Evaluation of Methods to Estimate Renal Function vs. Actual Drug Clearance in Individuals with SCI

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• Jennifer Lee, Pharm.D., BCPS
• Anthony Dang, Pharm.D., BCPS

Has no financial interest or relationships to disclose

• CME Staff Disclosures

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Objectives

At the conclusion of this activity, the participant will be able to:

1. Evaluate different methods of estimating GFR compared to patient-specific vancomycin and AG drug clearance ($CL_{DRUG}$) in SCI patients.

2. Determine if a new equation can be developed to more accurately estimate GFR in SCI patients in order to optimize dosing for vancomycin and AG.

3. Assess if there is a difference in the estimation of renal function between anatomical degrees of SCI when compared to $CL_{DRUG}$. 
VA Long Beach Healthcare System

- Tertiary Care Facility
- Total SCI beds: 90
Pre-Test Assessment Questions

- **T / F**: Higher peak and trough concentrations increase risk of aminoglycoside-induced ototoxicity and nephrotoxicity.

- **T / F**: Creatinine production declines with age, immobility, and reduced muscle mass.

- **T / F**: Individuals with spinal cord injury (SCI) have better drug clearance than the general population.
Creatinine

- A muscle breakdown product
- Produced at a constant rate
- Exclusively filtered by the kidneys

Chronic SCI

1. Limited Mobility
2. ↓ Muscle Mass
3. ↓ SCr
4. ↑ CrCl
5. Over-dosing
6. ↑ ADR

Vancomycin & Aminoglycosides

- Dose related toxicity:
  - Ototoxicity
  - Nephrotoxicity

- Primarily renal elimination

Methods to estimate GFR

- Cockcroft-Gault (CG) equation<sup>7</sup>
- Modified CG equation
- MDRD equation<sup>8</sup>
- CKD-EPI equation<sup>9</sup>
- 24-Hour endogenous creatinine clearance<sup>1,10</sup>

Cockcroft-Gault (CG)\textsuperscript{7}

\[ CL_{CG} \text{ (mL/min)} = \frac{[(140 - \text{age}) \times \text{IBW in kg}]}{(72 \times \text{SCr})}; \text{ (multiply 0.85 for females)} \]

Modified CG formula (CL\textsubscript{M}):

- SCr rounded to 1 mg/dL for patients with SCr < 1 mg/dL while using the actual SCr for patients with SCr \( \geq 1 \) mg/dL

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## Overestimation by CG

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdiarmid et al.¹</td>
<td>25 Paraplegic 11 Tetraplegic</td>
<td>$\text{CL}<em>{\text{CG}}$ vs. $\text{CL}</em>{24\text{H}}$ vs. 99mTc-DTPA</td>
<td>$\text{CL}_{24\text{H}}$ more accurate</td>
</tr>
<tr>
<td>Mirahmadi et al.²</td>
<td>22 Paraplegic 36 Tetraplegic 22 ambulatory</td>
<td>$\text{CL}<em>{\text{CG}}$ vs. $\text{CL}</em>{24\text{H}}$ vs. Autoanalyser</td>
<td>Correction factor: 0.8 for paraplegic 0.6 for tetraplegic</td>
</tr>
<tr>
<td>Lavezo et al.¹¹</td>
<td>14 SCI 14 control</td>
<td>Actual vs. Predicted $\text{CL}_{\text{VANCO}}$</td>
<td>↑half-life in SCI</td>
</tr>
</tbody>
</table>

MDRD equation\textsuperscript{8}

4-Variable MDRD:

\[ \text{eGFR} = 175 \times \text{standardized SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \ (\text{if black}) \times 0.742 \ (\text{if female}) \]

## CG vs. MDRD

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikkalingaiah KBM et al.</td>
<td>116 SCI</td>
<td>$\text{CL}<em>{24H}$ vs. $\text{CL}</em>\text{CG}$ vs. MDRD</td>
<td>Correction factor: 0.7 for MDRD 0.8 for $\text{CL}_\text{CG}$</td>
</tr>
<tr>
<td>Bookstaver PB et al.</td>
<td>71 non-SCI</td>
<td>Actual $\text{CL}<em>\text{AG}$ vs. $\text{CL}</em>\text{CG}$ vs. MDRD</td>
<td>MDRD better</td>
</tr>
<tr>
<td>Ryzner KL.</td>
<td>55 non-SCI</td>
<td>Actual $\text{CL}<em>\text{AG}$ vs. $\text{CL}</em>\text{CG}$ vs. MDRD</td>
<td>$\text{CL}_\text{CG}$ better</td>
</tr>
</tbody>
</table>

CKD-EPI equation

$$eGFR = 141 \times \min \left( \frac{SCr}{\kappa}, 1 \right)^{\alpha} \times \max \left( \frac{SCr}{\kappa}, 1 \right)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 [\text{if female}] \times 1.159 [\text{if black}]$$

where $\kappa$ is 0.7 for females and 0.9 for males,

$\alpha$ is -0.329 for females and -0.411 for males,

min indicates the minimum of $SCr/\kappa$ or 1,

& max indicates the maximum of $SCr/\kappa$ or 1.

# CG vs. CKD-EPI

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pai et al. (^{15})</td>
<td>2073 non-SCI</td>
<td>(CL_{AG} \text{ vs. } CL_{CG} \text{ vs. } \text{MDRD} \text{ vs. } \text{CKD-EPI})</td>
<td>(\text{CKD-EPI} &gt; \text{MDRD} &gt; CL_{CG})</td>
</tr>
</tbody>
</table>

24-Hour Endogenous Creatinine Clearance\textsuperscript{10}

\[
\text{CL}_{24\text{H}} \ (\text{mL/min}) = \frac{\text{urine creatinine } \times \text{ urine volume (mL)}}{\text{SCr } \times \text{ time (hours)} \times 60}
\]

Methodology

- IRB Approved
- Study Design: Retrospective chart review
- Study Period: 1/1/2008 – 12/31/08
Inclusion Criteria

- Patients at VALB with an ICD-9 diagnosis of spinal cord injury for >1 year
  - Received amikacin, gentamicin, tobramycin, or vancomycin with at least one steady state level
Exclusion Criteria

- Hemodialysis or acute kidney injury
- Limb amputation
- Multiple sclerosis
- Inappropriate data for monitoring
Methodology

- VA electronic medical record (Computerized Patient Record System)

- Pharmacokinetic calculations via non-steady state short infusion model\(^{16}\)
  \[ C_{\text{peak}} = \frac{(Dose/t_{\text{inf}}) \times (1-e^{-kt_{\text{inf}}})}{V_d} \times K_e \]
  \[ C_{\text{trough}} = C_{\text{peak}} \times e^{-kt} \]
  \[ CrCl (L/hr) = V_d \times K_e \]

Methodology

- Volume of distribution calculations\textsuperscript{17}:
  - Vancomycin
    - $V_d = 0.17(\text{age}) + 0.22(\text{TBW}) + 15$
  - Aminoglycosides
    - Peak levels were used to calculate $V_d$

\textsuperscript{17} Rushing TA. \textit{J Pharm Technol}, 2001; 17: 33-8.
Methodology

- Actual drug clearance ($CL_{DRUG}$)
- CG CrCl ($CL_{CG}$)
- Modified CG CrCl ($CL_{M}$)
- Adjusted 24-hour endogenous CrCl ($CL_{24H}$)
- MDRD equation
- CKD-EPI equation
Statistical Analyses

- 2-sided students t-test with alpha=0.01 for significance
- 95% Power
  - Determined Post Hoc given results
- Linear Regression
- All analyses performed using Microsoft® Excel
Results
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # of patients</td>
<td>141</td>
</tr>
<tr>
<td>Male/Female, N</td>
<td>140/1</td>
</tr>
<tr>
<td>Tetraplegic/ Paraplegic, N</td>
<td>89/52</td>
</tr>
<tr>
<td>Vancomycin/ Amikacin, N</td>
<td>109/32</td>
</tr>
<tr>
<td>SCr &gt;1 mg/dL, N</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.72 ± 10.54</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179.96 ± 7.01</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.35 ± 20.69</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.6 ± 5.78</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>0.74 ± 0.29</td>
</tr>
</tbody>
</table>
Evaluation of different methods to estimate GFR

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean ± S.D. (mL/min)</th>
<th>Difference from CL_{DRUG} (mL/min)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_{DRUG}</td>
<td>49.77 ± 19.97</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>MDRD</td>
<td>119.76 ± 61.49</td>
<td>69.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>90.71 ± 27.44</td>
<td>40.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CL_{24H}</td>
<td>85.16 ± 33.88</td>
<td>35.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CL_{CG}</td>
<td>91.24 ± 36.90</td>
<td>41.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CL_{M}</td>
<td>69.38 ± 13.49</td>
<td>19.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Difference between MDRD and $CL_{DRUG}$

Number of Patients

Abbreviations: MDRD, the Modification of Diet in Renal Disease equation; $CL_{DRUG}$, actual drug clearance.
Difference between \( CL_M \) and \( CL_{DRUG} \)

Abbreviations: \( CL_M \), modified Cockcroft-Gault formula; \( CL_{DRUG} \), actual drug clearance.
# Evaluation of $CL_M$ to estimate $CL_{DRUG}$ for vancomycin and AG

<table>
<thead>
<tr>
<th></th>
<th>Mean ± S.D. (mL/min)</th>
<th>Difference from $CL_{DRUG}$ (mL/min)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined Amikacin and Vancomycin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=141)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{DRUG}$</td>
<td>49.77 ± 19.97</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>$CL_M$</td>
<td>69.38 ± 13.49</td>
<td>19.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Amikacin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{DRUG}$</td>
<td>57.27 ± 28.22</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>$CL_M$</td>
<td>69.37 ± 14.08</td>
<td>12.1</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=109)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{DRUG}$</td>
<td>47.57 ± 16.34</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>$CL_M$</td>
<td>69.38 ± 13.38</td>
<td>21.81</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Determining SCI Study Equation

Actual Drug Clearance (mL/min)

Modified Cockcroft-Gault Predicted Drug Clearance (mL/min)

$y = 2.3286x^{0.7}$

$R = 0.4$
Linear Regression Plots

$y = 0.8425x + 6.7281$

$R = 0.4$

Actual Drug Clearance (mL/min)

Predicted Drug Clearance using $CL_{SCI}$ (mL/min)

Abbreviation: $CL_{SCI}$, spinal cord injury equation
**CL\textsubscript{DRUG} vs. CL\textsubscript{SCI}**

- T-Test showed no difference between SCI equation and actual drug clearance.

<table>
<thead>
<tr>
<th></th>
<th>Mean S.D. (mL/min)</th>
<th>Difference from CL\textsubscript{DRUG} (mL/min)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL\textsubscript{DRUG}</td>
<td>47.57 +/- 16.34</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CL\textsubscript{SCI}</td>
<td>45.22 +/- 6.16</td>
<td>-2.35</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Different anatomical degrees of SCI

<table>
<thead>
<tr>
<th>(N=141)</th>
<th>Mean Difference from $CL_{\text{DRUG}}$</th>
<th>S.D. (mL/min)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraplegics (n = 52)</td>
<td>Tetraplegics (n = 89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{\text{SCI}}$</td>
<td>-3.11</td>
<td>13.14</td>
<td>-5.39</td>
</tr>
<tr>
<td>$CL_{M}$</td>
<td>21.04</td>
<td>13.81</td>
<td>18.76</td>
</tr>
<tr>
<td>$CL_{24H}$</td>
<td>32.60</td>
<td>30.78</td>
<td>37.02</td>
</tr>
<tr>
<td>$CL_{CG}$</td>
<td>27.26</td>
<td>20.56</td>
<td>49.76</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>27.52</td>
<td>25.50</td>
<td>48.77</td>
</tr>
<tr>
<td>MDRD</td>
<td>40.68</td>
<td>40.71</td>
<td>50.64</td>
</tr>
</tbody>
</table>
DISCUSSION
Discussion

- Current methods for estimating GFR grossly overestimate drug clearance in chronic SCI patients compared to the SCI Study Equation
Discussion

- $CL_{SCI} = 2.3286 \times x^{0.7006}$, where $x = CL_M$ with SCr rounded to 1 if SCr < 1 for all SCI patients.
  - More accurate
  - More precise
Limitations

- Small number of patients in amikacin group
- Veterans population
- Variability inherent in using clinical data
- Assumption: $\text{CL}_{\text{CR}}=\text{CL}_V=\text{CL}_{\text{AG}}$
- Accuracy of vancomycin $V_d$
- Actual GFR values for > 60 ml/min
- Abbreviated MDRD
- No adjustment for BSA
- Retrospective study: limited control over certain confounding variables
Conclusion

• Current methods used to calculate $\text{CL}_{\text{CR}}$ overestimate $\text{CL}_{\text{DRUG}}$ in SCI patients

• The proposed SCI equation:

$$\text{CL}_{\text{SCI}} = 2.3^x^{0.7}$$

($x = \text{CL}_M$ with SCr rounded to 1 if SCr < 1)
Future Plans

- Validate $CL_{SCI}$ in a prospective analysis
- Further analysis with aminoglycosides
References


References


Post-Test Assessment Questions

- **T / F**: Higher peak and trough concentrations increase risk of aminoglycoside-induced ototoxicity and nephrotoxicity.

- **T / F**: Creatinine production declines with age, immobility, and reduced muscle mass.

- **T / F**: Individuals with spinal cord injury (SCI) have better drug clearance rates than the general population.
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