 5.78
SCr (mg dl^{-1})	0.74 ± 0.29

Abbreviations: BMI, body mass index; SCr, serum creatinine.

Table 2 Evaluation of different methods to estimate GFR

n = *141*	*Mean ± s.d.* ($ml\,min^{-1}$)	*Difference from* CL_{DRUG} ($ml\,min^{-1}$)	P-*value*
CL_{DRUG}	49.77 ± 19.97	0	—
MDRD	119.76 ± 61.49	69.99	<0.001
CKD-EPI	90.71 ± 27.44	40.94	<0.001
CL_{24H}	85.16 ± 33.88	35.39	<0.001
CL_{CG}	91.24 ± 36.90	41.47	<0.001
CL_M	69.38 ± 13.49	19.61	<0.001

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CL_{CG}, the Cockcroft-Gault formula; CL_{DRUG}, actual drug clearance; CL_M, modified Cockcroft–Gault formula; CL_{24H}, 24-h endogenous creatinine clearance; GFR, glomerular filtration rate; MDRD, the Modification of Diet in Renal Disease equation; s.d., standard deviation.

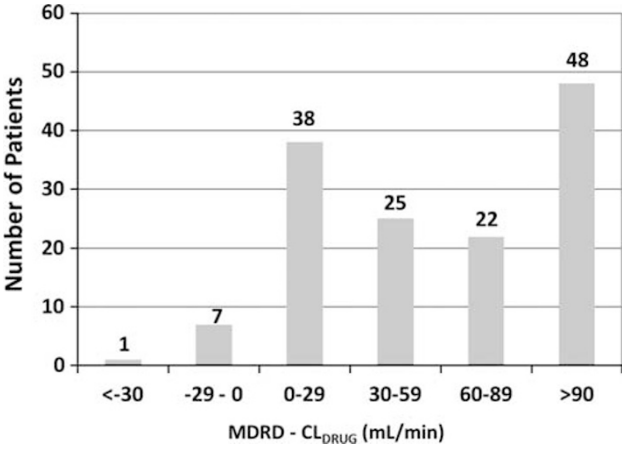

Figure 1 Difference between the Modification of Diet in Renal Disease equation (MDRD) and actual drug clearance (CL_{DRUG}).

(95 of 141) of the patients had overestimation of clearance by $\geqslant 30\,ml\,min^{-1}$ when using MDRD to predict empiric dosing for vancomycin and AG ($P<0.001$). Levey *et al.*[10] demonstrated that CKD-EPI was less biased and more accurate than MDRD. Likewise, our findings showed that estimated GFR by CKD-EPI was closer to CL_{DRUG} than MDRD (Table 2). Despite this, CKD-EPI significantly overestimated CL_{DRUG} by more than 80%. Compared with MDRD, CL_{CG}, CKD-EPI and CL_{24H}, CL_M showed better prediction of CL_{DRUG}. A total of 66% (93 of 141 patients) had estimated clearance from CL_M within ± $30\,ml\,min^{-1}$ of CL_{DRUG} ($P<0.001$) (Figure 2). In all, 1% (2 of 141) of the patients had underestimation of clearance whereas 33% (46 of 141) of the patients had overestimation of clearance by $\geqslant 30\,ml\,min^{-1}$, when using CL_M to predict empiric dosing for vancomycin and AG ($P<0.001$) (Figure 2). In spite of substantial improvement by modification of the existing CG formula, CL_M significantly overestimated CL_{DRUG} by ~40%.

Table 3 presents evaluation of CL_M to estimate CL_{DRUG} for vancomycin and AG separately. The mean difference between CL_M and CL_{DRUG} for combined amikacin and vancomycin groups is $19.61\,ml\,min^{-1}$ ($P<0.001$) where CL_M overestimated CL_{DRUG} by $\sim 20\,ml\,min^{-1}$. However, when the groups are separated, the mean difference between

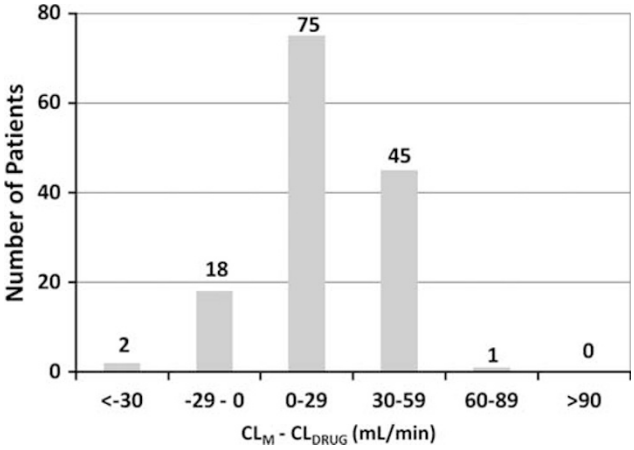

Figure 2 Difference between the modified Cockcroft–Gault formula and actual drug clearance.

Table 3 Evaluation of CL_M to estimate CL_{DRUG} for vancomycin and AG

	Mean ± s.d. ($ml\,min^{-1}$)	*Difference from* CL_{DRUG} ($ml\,min^{-1}$)	P-*value*
Combined amikacin and vancomycin (n = 141)			
CLDRUG	49.77 ± 19.97	0	—
CL_M	69.38 ± 13.49	19.61	<0.001
Amikacin (n = 32)			
CL_{DRUG}	57.27 ± 28.22	0	—
CL_M	69.37 ± 14.08	12.1	0.033
Vancomycin (n = 109)			
CL_{DRUG}	47.57 ± 16.34	0	—
CL_M	69.38 ± 13.38	21.81	<0.001

Abbreviations: AG, aminoglycosides; CL_{DRUG}, actual drug clearance; CL_M, modified Cockcroft–Gault formula; s.d., standard deviation.

CL_M and CL_{DRUG} for amikacin group is $12.1\,ml\,min^{-1}$ ($P=0.033$), while the difference for vancomycin is $21.81\,ml\,min^{-1}$ ($P<0.001$). As the mean difference between the predicted and actual clearance for amikacin group was statistically insignificant and included 32 of 141 patients, only the vancomycin group was used to develop a new SCI equation for estimating GFR.

Figure 3 depicts plots of patient-specific CL_{DRUG} based on pharmacokinetic level analysis versus CL_M for the vancomycin group. In order to improve CL_M's ability to predict CL_{DRUG}, the best-fit line is drawn between the two and expressed by the equation $y = 2.3 \times x^{0.7}$ where x equals CL_M and y equals CL_{DRUG} in $ml\,min^{-1}$. This newly developed SCI equation (CL_{SCI}) may better predict CL_{DRUG} based on CL_M. Figure 4 presents linear regression plots of CL_{DRUG} versus CL_{SCI}. The regression equation found is $y = 0.8425x + 6.7281$ ($r = 0.4$, P-value <0.001), where x equals CL_{SCI}, y the CL_{DRUG} and r the correlation coefficient. The dotted line in Figure 4 represents a line with a slope of 1 that indicates a perfectly one-to-one association between CL_{SCI} and CL_{DRUG}. The point where the dotted line and regression line meet is $43\,ml\,min^{-1}$. $CL_{SCI} < 43\,ml\,min^{-1}$ may overestimate CL_{DRUG} whereas $CL_{SCI} > 43\,ml\,min^{-1}$ may underestimate CL_{DRUG}.

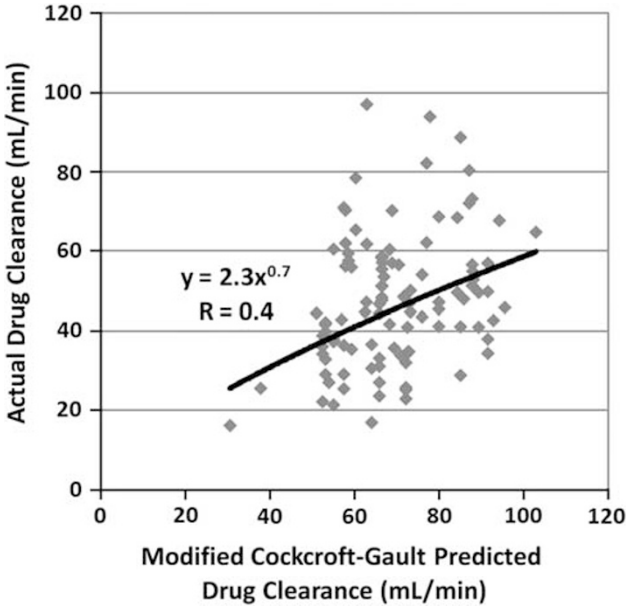

Figure 3 Plots of actual drug clearance versus modified Cockcroft–Gault predicted drug clearance.

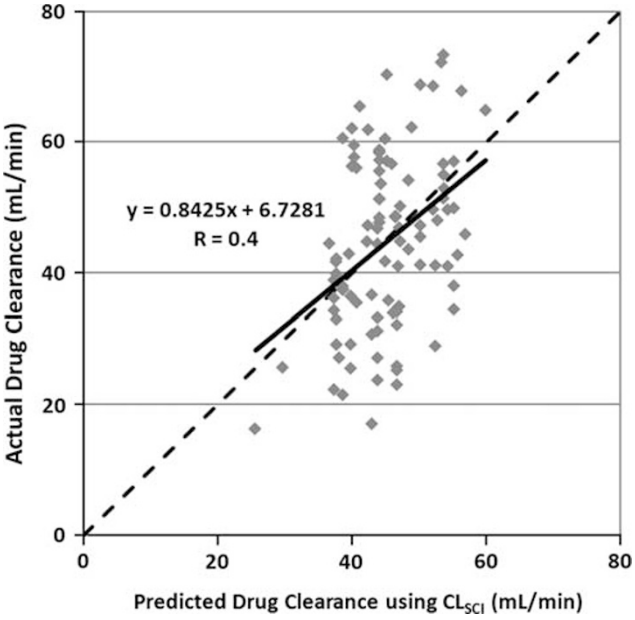

Figure 4 Linear regression plots of actual drug clearance versus predicted drug clearance using adjusted equation.

The mean difference between CL_{SCI} and CL_{DRUG} for the vancomycin group is $-2.35\,ml\,min^{-1}$ where CL_{SCI} underestimates CL_{DRUG} by $\sim 5\%$, however, there is no statistical significance (P-value = 0.16).

Table 4 illustrates evaluation of methods to predict CL_{DRUG} for different anatomical degrees of SCI. The mean difference between CL_{SCI} and CL_{DRUG} was not statistically significant when separated into paraplegics and tetraplegics. Similar finding was noted for CL_M and CL_{24H}. On the contrary, the mean differences between CL_{CG}, CKD-EPI, and MDRD and CL_{DRUG} were statistically significant between the two anatomical degrees of SCI where tetraplegics had a gross overestimation of CL_{DRUG} compared with paraplegics.

Table 4 Evaluation of methods to predict CL_{DRUG} for different anatomical degrees of SCI

	Mean difference from CL_{DRUG} ± s.d. ($ml\,min^{-1}$)		P-*value*
	Paraplegics (n = *52*)	*Tetraplegics* (n = *89*)	
CL_{SCI}	−3.11 ± 13.14	−5.39 ± 21.16	0.48
CL_M	21.04 ± 13.81	18.76 ± 22.26	0.5
CL_{24H}	32.60 ± 30.78	37.02 ± 35.29	0.45
CL_{CG}	27.26 ± 20.56	49.76 ± 38.55	<0.001
CKD-EPI	27.52 ± 25.50	48.77 ± 24.76	<0.001
MDRD	40.68 ± 40.71	50.64 ± 64.56	<0.001

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CL_{DRUG}, actual drug clearance; CL_{CG}, the Cockcroft–Gault formula; CL_M, modified Cockcroft-Gault formula; CL_{SCI}, spinal cord injury equation; CL_{24H}, 24-h endogenous creatinine clearance; MDRD, the Modification of Diet in Renal Disease equation; SCI, spinal cord injury; s.d., standard deviation.

Discussion

SCr is used to estimate the dose of potentially toxic drugs eliminated primarily by the kidneys. SCI patients have significantly lower SCr compared with non-SCI patients due to immobility and muscle atrophy. In this study, MDRD was found to significantly overestimate CL_{DRUG} by more than two times higher than the actual on average. This could result in supratherapeutic vancomycin and AG peak, and trough levels where potential for nephrotoxicity and/or ototoxicity could drastically increase. This could be devastating to many SCI patients who have existing renal insufficiency.

MDRD was derived from a study of relatively young population (mean age 51 ± 13 years) with chronic kidney disease, primarily to stage kidney disease. The data on its use specifically for drug dosing are scarce and inconsistent. A study by Bookstaver *et al.*[14] reported that MDRD performed better than CL_{CG} in estimating AG clearance. On the other hand, a more recent study done by Ryzner[11] found that CL_{CG} correlated better with actual AG clearance compared with MDRD. The results from our investigation are consistent with that of the Ryzner where the mean difference between CL_{CG} and CL_{DRUG} was smaller than the difference between MDRD and CL_{DRUG} ($P<0.001$).

In 2009, Levey *et al.*[10] stated that clinicians should be aware of limitations of all creatinine-based equations in patients with extremely low muscle mass. The serum concentration of creatinine is greatly influenced by muscle mass, and all equations evaluated in this study include SCr to a various degree. Although some equations attempt to capture the difference in creatinine production by age, weight, gender and/or race, they do not capture all factors, especially SCI. Consequently, using such equations in SCI

patients with significantly reduced muscle mass and SCr would result in considerable overestimation of GFR.

Despite overestimation, CL_M was closest to CL_{DRUG}. Compared with 50% (70 out of 141) of patients with estimated GFR from MDRD, only 1 out of 141 patients with estimated GFR from CL_M was found to have CL_{DRUG} overestimated by $\geqslant 60\,ml\,min^{-1}$. Hence, an adjustment was made to the CL_M equation to further improve dosing for vancomycin in SCI patients.

The line of best fit between CL_M and CL_{DRUG} was drawn in this study.

The newly developed SCI equation for estimating CL_{DRUG} is expressed as the following:

$CL_{SCI}\ (ml\,min^{-1}) = 2.3 \times x^{0.7}$, where x equals CL_M.

This may better estimate actual vancomycin clearance; thus, optimize dosing for vancomycin in SCI patients. According to the regression equation $y = 0.8425x + 6.7281$ ($r = 0.4$, P-value < 0.001), there is close to one-to-one association between CL_{SCI} and CL_{DRUG} with moderate correlation. CL_{SCI} may slightly underestimate CL_{DRUG}, however, there is no statistically significant difference between the two.

Compared with paraplegics, tetraplegics had a gross overestimation of CL_{DRUG} when using CL_{CG}, CKD-EPI and MDRD to estimate CL_{DRUG} ($P < 0.001$). This may be due to higher extent of muscle atrophy and immobility in tetraplegics resulting in lower SCr. As all three equations have SCr in the denominator, estimated GFR would be higher in tetraplegics. On the other hand, there was no statistically significant difference between the two groups when using CL_M and CL_{24H} to estimate CL_{DRUG}. As both equations either round SCr up to $1\,mg\,dl^{-1}$ for patients with SCr $< 1\,mg\,dl^{-1}$ or use a ratio of urine creatinine to SCr, lower SCr in tetraplegics may have been blunted.

This study has several limitations. The AG group had only 32 amikacin patients. Hence, there is not enough power to determine statistical significance to analyze amikacin group separately from that of the vancomycin, and the data may not be generalized to gentamicin and tobramycin. The study was conducted in a veterans population, with nearly all male (99%) of advanced age (mean 66 years), thus, the data might not extrapolate to other populations with SCI. Although CG mentions the use of the aid of bladder retention catheter in paraplegics, the study does not mention whether the catheter was the sole method of bladder emptying. If there is a significant difference in the bladder emptying methods between this study, which had $<3\%$ of patients who had spontaneous voiding, and that of the CG, assessment of CL_{24H} could be inaccurate. Other limitations include the variability inherent in using clinical data, assumption that both AG clearance and vancomycin clearance equal CL_{CR}, and the assumption that the equations used to calculate Vd are accurate in our study population. It is recommended that laboratories report GFR as $>60\,ml\,min^{-1}$ instead of the actual value.[19] In this study, we reported the actual values obtained by MDRD and CKD-EPI to evaluate the study outcome. In addition, the abbreviated form of MDRD was used in this study. Finally, our study did not adjust the equations including CL_{CG} for body surface area. This is consistent with the recommendation by the National Kidney Disease Education Program that does not recommend routine adjustment for body surface area.[20]

Despite these limitations, this study suggests that compared with different methods of estimating GFR, $CL_{SCI} = y = 2.3 \times x^{0.7}$ more accurately estimates GFR to dose vancomycin, thus, achieving serum levels closer to goal in chronic SCI patients.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank Patricia Chun, Pharm D for her continuous support of research and Rebecca Chumbley, Pharm D for her expert opinion on SCI.

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