Effects of Renal Disease on Pharmacokinetics

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October 11, 2012
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Clinical Center

GOALS of Effects of Renal Disease on Pharmacokinetics Lecture

A. Dose Adjustment in patients with renal Impairment
B. Effect of Renal Disease on:
   Renal Drug Elimination
   Hepatic Drug Metabolism
   Drug Transporters
   Drug Distribution
   Drug Absorption

Drug Disposition in Kidney Disease

Therapeutics in Kidney Disease
Challenges, Innovations, Opportunities

Supplement to
The Journal of Clinical Pharmacology
January 2012 – Volume 52 – Suppl. 1
GOALS Of Effects of Renal Disease on PK Lecture

- **DOSE ADJUSTMENT** in Patients with Renal Impairment

  Statement of the Problem

  How is renal function assessed?

  How is drug dose adjusted based on this assessment?

PATHOPHYSIOLOGIC FACTORS

*NOT ACCOUNTED FOR IN DRUG DOSING*®

* Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.
Central Role of **DRUG LABEL**

The **DRUG LABEL** is the primary source of drug prescribing information and is reviewed by the FDA as part of the drug approval process. As such the drug label is *a distillate of the entire drug development process.*

**INFORMATION CONTENT OF CURRENT DRUG LABELS*  

<table>
<thead>
<tr>
<th>CORE INFORMATION CATEGORY</th>
<th>Inclusion of Desirable Data Elements</th>
<th>MEAN (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM OF ACTION</strong></td>
<td>88% (84% - 93%)</td>
<td></td>
</tr>
<tr>
<td><strong>PHARMACODYNAMICS</strong></td>
<td>43% (37% - 49%)</td>
<td></td>
</tr>
<tr>
<td><strong>DRUG METABOLISM</strong></td>
<td>23% (16% - 29%)</td>
<td></td>
</tr>
<tr>
<td><strong>PHARMACOKINETICS</strong></td>
<td>42% (35% - 49%)</td>
<td></td>
</tr>
<tr>
<td><strong>DOSE ADJUSTMENT</strong></td>
<td>37% (32% - 42%)</td>
<td></td>
</tr>
</tbody>
</table>


**FDA GUIDANCE FOR INDUSTRY**


AVAILABLE AT:  
http://www.fda.gov/cder/guidance/index.htm
GOALS of Renal Disease Effects Lecture

- **DOSE ADJUSTMENT** in Patients with Renal Impairment
  - Statement of the Problem
  - How is renal function assessed?
  - How is drug dose adjusted based on this assessment?

ELIMINATION by Different Routes

<table>
<thead>
<tr>
<th>MEASUREMENTS</th>
<th>RENAL</th>
<th>HEPATIC</th>
<th>DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Flow</td>
<td>+*</td>
<td>+*</td>
<td>+</td>
</tr>
<tr>
<td>Afferent Conc.</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Efferent Conc.</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Eliminated Drug</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

*not actually measured in routine PK studies

RENAL CLEARANCE EQUATION

\[
CL = \frac{U \times V}{P}
\]

U = URINE CONCENTRATION
V = URINE VOLUME / TIME
P = PLASMA CONCENTRATION
CLEARANCE TECHNIQUES FOR ASSESSING RENAL FUNCTION

GLOMERULAR FILTRATION:
Normal: 120 – 130 mL/min/1.73 m²

CLEARANCE MARKERS:
Inulin
Creatinine
125I-Iothalamate

RENAL BLOOD FLOW:
Normal: 1,209 256 mL/min/1.73 m²
982 184 mL/min/1.73 m²

CLEARANCE MARKER:
Para-Aminohippuric Acid

GOALS of Renal Disease Effects Lecture
- How is renal function assessed?

In adults with stable renal function, estimated from the Cockcroft and Gault equation for creatinine clearance, or the Modification of Diet in Renal Disease (MDRD) Study equation for estimating GFR.

Assessment of Renal Function
- Cockcroft-Gault equation:
- Creatinine Clearance: ml/min

- MDRD Study equation:
  - eGFR: ml/min/1.73 meter square*

  *Numeric value for GFR<60 ml/min/m2
**COCKCROFT & GAULT EQUATION**

\[
\text{CL}_{\text{Cr}} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times (\text{serum Cr in mg/dL})}
\]

[reduce estimate by 15% for women]


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**Estimation of GFR**

- The MDRD equation* estimates GFR from serum creatinine and is more accurate compared to the (125I)-iothalamate standard.
- Based on CKD population, using standardized creatinine assays* (traceable to IDMS reference measurement) that reduce variability between laboratories.
- However, it tends to underestimate high GFRs and may also overestimate low GFRs.

*MDRD 4 parameter equation
Estimation of GFR

- The CKD-Epidemiology Collaboration proposed a new equation: **CKD-EPI** (same variables as the 4 parameter MDRD).
- Accurate at GFR > 60 ml/min/1.73m²
- Normal and CKD subject population


GFR Estimating Equations

Stevens LA, et al.
Advances in GFR-estimating equations
*Curr Opin Nephrol Hypertens* 2010;19:298-307

Schwartz GJ, et al.
New equations to estimate GFR in children with CKD

Renal Clearance of Drugs

- Generally, there is a linear correlation between the clearance of creatinine and the clearance of drugs excreted via the kidneys.
- We take advantage of this correlation when making dose adjustments in patients with impaired renal function.
**STEADY STATE CONCENTRATION**

Continuous Infusion:

\[ C_{ss} = \frac{I}{CL_E} \]

Intermittent Dosing:

\[ \bar{C}_{ss} = \frac{DOSE}{\tau CL_E} \]

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**ADDITIVITY OF CLEARANCES**

\[ CL_E = CL_R + CL_{NR} \]

\( CL_R = \) RENAL CLEARANCE  
\( CL_{NR} = \) NON-RENAL CLEARANCE

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**Professor Luzius Dettli**


Focus: Nephro-pharmacology
**DETTLI Approach**

\[ \text{CL}_R = \alpha \text{CL}_\text{Cr} \]

\[ \text{CL}_E = \text{CL}_R + \text{CL}_\text{NR} \]

*From: Dettli L. Med Clin North Am 1974;58:977-85

**NOMOGRAM FOR CIMETIDINE DOSING**


**Key ASSUMPTIONS of Dettli Method**

- \( \text{CL}_\text{NR} \) remains **CONSTANT** when renal function is impaired.
- \( \text{CL}_R \) declines in **LINEAR FASHION** with \( \text{CL}_\text{CR} \)
  
  - **Intact Nephron** Hypothesis
  - Some drugs ↓ SECRETION > GFR with aging*

A 67-year-old veteran had been functionally anephric, requiring outpatient hemodialysis for several years. He was hospitalized for revision of his arteriovenous shunt and postoperatively complained of symptoms of gastroesophageal reflux. This complaint prompted institution of cimetidine therapy in a dose of 300 mg every 6 hours.

Rationale for Prescribed Cimetidine Dose:

At that time, 600 mg every 6 hours was the usual cimetidine dose for patients with normal renal function and the Physician’s Desk Reference recommended halving the cimetidine dose for patients “with creatinine clearance less than 30 cc/min”.

Three days later the patient was noted to be confused. The nephrology team reevaluated the patient and agreed to discontinue cimetidine as suggested by the attending internist/clinical pharmacologist. Two days later the patient was alert and was discharged from the hospital to resume outpatient hemodialysis therapy.
**LABELING FOR CIMETIDINE**

- **DOSAGE ADJUSTMENT**
  1/2 normal dose if $\text{CL}_\text{CR} < 30 \text{ mL/min}$

- **PHARMACOKINETICS**
  Following I.V. or I.M. administration in normal subjects,
  - ~ 75% of drug is recovered from the urine as parent compound.


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**NOMOGRAM FOR CIMETIDINE DOSING**


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**DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT**

\[ \bar{C}_{ss} = \frac{\text{DOSE}}{\tau} = \frac{\text{DOSE}}{\text{CL}_\text{E}} \]

- MAINTAIN USUAL DOSING INTERVAL BUT REDUCE DOSE IN PROPORTION TO $\frac{1}{\text{CL}_\text{E}}$
- MAINTAIN USUAL DOSE BUT INCREASE DOSING INTERVAL IN PROPORTION TO $\frac{1}{\text{CL}_\text{E}}$
- ADJUST BOTH DOSE AND DOSING INTERVAL
**GOALS of Renal Disease Effects Lecture**

- **EFFECT OF RENAL DISEASE ON RENAL DRUG ELIMINATION**
  - *MECHANISMS* of RENAL DRUG ELIMINATION
  - CONCEPT OF RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION

**MECHANISMS of Renal Drug Elimination**

- Glomerular Filtration
- Renal Tubular Secretion
- Reabsorption by Non-Ionic Diffusion
- Active Reabsorption

**MECHANISMS OF RENAL ELIMINATION**

**GLOMERULAR FILTRATION**

- Affects all drugs and metabolites of appropriate molecular size.
- *Influenced* by protein binding
  
  \[ \text{Drug Filtration Rate} = \text{GFR} \times f_u \times [\text{Drug}] \]
  
  \((f_u = \text{free fraction})\)

**RENAL TUBULAR SECRETION**

- *Not influenced* by protein binding
- May be affected by other drugs, etc.

**EXAMPLES:**

**Active Drugs:**
- ACIDS – Penicillin
- BASES – Procainamide

**Metabolites:**
- Glucuronides, Hippurates, etc.
RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION

RESTRICTIVE:
Clearance DEPENDS on Protein Binding.
KIDNEY: Drug Filtration Rate = \( f_u \cdot GFR \)
LIVER: \( CL = f_u \cdot CL_{int} \)

NONRESTRICTIVE:
Clearance INDEPENDENT of Protein Binding
KIDNEY: \( CL = Q \) (renal blood flow)

EXAMPLE: PARA-AMINOHIPPURATE CLEARANCE MEASURES RENAL BLOOD FLOW.

INTRINSIC CLEARANCE

INTRINSIC CLEARANCE IS THE ELIMINATION CLEARANCE THAT WOULD BE OBSERVED IN THE ABSENCE OF ANY PROTEIN BINDING RESTRICTIONS.

RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION

RESTRICTIVE:
Clearance DEPENDS on Protein Binding
KIDNEY: Drug Filtration Rate = \( f_u \cdot GFR \)
LIVER: \( CL = f_u \cdot CL_{int} \)

NONRESTRICTIVE:
Clearance INDEPENDENT of Protein Binding
KIDNEY: \( CL = Q \) (renal blood flow)
LIVER: \( CL = Q \) (hepatic blood flow)
Renal REABSORPTION Mechanisms

REABSORPTION BY NON-IONIC DIFFUSION

- Affects weak acids and weak bases.
- Only important if excretion of free drug is major elimination pathway.

EXAMPLES:
- Weak Acids: PHENOBARBITAL
- Weak Bases: QUINIDINE

ACTIVE REABSORPTION

- Affects ions, not proved for other drugs.

EXAMPLES:
- Halides: FLUORIDE, BROMIDE
- Alkaline Metals: LITHIUM

RENAL EXCRETION of DRUGS

INTACT NEPHRON HYPOTHESIS: Provides a basis for dose adjustment when renal excretion of drug is impaired.

- Regardless of mechanism, renal drug elimination declines in parallel with decreases in GFR.
- Therefore, $\text{CL}_{\text{cr}}$ can be used to assess impact of renal impairment on renal excretion of drugs.

WHAT ABOUT OTHER EXCRETION ROUTES?

GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON DRUG METABOLISM and TRANSPORT
CRF – Effects on Drug Metabolism and Transport

TD Nolin, J Naud, FA Leblond, V Pichette
Emerging Evidence of the Impact of Kidney Disease on Drug Metabolism and Transport

CRF – Effects on Drug Metabolism and Transport

AW Dreisbach
The influence of chronic renal failure on drug metabolism and transport.

Effect of CRF on Non-Renal Drug Clearance in Humans

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>CLNR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>-50</td>
</tr>
<tr>
<td>Morphine</td>
<td>-40</td>
</tr>
<tr>
<td>Procainamide</td>
<td>-60</td>
</tr>
<tr>
<td>Verapamil</td>
<td>-54</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>-66</td>
</tr>
<tr>
<td>Warfarin</td>
<td>-50</td>
</tr>
<tr>
<td>TPMT</td>
<td></td>
</tr>
<tr>
<td>UGT2B7</td>
<td></td>
</tr>
<tr>
<td>NAT-2</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td></td>
</tr>
</tbody>
</table>


Effect of CRF on Drug Transport

Impaired transport function in renal failure (intestine, liver, kidney)

- P-Glycoprotein
- Organic Anion Transporting Polypeptide (OATP)
  
  *Fexofenadine is a substrate for both*

Effect of CRF on Bioavailability

Studies in human subjects:

- Propranolol +300 % CYP2D6
- Erythromycin +100 % CYP3A4
- Propoxyphene +100 % CYP3A4
- Dydrocodeine +70 % CYP2D6

Effects of Uremic Toxins

- Indoxyl sulfate
- CMPF-propanoic acid
- Parathyroid hormone (PTH)
- Cytokines (chronic inflammation)

*Inhibition of drug metabolism and transport reversed by hemodialysis*
Effects of Hemodialysis

Advanced CRF:
Stage IV (GFR 15-29 ml/min)
Stage V (GFR 0-15 ml/min)

Hemodialysis may reverse the inhibition of drug metabolizing enzymes and transporters.

Phase I and Phase II Metabolic Reactions

GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON DRUG METABOLISM

- EXAMPLES:
  PROCAINAMIDE - Acetylation
  PHENYTOIN - Hydroxylation
**Procainamide Acetylation**

![Chemical Structure of Procainamide]

**Procainamide Kinetics in Dialysis Patients**

<table>
<thead>
<tr>
<th>Functionally Normal</th>
<th>Functionally Anephric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>(T_{1/2}) (hr)</td>
<td>2.6</td>
</tr>
<tr>
<td>(CL_E) (L/kg)</td>
<td>809</td>
</tr>
<tr>
<td>(CL_R) (L/kg)</td>
<td>426</td>
</tr>
<tr>
<td>(CL_NR) (L/kg)</td>
<td>383</td>
</tr>
<tr>
<td>(V_d(\text{ss})) (L/kg)</td>
<td>1.95</td>
</tr>
</tbody>
</table>


**Procainamide Dosing Nomogram**

![Procainamide Dosing Nomogram]

\[ CL_E = CL_R + CL_NR \]
NAPA ELIMINATION HALF LIFE IN FUNCTIONALLY ANEPRIC PATIENTS

• HEALTHY SUBJECTS: 6.2 hr
• PREDICTED for DIALYSIS PATIENTS: 42.8 hr *
• MEASURED in DIALYSIS PATIENTS: 41.9 hr *

* See Study Problem at end of Chapter 5.

PHENYTOIN HYDROXYLATION BY P450

CYP2C9: Major, CYP2C19: Minor

Effect of Renal Disease on PHENYTOIN PROTEIN BINDING
PHENYTOIN KINETICS IN DIALYSIS PATIENTS*

<table>
<thead>
<tr>
<th></th>
<th>NORMALS (N = 4)</th>
<th>UREMIC PATIENTS (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% UNBOUND (fu)</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>CL-\text{H}</td>
<td>2.46 L/hr</td>
<td>7.63 L/hr</td>
</tr>
<tr>
<td>CL-\text{int}</td>
<td>20.3 L/hr</td>
<td>29.9 L/hr             NS</td>
</tr>
</tbody>
</table>

\[ \text{CL-\text{H}} = f_u \cdot \text{CL-\text{int}} \quad \text{So: } \text{CL-\text{int}} = \frac{\text{CL-\text{H}}}{f_u} \]


---

Effect of \textit{PROTEIN BINDING Changes} on \textit{Phenytoin} Plasma Concentration

\[
\bar{C}_{\text{SS}} = \frac{\text{DOSE}/\tau}{\text{CL}_E}
\]

\[
\bar{C}_{\text{SS},u}/f_u = \frac{\text{DOSE}/\tau}{f_u \cdot \text{CL}_{\text{INT}}}
\]

\text{PHENYTOIN > 98\% ELIMINATED BY HEPATIC METABOLISM, SO } \text{CL}_E = \text{CL}_\text{H}

---

\text{FREE AND TOTAL PHENYTOIN LEVELS (DOSE = 300 MG/DAY)}

- Normal Renal Function
- Functionally Anephric

[Graph showing free and total phenytoin levels with normal and anephric conditions.]

---

20
**THERAPEUTIC RANGE of Phenytoin Levels in Dialysis Patients**

*RISK is that TOTAL levels below the usual range of 10 – 20 μg/mL will prompt inappropriate dose adjustment in dialysis patients.*

**THERAPEUTIC RANGE FOR DIALYSIS PTS:**
- Based on “Total Levels”: 5 - 10 μg/mL
- Based on “Free Levels”: 0.8 - 1.6 μg/mL

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**GOALS of Renal Disease Effects Lecture**

• **EFFECT OF RENAL DISEASE ON DRUG DISTRIBUTION**
  - **PLASMA PROTEIN BINDING**
    - *EXAMPLE*: PHENYTOIN
  - **TISSUE BINDING**
    - *EXAMPLE*: DIGOXIN

---

**Effect of Renal Disease on BINDING TO PLASMA PROTEINS***

<table>
<thead>
<tr>
<th>BASIC OR NEUTRAL DRUGS</th>
<th>NORMAL OR SLIGHTLY REDUCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACIDIC DRUGS</td>
<td>REDUCED FOR MOST</td>
</tr>
</tbody>
</table>

Effect of Binding Changes on
APPARENT DISTRIBUTION VOLUME*

\[ V_d = ECF + \phi f_u (BW - ECF) \]

\[ \Phi = \text{TISSUE/PLASMA PARTITION RATIO} \]
\[ f_u = \text{FRACTION NOT BOUND TO PLASMA PROTEINS} \]

FOR PHENYTOIN: \( \Phi = 10.4 \)


PHENYTOIN DISTRIBUTION
IN DIALYSIS PATIENTS*

<table>
<thead>
<tr>
<th></th>
<th>NORMALS</th>
<th>UREMIC PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>% UNBOUND ( f_u )</td>
<td>12% (^†)</td>
<td>26%</td>
</tr>
<tr>
<td>( V_d \text{(AREA)} )</td>
<td>0.64 L/kg</td>
<td>1.40 L/kg</td>
</tr>
</tbody>
</table>

\(^†\) USUAL VALUE IN NORMAL SUBJECTS ~ 9%


GOALS OF RENAL DISEASE EFFECTS LECTURE

• EFFECT OF RENAL DISEASE ON DRUG DISTRIBUTION
  - PLASMA PROTEIN BINDING
    
    EXAMPLE: PHENYTOIN
  - TISSUE BINDING
    
    EXAMPLE: DIGOXIN
IMPAIRED RENAL FUNCTION REDUCES DIGOXIN DISTRIBUTION VOLUME*

\[ V_d = 3.84 \cdot \text{wt (kg)} + 3.12 \cdot \text{CL}_{\text{Cr}} \text{(mL/min)} \]


CRITERIA FOR NORMAL ABSORPTION OF 25 GRAM D-XYLOSE DOSE

- 5-hr URINE RECOVERY > 4 g
- [SERUM] 1 hr AFTER DOSE ≥ 0.2 mg/mL
- % DOSE ABSORBED > 42%
- \( k_a \) > 0.37 hr\(^{-1}\)

EFFECT OF RENAL DISEASE ON D-XYLOSE ABSORPTION*

<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>( k_a ) (hr(^{-1}))</th>
<th>( k_o ) (hr(^{-1}))</th>
<th>% DOSE ABSORBED</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMALS</td>
<td>1.03 ± 0.33</td>
<td>0.49 ± 0.35</td>
<td>69.4 ± 13.6</td>
</tr>
<tr>
<td>MODERATE</td>
<td>0.64 ± 0.28</td>
<td>0.19 ± 0.15</td>
<td>77.4 ± 14.8</td>
</tr>
<tr>
<td>DIALYSIS</td>
<td>0.56 ± 0.42</td>
<td>0.67 ± 0.61</td>
<td>48.6 ± 13.3</td>
</tr>
</tbody>
</table>

**FUROSEMIDE**

![Chemical Structure of Furosemide]

**BIOPHARMACEUTIC CLASSIFICATION OF FUROSEMIDE**


**BIOPHARMACEUTIC DRUG CLASSIFICATION OF FUROSEMIDE**

**CLASS IV:**
- **LOW SOLUBILITY-LOW PERMEABILITY**
  - *in vitro – in vivo* correlation poor
  - good bioavailability not expected

**Biopharmaceuticals Classification System (BCS)**

- Class I (high S, high P)
  *Enzyme effects* predominate
- Class II (low S, high P)
  *Both enzymes and transporters*
- Class III (high S, low P)
  *Transporter effects* predominate


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**FDA GUIDANCE FOR INDUSTRY**

*PHARMACOKINETICS IN PATIENTS WITH IMPAIRED RENAL FUNCTION* – Study Design, Data Analysis, and Impact on Dosing and Labeling (1998)

AVAILABLE AT:
http://www.fda.gov/cder/guidance/index.htm

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**BASIC “FULL” STUDY DESIGN**
A revision of this guidance document is currently under way (initiated in 2008).

A concept paper/draft guidance has been posted by the FDA regarding revised recommendations for PK studies in patients with impaired renal function. (March 2010-Revision 1)

US FDA Perspective:
S-M Huang, R Temple, S Xiao, L Zhang, LJ Lesko