Dose Adjustments in Patients with Impaired Renal Function

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Chronic Kidney Disease

- Major world-wide health concern
- In US number of patients requiring dialysis or transplant is projected to increase from 340,000 in 1999 to 651,000 in 2010
- National Kidney Foundation-attempts to standardize definition, stages and laboratory tests to assess kidney function

Chronic Kidney Disease - Definition

“Kidney damage for three months or more, with or without decreased GFR, manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests”

GFR < 60 mL per minute per 1.73 m² for three months or more, with or without kidney damage

National Kidney Foundation, 2004
Renal Drug Clearance

- Glomerular Filtration
- Tubular Secretion
- Tubular Re-absorption

- 20-25% Cardiac output or 1.1L/min goes to kidneys
- 10% of it is filtered at glomerulus
- Normal GFR is 120 ml/min for a 70kg, 20 year old man
Effect of Renal Dysfunction on PK processes

• Absorption
  - increased $t_{\text{max}}$ for certain drugs in severe renal dysfunction
  - Changes pre-systemic elimination

• Distribution
  - Plasma protein binding of many acidic drugs decrease in renal impairment
  - $\alpha_1$-Acid glycoprotein levels may show an increase
  - Changes in volume of distribution

• Metabolism
  - Renal dysfunction may alter even non-renal elimination
  - Accumulation of active metabolites

• Elimination
  - Transporters
  - Renal failure may affect multiple organ systems

Dose adjustments!
Estimation of Renal Function

- GFR as overall measure of renal function
- Exogenous markers like inulin – not widely used clinically
- Most popular- Creatinine clearance from serum creatinine (Cockcroft-Gault equation)
- eGFR from Modification of Diet in Renal Disease (MDRD) study

Normal values for GFR in Men and Women

Wesson LG. Physiology of the Human Kidney 1969: 96-108
Xiao S. Clinical pharmacology Advisory Committee, 2008, CDER/FDA
Ideal Markers for GFR

- Freely filterable at the glomerulus
- Neither secreted nor reabsorbed by the tubules
- Steady state concentrations in blood
- No extra-renal route of excretion
- Easily and accurately measured
Exogenous Markers

Inulin

- Gold standard
- Constant infusion and bladder catheterization for good reproducibility
- Significant blood sample volume
- Assay is difficult
- Expensive and time consuming
- Limited to investigational research
Endogenous markers
Creatinine

- Filtered by the glomerulus
- No protein binding
- Generation determined by muscle mass and dietary intake
- Need 24-hour urine collection and blood sampling during the collection period
- Cumbersome for timed urinary collection
- Susceptible to error
## National Kidney Foundation Defines Five Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Kidney damage, Normal or ↑GFR</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Kidney damage, mild ↓GFR</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderate ↓GFR</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severe ↓GFR</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 (Dialysis)</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>
Renal Impairment

- GFR <60 mL/min/1.73 m² for 3 months - classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage
- GFR <90 mL/min/1.73 m² would be abnormal in a young adult
- GFR of 60–89 mL/min/1.73 m² could be normal from approximately 8 weeks to 1 year of age and in older individuals
- It is unclear whether individuals with chronically decreased GFR in the range of 60 to 89 mL/min/1.73 m² without kidney damage are at increased risk for adverse outcomes, such as toxicity from drugs excreted by the kidney or acute kidney failure

NKF/KDOQI guidelines
NKF-KDOQI Recommendations

Adults

Cockcroft-Gault equation
MDRD (modification of diet in renal disease) equation

Children

Schwartz equation
GFR (ml/min) = 0.55 x Length/Scr

Counahan-Barratt equation
GFR (ml/min/1.73m²) = 0.43 X Length/Scr
Cockcroft-Gault Equation

- Derived from 249 men aged 18-92, with and without CKD
- No women were included!
- Factor for females is hypothetical
- Estimates are not adjusted for BSA
- Available modifications-use of ideal/adjusted body weight

\[
CrCl \text{ (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times (0.85 \text{ for females})
\]

- Most widely used
- Used by FDA for labeling decisions
Cockcroft - Gault Equation – IBW

\[ \text{CrCl} = \frac{[(140 - \text{age}) \times \text{IBW}]}{(\text{Scr} \times 72)} \times (0.85 \text{ for females}) \]

- if the total body weight (TBW) is less than the IBW, then the TBW is used for calculating the CrCl
- If the patient is > 65 yr and creatinine < 1.0, use 1 to calculate the creatinine clearance.
Ideal Body Weight

Males

\[ \text{IBW} = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5ft} \]

Females

\[ \text{IBW} = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5ft} \]
Cockcroft - Gault Equation – ABW

Adjusted body weight (ABW)

\[ \text{CrCl} = \frac{[(140 - \text{age}) \times \text{ABW}]}{\text{Scr} \times 72} \times 0.85 \text{ for females} \]

\[ \text{ABW} = \text{IBW} + 0.3(\text{TBW} - \text{IBW}) \]

- ABW calculation exception: ABW of aminoglycoside uses 0.4 instead of 0.3 in the equation
- ABW only used when the TBW is 25% greater than IBW. In all other cases, the IBW is used
- Studies have shown ABW is the best approach for calculating CrCL in the elderly population
Estimated GFR (eGFR) from MDRD Study

Derived from 1628 men and women with CKD
GFR adjusted to BSA-accounts for different body sizes
Standardized serum creatinine values

\[ eGFR \text{ (ml/min/1.73 m}^2\text{)} = 175 \times (SCr_{\text{std}})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if African-American)} \]

- Several versions available

SCr_{std}: serum creatinine from a standardized assay
Accuracy of SrCr Based Methods

- Overall, MDRD are more accurate than the Cockcroft-Gault in some studies whereas the two are similar in other studies.
- MDRD is reasonably accurate in non-hospitalized patients with CKD.
- Cockcroft-Gault is less accurate than the MDRD in older and obese people.
- Both are less accurate than the measured GFR in population without CKD (GFR > 60 ml/min/1.73m$^2$) such as type I diabetes without micro-albuminuria and potential kidney donors.
Limitations of Creatinine Based Estimates

- Serum creatinine is influenced by factors other than GFR (Muscle mass, diet, tubular secretion rate)
- Equations use age, sex, race and weight, but may not cover all factors involved
- Not accurate in individuals with extreme muscle mass or big size, dietary habits (important in frail, elderly, cancer patients and low muscle mass)
- Kidney function should be at steady state
- Issues when kidney function rapidly changes
- Narrow therapeutic/toxic drugs
FDA’s Approach

“If a correlation is established between either measure of renal function (CrCl or eGFR) and the drug’s PK, this relationship, together with our understanding of the PK/PD relationships for both therapeutic and adverse responses, should form the basis of dosing recommendations in patients with varying degrees of renal function impairment Most widely used”

✓ Both C-G estimates and MDRD are required
✓ Additional measures, if available, to differentiate GF and tubular secretion/absorption
Recommendation from Scientific Communities

• National Kidney foundation: Among adults, the MDRD Study equation may perform better than the Cockcroft-Gault equation.

http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g4.htm

• American Society of Nephrology, American Association for Clinical Chemistry, American Diabetes Association, College of American Pathologists and National Kidney Disease Educational Program: MDRD

Clearance Measurements May Be Necessary to Estimate GFR

- Extremes of age (elderly, children)
- Extremes of body size (obesity, type 2 diabetes, low body mass index, ie, $<18.5 \text{ kg/m}^2$)
- Severe malnutrition (cirrhosis, end-stage renal failure)
- Grossly abnormal muscle mass (amputation, paralysis)
- High or low intake of creatinine of creatine (vegetarian diet, dietary supplements)
- Pregnancy
- Rapidly changing kidney function
- Prior to dosing (high toxicity drugs, excreted by the kidney)
- Prior to kidney donation
Examples of Suggested Dose Adjustments Based on Renal Function from Cockcroft-Gault Equation

<table>
<thead>
<tr>
<th>ADME</th>
<th>Renal function (ml/min)</th>
<th>Fold-change in exposure (AUC)</th>
<th>Initial dose (mg)</th>
<th>Daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CrCl &gt;80</td>
<td>Control</td>
<td>1.5-fold (mild)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>CrCl 50–80</td>
<td>1.5-fold (moderate)</td>
<td>3</td>
<td>3–6</td>
</tr>
<tr>
<td></td>
<td>CrCl 30–50</td>
<td>2.6-fold (moderate)</td>
<td>1.5</td>
<td>1.5–3</td>
</tr>
<tr>
<td></td>
<td>CrCl 10–30</td>
<td>4.8-fold (severe)</td>
<td>1.5</td>
<td>1.5–3</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;10</td>
<td><em>b</em></td>
<td><em>b</em></td>
<td><em>b</em></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>CrCl &gt;50</td>
<td>Control</td>
<td>1.9-fold (moderate)</td>
<td>600 q24h</td>
</tr>
<tr>
<td></td>
<td>CrCl 30–49</td>
<td>3.4-fold (severe)</td>
<td>600 q72h</td>
<td>600 q96h</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30</td>
<td>7-fold (ESRD)</td>
<td>600 q72h</td>
<td>600 q96h</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>600 q72h</td>
<td>600 q96h</td>
<td>600 q96h</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>CrCl &gt;80</td>
<td>Control</td>
<td>1-fold (mild)</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>CrCl 50–80</td>
<td>1-fold (moderate)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td></td>
<td>CrCl 30–50</td>
<td>3-fold (severe)</td>
<td>5–10</td>
<td>5–10</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30</td>
<td>5–10</td>
<td>5–10</td>
<td>5–10</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>CrCl &lt;30</td>
<td>Control</td>
<td>1.9-fold (severe)</td>
<td>800 q.d.</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4- to 5-fold (severe)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>400 q.d.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>400 q.d.&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

fe: Fraction of oral dose excreted unchanged in urine, F: Bioavailability

S-M Huang <i>et al.</i> Clinical Pharmacology & Therapeutics (2009) 86 5, 475–479
http://www.accessdata.fda.gov/scripts/cder/drugsatfda
Estimation of Kidney Function in Adults for Medication Dosage

- FDA labeling guides dose adjustments for patients with impaired renal function
- Serum creatinine, measured CrCL or estimated CrCL as markers for kidney function
- Uses Cockcroft-Gault equation for eCrCL
- Labels developed prior to standardized calibration of creatinine assays
- MDRD study equations provide estimated GFR
NKDEP Approach

- Lab to lab variability in creatinine estimation methods
- FDA drug labels depend on creatinine assay used in PK studies
- Difficulty translating PK dose recommendations to clinics

Solution:

- Use of standardized creatinine methods
- Re-express current drug dosing recommendations!
Head to Head Comparison
eCrCl, eGFR and measured GFR

Little difference in recommended dose for most patients and most drugs when eCrCL or eGFR were used

*Standardized creatinine assays*
NKDEP Suggestions

- Use single kidney function estimate to guide detection, evaluation and management of CKD and drug dosing
- Use eGFR or eCrCL for dosing
- For eGFR in very large or small patients, multiply eGFR with estimated body surface area (BSA)
  \[
  \frac{\text{eGFR}}{1.73\text{m}^2} \times \text{BSA}_{\text{Estimated}} = \text{eGFR for dosing (ml/min)}
  \]
- Use exogenous filtration markers:
  - narrow therapeutic index drugs
  - individuals with different eGFR and eCrCL estimates
  - where creatinine based methods are inaccurate
Impact of IDMS Standardized Creatinine Assays

Standardize creatinine assays based on isotope dilution mass spectrometry (IDMS)

- Less variability in assessing kidney function
- Consistent drug dosing
- IDMS traceable creatinine values make eGFR more accurate with MDRD equations
- Use of Cockcroft-Gault equation with IDMS traceable creatinine values may result in higher eCrCL values
- CrCL based on serum and urine creatinine measurements will be minimally affected if the calibration scheme is same for both urine and serum creatinine
Limitations of Serum Creatinine-Based Estimate

- Serum creatinine is influenced by factors other than GFR, like muscle mass, diet and tubular secretion.
- Covariates (age, sex, race and weight) may not always capture differences in creatinine generation.
- Inaccurate in individuals with extreme body mass and unusual dietary habits.
- Assumes kidney function to be at steady state. May create problems when kidney function rapidly changes.
- Not suitable for narrow therapeutic index or toxic drugs, and in patients where serum creatinine approach may be inaccurate.
Conclusions

- Narrow therapeutic index, water solubility, urinary excretion in unchanged form, renally eliminated active metabolites etc warrants dose adjustments in renal insufficiency

- Properties of accumulating metabolites and dialysis procedures complicates the situation

- No alternative to carefully designed PK and PK-PD studies in renal insufficiency to establish dosing regimens

- Individual CrCL or GFR estimates can be used to evaluate renal function and dose adjustments