Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Calculating Drug Doses in CKD

Section Leaders:
Darren Grabe and Lesley Stevens
Outline

• The paradigm and the problem
• Impact of CKD on pharmacokinetics
• Determination of drug dosing guidelines
• Determination of individualized patient dose
• Breakout group discussion points
Paradigm and the Problem

• PK studies in patients with CKD are performed “when drug or its active metabolites exhibit a narrow therapeutic index and when excretion and/or metabolism occurs primarily via renal mechanisms”

• GFR (or dialysis modality) is assumed to capture all aspects of the effect of kidney disease on PK of a drug, under the “intact nephron hypothesis”

• The problem: No incorporation of other factors that may not correlate with GFR, but are present in patients with CKD, eg hyypoalbuminemia or drug interactions
## Impact of CKD on Pharmacokinetics

<table>
<thead>
<tr>
<th>Factors involved in PK</th>
<th>Kidney disease effects</th>
<th>Measured specifically for incorporation into drug dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>+</td>
<td>N</td>
</tr>
<tr>
<td>Intestinal and first pass metabolism</td>
<td>+</td>
<td>N</td>
</tr>
<tr>
<td>Distribution</td>
<td>++</td>
<td>N</td>
</tr>
<tr>
<td>Clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>+++</td>
<td>Y</td>
</tr>
<tr>
<td>Nonrenal</td>
<td>++</td>
<td>N</td>
</tr>
</tbody>
</table>

Number of ‘+’ indicates magnitude of available data.
CAP, 2003, Fresh Frozen Serum, N = 5624
Creatinine = 0.90 mg/dL (79.7 µmol/L)

VERTICAL BARS = ±1.96*SD for distribution of participant results

• Fexofenadine and midazolam are both CYP3A4 substrates.
• CL of Fexofenadine reduced in CKD
  – 2.8 fold higher AUC compared to control
• CL of Midazolam unchanged in CKD


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Duloxetine pharmacokinetics in CKD


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### Duloxetine pharmacokinetics in CKD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Status</th>
<th>Least squares geometric mean</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucuronide conjugate of 4-hydroxy duloxetine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax [ng/mL]</td>
<td>ESRD</td>
<td>585</td>
<td>0.0006</td>
</tr>
<tr>
<td>Healthy control</td>
<td>235</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC∞ [ng•hr/mL]</td>
<td>ESRD</td>
<td>36,686</td>
<td>0.0001</td>
</tr>
<tr>
<td>Healthy control</td>
<td>3936</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Calculation of daptomycin dose

• Kidney disease (CrCl < 30 mL/min) increases risk of daptomycin failure by ~80%
• Package labeling for CrCl < 30 mL/min and hemodialysis
  – 4-6 mg/kg every 48 hrs or after hemodialysis session
• Conflicting data regarding proper schedule and dose
  – Should dose be increased, interval adjusted?
  – Should dose be given during hemodialysis?
## Comparison of Daptomycin PK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study A&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Study B&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/mL)</td>
<td>60 ± 7</td>
<td>51 ± 29</td>
</tr>
<tr>
<td>$\text{AUC}_{0-68}$ (μg * hr/mL)</td>
<td>1351 ± 151</td>
<td>NA</td>
</tr>
<tr>
<td>$\text{AUC}_{0-72}$ (μg * hr/mL)</td>
<td>NA</td>
<td>1520 ± 585</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (68hrs) (μg/mL)</td>
<td>10.9 ± 3.3</td>
<td>NA</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (72hrs) (μg/mL)</td>
<td>NA</td>
<td>7.5 ± 3.9</td>
</tr>
</tbody>
</table>

Development of Drug Dosing Guidelines: 
**Half-life**

- Used to predict time to steady state
  
  \[ T_{1/2} = 0.693 \frac{V_d}{Cl} \]

- If \( T_{1/2} \) changes due to \( V_d \) vs \( Cl \), then has different implications for dose adjustment
  - \( \Delta V_d \) → Loading dose adjustment
  - \( \Delta Cl \) → Maintenance dose

- The relative magnitude of an effect of CKD on \( V_d \) vs \( Cl \) may change as the GFR falls

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Development of Drug Dosing Guidelines: 
**Loading dose**

- Required if long half life and need to achieve steady state rapidly

- In the absence of a loading dose
  - Time to reach 90% of max concentration is $3.3 \times T_{1/2}$
  - If this is too long relative to the clinical situation, then require loading dose

\[
\text{Loading dose} = (C_{\text{initial}}) (V_d)
\]

- **Usual loading dose** = Normal $V_d$
- **Modified loading dose** = patient’s $V_d$

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Development of Drug Dosing Guidelines: *Maintenance Dose*

- **Goal:** Dosing regimen that maintains the desired steady-state drug concentrations as would occur if the patient did not have CKD

- Change in clearance requires a change in dose to maintain drug concentration

\[
\text{Maintenance dose} = (C_{\text{average}}) \cdot (CI)
\]

- Strategies
  - Continuous infusion: modify rate of infusion
  - Intermittent dosing:
    - Vary dose: Constant levels
    - Vary frequency: Possible fluctuating levels

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Measuring Drug Levels

• Total drug vs active drug
  – E.g. Phenytoin
• Importance of hypoalbuminemia
## Determination of Individualized Patient Dose

<table>
<thead>
<tr>
<th>Factor</th>
<th>Method of Ascertainment</th>
<th>Modify</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>eGFR/eCrCl</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>Level of drug after initial dose*</td>
<td>Loading</td>
</tr>
<tr>
<td>Urgency of clinical situation</td>
<td>Clinical judgment</td>
<td>Loading</td>
</tr>
<tr>
<td>Impact of fluctuations in steady state levels</td>
<td>Clinical judgment</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Patient’s financial situation</td>
<td>Clinical judgment</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Medication interactions</td>
<td>Profile review</td>
<td>Loading, maintenance</td>
</tr>
</tbody>
</table>

*Difficult to ascertain for drugs where levels not routinely available, or for oral drugs*
Dialysis

- Removes drug either intermittently or continuously
- Total clearance of drug dependent on
  - Residual kidney function
  - Dialysis clearance
  - Non-renal clearance
- Clearance dependent on
  - Drug properties (e.g. MW, hydrophilicity, PPB, Vd)
  - Dialysis properties (e.g. flow rate, volume, duration)
  - Membrane properties (e.g. pore size, surface area)

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