A More Accurate Method to Estimate Aminoglycoside Clearance From Serum Creatinine in Patients With Spinal Cord Injury

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Abstract

Background: Current literature reports that the traditional methods overestimate renal function in spinal cord injury (SCI); however, there is no accepted standard method. **Objective:** This study evaluated 6 published methods against measured aminoglycoside (AG) drug clearance and determined the frequency with which each method would achieve target peak and trough AG concentrations within a specified range. **Methods:** A chart-based investigation was conducted at a hospital with a large SCI population, and a total of 35 patients met the inclusion criteria: a diagnosis of long-standing SCI, administration of AG via intravenous infusion, and at least one set of steady-state AG peak and trough concentrations. Pharmacokinetic analysis was performed to compare the measured AG clearance values against the values resulting from 6 methods of estimating the glomerular filtration rate (GFR). Patient-specific pharmacokinetic parameters were used to simulate steady-state peak and trough AG concentrations from doses derived from each method. **Results:** Compared with the other methods, the Lee–Dang method was found to be more accurate, with the smallest magnitude of variance from the measured AG clearance values. Five alternative methods significantly overestimated AG clearance, by approximately 70% to 160% ($P < .05$). The Lee–Dang method underestimated AG clearance (by 10%), however not to a significant degree ($P = .079$). Compared with the alternative methods, the Lee–Dang method resulted in a higher frequency of steady-state peak and trough AG concentrations within the target range specified. **Conclusion:** The Lee–Dang equation for predicting GFR was more accurate relative to the other methods in the study population of patients with long-term SCI.

Keywords

aminoglycosides, drug safety, pharmacokinetics, glomerular filtration rate, creatinine clearance, spinal cord injury

Introduction

The National Kidney Disease Education Program recommends using either the Cockcroft–Gault (CG) creatinine clearance (CL_{CG}) or Modification of Diet in Renal Disease (MDRD) equation when determining dosages of drugs that are primarily eliminated by the kidneys.¹ Both CG and MDRD methods contain serum creatinine (SCr) in their denominator inversely proportional to creatinine clearance (CL_{CR}) or glomerular filtration rate (GFR). In spite of the fact that these methods attempt to take into account the difference in creatinine production by age, weight, gender, and/or race, they do not capture the key factor of spinal cord injury (SCI), significantly reduced SCr due to chronic immobility and muscle atrophy. As a result, using such equations in individuals with SCI would result in a gross overestimation of their renal function that will increase the risk of drug toxicity and/or adverse drug reactions (ADRs).^{2–4}

Current literature does not advocate using the original CL_{CG} or MDRD equations to estimate renal function in

SCI; however, there is no accepted standard method recommended. Furthermore, there is no head-to-head comparison of the various methods published to date. Recognizing the need for a clinically feasible method that can accurately estimate renal function in SCI, we evaluated 6 published methods against measured aminoglycoside (AG) drug clearance that mirrors CL_{CR} . In addition, the patient-specific pharmacokinetic (PK) parameters were used to simulate steady-state peak and trough AG concentrations using 6 different methods in order to determine the frequency with which each method would have achieved the target peak and trough AG concentrations.

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Materials and Methods

This study was a noninterventional chart-based investigation, and the protocol was reviewed and approved by the institution's institutional review board.

All hospitalized patients with a diagnosis of SCI through ICD-9 codes at a Veterans Affairs medical center who received AG (amikacin, gentamicin, or tobramycin) with at least one set of steady-state peak and trough drug concentrations from 2009 to 2013 were evaluated for enrollment in this study. Patients were excluded from the study if they had a limb amputation, received dialysis treatment, experienced an acute change in their renal function (defined as >0.3 mg/dL change in SCr ± 7 days around the AG concentrations), had a history of SCI less than 1 year, had diagnosis of multiple sclerosis, or had inappropriate data for monitoring, such as drug concentrations drawn during the distribution phase, drawn at non-steady-state, or reported as below the sensitivity of the assay, or their antibiotic doses had not been documented.

Patient demographics, degree of SCI, AG administration records, sampling times, SCr concentrations, and 24-hour endogenous creatinine clearance (CL_{24H}) were obtained and recorded. The method of bladder emptying was documented, and 24-hour timed urine was collected according to Lippincott's nursing procedures and skills.⁵ Ideal body weight (IBW) was determined by using the method of Devine⁶ and body surface area (BSA) by the Mosteller formula.⁷ The dose of AG was infused over 30 minutes. Empiric AG volume of distribution (V_d) was calculated as 30% of dosing weight, where dosing weight was defined as lesser of the actual and IBW for nonobese patients and adjusted body weight for the obese (adjusted body weight = $IBW + 0.4$ [actual weight - IBW] for individuals with $>115\%$ IBW).⁸⁻¹¹ Empiric AG clearance (CL_{AG}) was equal to the estimated GFR values, as AG is eliminated almost entirely by the kidney, and its clearance depends on the GFR.¹²⁻¹⁴ Estimation of the PK parameters of AG was made using a 1-compartment open model. Concentrations of AG were determined by an enzyme immunoassay.¹⁵ Patient-specific CL_{AG} , determined from the measured serum drug concentrations using the method of Sawchuk et al,¹⁶ was compared to empiric CL_{AG} predicted by 6 methods of estimating renal function in SCI: 0.7MDRD, 0.8CG, Lee-Dang, Segal, CKD-EPI, and CL_{24H} (Table 1). Based on the estimated CL_{CR} values, steady-state peak and trough AG concentrations were simulated from the dosing regimen (median dose rounded to the nearest 50th mg for amikacin and 10th mg for gentamicin, and dosing intervals of 8, 12, or 24 hours) that would have been recommended by each method.

The formulas used to determine AG PK parameters are as follow¹⁷:

Table 1. Comparison of Equations to Predict Creatinine Clearance or Glomerular Filtration Rate From Serum Creatinine Concentration.

24-Hour endogenous creatinine clearance (CL_{24H}) method ¹⁸
$GFR = CL_{CR} \text{ (mL/min)} = [\text{urine creatinine} \times \text{urine volume (mL)}] / [\text{SCr} \times \text{time (hours)} \times 60]$
Cockcroft-Gault (CG) method ¹⁷
$GFR = CL_{CR} \text{ (mL/min)} = [(140 - \text{age}) \times \text{IBW in kg}] / (72 \times \text{SCr})$; (multiply 0.85 for females); (actual body weight if $< \text{IBW}$)
Modification of Diet in Renal Disease (MDRD) method ^{a,19,20}
$GFR \text{ (mL/min)} = 175 \times \text{standardized SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)} \times \text{BSA}/1.73$
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method ^{a,21}
$GFR \text{ (mL/min)} = 141 \times \min(\text{SCr}/\kappa, 1)^\alpha \times \max(\text{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]} \times \text{BSA}/1.73$, where κ 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/κ or 1, and max indicates the maximum of SCr/κ or 1
Chikkalingaiah method ²²
0.7MDRD; 0.8CG
Lee-Dang method ²³
$GFR = CL_{CR} \text{ (mL/min)} = 2.3 \times CL_M^{0.7}$, where CL_M corresponds to a modified Cockcroft-Gault method with SCr rounded to 1 mg/dL for all patients with SCr < 1 mg/dL while using the actual SCr for patients with SCr ≥ 1 mg/dL
Segal method ²⁴
$GFR = CL_{CR} \text{ (mL/min)} = e^{-0.5746} \times \text{age}^{0.7202} \times \text{CG}^{0.5870} \times (\text{years of SCI duration} + 1)^{-0.1284}$

Abbreviations: CL_{CR} , creatinine clearance; GFR, glomerular filtration rate; SCr, serum creatinine; IBW, ideal body weight; BSA, body surface area.

^aTo enable the expression of comparisons among different methods in the same unit (mL/min), GFR values normalized to a BSA of 1.73 m^2 were converted to uncorrected values.

$$C_{\text{trough}} = C_{\text{peak}} * e^{-k_e t}$$

$$C_{\text{peak}} = \frac{(\text{Dose} / t_{\text{in}}) * (1 - e^{-k_e t_{\text{in}}})}{V_d * k_e}$$

$$CL_{CR} \text{ (ml / min)} = \frac{V_d * K_e}{0.06}$$

Where C_{trough} is the trough concentration, C_{peak} the peak concentration, k_e the elimination-rate constant, t the time from peak to trough, and t_{in} the infusion time.

Comparison of PK parameters between the paraplegic and tetraplegic groups was performed using Wilcoxon rank-sum test. Analyses between the measured CL_{AG} values and each of the different methods to estimate GFR were conducted using the paired Student's t test or Wilcoxon

Table 2. Baseline Patient Characteristics.

Characteristic	N or Mean $\pm$ SD
Number of patients	35
Male/female, n	35/0
Paraplegia/tetraplegia, n	15/20
Black/White or other, n	9/26
Age, years	65.31 $\pm$ 12.68
Height, m	1.80 $\pm$ 0.07
Weight, kg	84.05 $\pm$ 19.97
BMI, kg/m ²	26.07 $\pm$ 6.33
SCr, mg/dL	0.713 $\pm$ 0.329
SCr > 1, mg/dL, n	6
Amikacin/gentamicin, n	32/3

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

Table 3. Pharmacokinetics of Aminoglycoside in Patients With SCI.

Pharmacokinetic Parameter	Paraplegia (n = 15)	Tetraplegia (n = 20)	P Value
Volume of distribution (L/kg)	0.30 $\pm$ 0.08	0.27 $\pm$ 0.10	.184
Half-life (h)	5.23 $\pm$ 1.64	5.94 $\pm$ 2.52	.655
Elimination rate constant (h ⁻¹)	0.15 $\pm$ 0.05	0.14 $\pm$ 0.05	.655
CL _{AG} (mL/kg/min)	0.76 $\pm$ 0.27	0.62 $\pm$ 0.21	.102

Abbreviations: SCI, spinal cord injury; CL_{AG}, measured patient-specific AG clearance.

signed-rank test as appropriate. Values of $P < .05$ were considered significant.

Results

The study population entirely used an aid of bladder retention catheter for 24-hour urine collection: 89% had indwelling catheters and 11% external condom catheters. Baseline patient characteristics are presented in Table 2. Approximately 80% of patients (29/35) had a SCr concentration of <1 mg/dL, which was rounded up to 1 mg/dL when using the Lee–Dang equation to estimate CL_{CR}. There were no patients on tobramycin who met the inclusion criteria, as amikacin and gentamicin are the formulary AG at the study institution.

The PK parameters of AG in paraplegia versus tetraplegia are depicted in Table 3. The mean patient-specific V_d values in paraplegia was slightly higher than in tetraplegia; however, the difference was not statistically significant ($P = .184$). V_d of the study population was within the range reported in the literature.^{8–11} The mean measured AG clearance and elimination-rate constant were marginally lower and thus half-life higher in tetraplegia compared with paraplegia ($P = .102$).

Table 4. Variation Between Calculated and Documented Aminoglycoside Clearance Values (n = 35).

Method of Calculation	Mean $\pm$ SD of Calculated Value, mL/min	Variance From Mean Documented Patient-Specific Value, mL/min	P Value
CL _{Lee-Dang}	45.47 $\pm$ 6.42	−6.09 $\pm$ 15.58	.079
CL _{24h}	87.66 $\pm$ 37.53	36.10 $\pm$ 32.46	<.05
CL _{0.8CG}	100.10 $\pm$ 48.20	48.54 $\pm$ 44.59	<.05
CL _{0.7MRDR}	115.91 $\pm$ 58.66	64.35 $\pm$ 54.95	<.05
CL _{CKD-EPI}	118.74 $\pm$ 34.99	67.18 $\pm$ 29.60	<.05
CL _{Segal}	134.32 $\pm$ 33.91	82.76 $\pm$ 34.75	<.05

Abbreviations: CL_{Lee-Dang}, Lee–Dang method; CL_{24h}, 24-hour endogenous creatinine clearance method; CL_{0.8CG}, 0.8 Cockcroft–Gault method; CL_{0.7MRDR}, 0.7 Modification of Diet in Renal Disease method; CL_{CKD-EPI}, Chronic Kidney Disease Epidemiology Collaboration method; CL_{Segal}, Segal method.

Table 4 presents data indicating the magnitude of variance between the CL_{CR} estimates yielded by each of the 6 evaluated methods and the mean of aggregated documented patient-specific AG clearance values. The data demonstrated that relative to the Lee–Dang equation, the 5 alternative methods all significantly overestimated GFR ($P < .05$). The degree of discrepancy between the predicted and measured clearance values was greatest with the use of the Segal equation, which produced overestimates of approximately 160%. Even the best of the comparator methods, the CL_{24h} equation, significantly overestimated AG clearance by approximately 70% ($P < .05$). The mean difference between the values predicted by the Lee–Dang equation and measured AG clearance values was −6 mL/min; thus, the Lee–Dang equation underestimated AG clearance by approximately 10%, but this was not a statistically significant difference ($P = .079$).

The patient-specific PK parameters derived from each of the 6 methods of estimating renal function in SCI were used to simulate steady-state peak and trough serum AG concentrations, using the first-order kinetics. Tables 5 and 6 show the percentages of patients who would have achieved goal serum AG concentrations for each of the dosing method. The Lee–Dang method yielded the highest frequency (94%) of producing both the steady-state peak and trough amikacin concentrations within the usual goal of 20 to 35 and 2 to 8 μ g/mL, respectively. The other 5 methods produced markedly lower frequencies (13% to 59%) of producing both the steady-state peak and trough amikacin concentrations within the usual goal range. For gentamicin, 3 out of 3 patients had both the steady-state peak and trough concentrations within the usual goal of 4 to 8 and 0.5 to 2 μ g/mL, respectively, using the Lee–Dang method. The frequency of producing both the steady-state peak and trough gentamicin concentrations within the usual goal range was 1 or 2 out of 3 patients for the other 5 methods.

Table 5. Number (%) of Simulated Steady-State Amikacin Concentrations at Various Ranges by Each Method (n = 32).

Serum Amikacin Concentration (μg/L)	CL _{Lee-Dang} (%)	CL _{24h} (%)	0.8CG (%)	0.7MDRD (%)	CKD-EPI (%)	CL _{Segal} (%)
C _{max} < 20	1 (3)	0	0	0	0	0
C _{max} 20-35	30 (94)	21 (66)	19 (59)	16 (50)	13 (41)	8 (25)
C _{max} > 35	1 (3)	11 (34)	13 (41)	16 (50)	19 (59)	24 (75)
C _{min} < 2	0	0	0	0	0	0
C _{min} 2-8	31 (97)	22 (69)	16 (50)	12 (38)	9 (28)	4 (13)
C _{min} > 8	1 (3)	10 (31)	16 (50)	20 (63)	23 (72)	28 (88)
C _{max} 20-35 and C _{min} 2-8	30 (94)	19 (59)	13 (41)	11 (34)	7 (22)	4 (13)

Abbreviations: CL_{Lee-Dang}, Lee–Dang method; CL_{24h}, 24-hour endogenous creatinine clearance method; CL_{0.8CG}, 0.8 Cockcroft–Gault method; CL_{0.7MDRD}, 0.7 Modification of Diet in Renal Disease method; CL_{CKD-EPI}, Chronic Kidney Disease Epidemiology Collaboration method; CL_{Segal}, Segal method; C_{max}, steady-state peak plasma concentration; C_{min}, steady-state trough plasma concentration.

Table 6. Number (%) of Simulated Steady-State Gentamicin Concentrations at Various Ranges by Each Method (n = 3).

Serum Gentamicin Concentration (μg/L)	CL _{Lee-Dang} (%)	CL _{24h} (%)	0.8CG (%)	0.7MDRD (%)	CKD-EPI (%)	CL _{Segal} (%)
C _{max} < 4	0	0	0	0	0	0
C _{max} 4-8	3 (100)	2 (67)	2 (67)	2 (67)	1 (33)	1 (33)
C _{max} > 8	0	1 (33)	1 (33)	1 (33)	2 (67)	2 (67)
C _{min} < 0.5	0	0	0	0	0	0
C _{min} 0.5-2	3 (100)	1 (33)	2 (67)	1 (33)	1 (33)	1 (33)
C _{min} > 2	0	2 (67)	1 (33)	2 (67)	2 (67)	2 (67)
C _{max} 4-8 and C _{min} 0.5-2	3 (100)	1 (33)	2 (67)	1 (33)	1 (33)	1 (33)

Abbreviations: CL_{Lee-Dang}, Lee–Dang method; CL_{24h}, 24-hour endogenous creatinine clearance method; CL_{0.8CG}, 0.8 Cockcroft–Gault method; CL_{0.7MDRD}, 0.7 Modification of Diet in Renal Disease method; CL_{CKD-EPI}, Chronic Kidney Disease Epidemiology Collaboration method; CL_{Segal}, Segal method; C_{max}, steady-state peak plasma concentration; C_{min}, steady-state trough plasma concentration.

Discussion

SCr determinations are used to estimate the dose of potentially toxic drugs eliminated primarily by the kidneys. Current literature reports several different methods to predict renal function; however, there is no accepted standard method that can reliably predict CL_{CR} in SCI.

This study evaluated 6 different methods to estimate renal function in SCI against measured AG clearance that mirrors CL_{CR}. The data show that only the Lee–Dang equation is accurate in estimating CL_{CR}, thus accurate in estimating AG clearance, and the slight underestimation is not statistically significant. On the other hand, the use of the CL_{24h}, 0.7MDRD, 0.8CG, CKD-EPI, and Segal equations considerably overestimated AG clearance, yielding values at least 70% higher than the measured AG clearance values ($P < .05$). Such findings were confirmed by greater than 90% of the simulated steady-state peak and trough serum AG concentrations resulting in therapeutic goal levels using the Lee–Dang equation, whereas less than 60% of the simulations achieved goal levels using the other 5 methods. In clinical practice, the use of the equations that overestimate CL_{CR} to such extent will lead to above-target AG concentrations and substantially

increase the risk of drug toxicity such as nephrotoxicity or ototoxicity. This could be devastating to many SCI patients who have existing renal insufficiency.

Creatinine-based formulas used in estimating renal function for purposes of medication dosage determination should be applied with extreme caution in patients with SCI. Exceedingly low muscle mass and immobility in patients with long-term SCI are the main contributing factors to substantially reduced serum concentrations of creatinine; this could lead to falsely high CL_{CR} determinations resulting in higher than targeted drug concentrations that increase the risk of ADRs. Although the equations attempt to take into account differences in creatinine production in SCI via modifications of the original equations or incorporation of SCI variables, their dependence on SCr values is not avoidable.

The study population had multiple comorbidities that may have adversely affected the renal function: diabetes, hypertension, history of multiple infections, hepatic disease, and so on. Such conditions were not accounted for in the predictive methods to estimate GFR, and thus could have contributed to the measured AG clearance values being significantly lower than the estimated CL_{CR}.

In addition to the problems inherent in any chart review of previously collected clinical data, this study had several limitations. First, the study was conducted in a population of exclusively elderly male patients (mean age = 65 years); therefore, the resulting data may not be extrapolated to other populations with SCI. Second, while it is recommended that laboratories report the GFR as >60 mL/min as opposed to the actual value, we used the actual values obtained by the MDRD and CKD-EPI methods to evaluate the study outcome. Third, the abbreviated version of the MDRD formula was used, and dietary influences were not controlled for in this study. Fourth, the sample size was small (n = 35), primarily because the drug monitoring data for a number of patients were deemed inappropriate for study inclusion. Fifth, the level of SCI was not sufficiently quantified in order to exclude SCI patients with preserved motor function and relatively unaltered SCr. Last, the study assumed that drug concentrations are at steady-state in cases involving a change in SCr less than or equal to 0.3 mg/dL and that AG clearance was equivalent to CL_{CR}.

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Declaration of Conflicting Interests

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