Effects of Renal Disease on Pharmacokinetics

Juan J. L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program
October 17, 2013

Office of Clinical Research Training
and Medical Education
National Institutes of Health
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.*
<table>
<thead>
<tr>
<th>CORE INFORMATION CATEGORY</th>
<th>Inclusion of Desirable Data Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (95% CI)</td>
</tr>
<tr>
<td><strong>MECHANISM OF ACTION</strong></td>
<td>88% (84% - 93%)</td>
</tr>
<tr>
<td><strong>PHARMACODYNAMICS</strong></td>
<td>43% (37% - 49%)</td>
</tr>
<tr>
<td><strong>DRUG METABOLISM</strong></td>
<td>23% (16% - 29%)</td>
</tr>
<tr>
<td><strong>PHARMACOKINETICS</strong></td>
<td>42% (35% - 49%)</td>
</tr>
<tr>
<td><strong>DOSE ADJUSTMENT</strong></td>
<td>37% (32% - 42%)</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 Concentration</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Efferent Concentration</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
\(^{125}\)I-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
\[ \text{CL}_{\text{Cr}} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum Cr in mg/dL}} \]

[reduce estimate by 15% for women]

COCKCROFT & GAULT EQUATION

\[
CL_{Cr} = \frac{I}{P}
\]

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

[reduce estimate by 15% for women]

Terms in red estimate creatinine synthesis rate.
Estimation of GFR

- The **MDRD equation** estimates GFR from serum creatinine and is *more accurate* compared to the (125)I-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 overestimates low GFRs.

*MDRD 4 parameter equation


Lalonde RL, Wagner JA. *Clin Pharmacol Ther 2009;86:557-561*
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

Levey *et al.* *Ann Intern Med* 2009;150:604-12
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:**

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

Focus: Nephro-pharmacology
ADDITIVITY OF CLEARANCES

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

\( \text{CL}_R = \text{RENA L CLEARANCE} \)

\( \text{CL}_{NR} = \text{NON-RENA L CLEARANCE} \)
DETTLI Approach*

\[
CL_R = \alpha CL_{Cr}
\]

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

* Dettli L. Med Clin North Am 1974;58:977-85
NOMOGRAM FOR CIMETIDINE DOSING*

Key ASSUMPTIONS of Dettli Method

- $CL_{NR}$ remains CONSTANT when renal function is impaired.
- $CL_{R}$ declines in LINEAR FASHION with $CL_{CR}$
  - 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 CL_{Cr} < 30 mL/min

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

NOMOGRAM FOR CIMETIDINE DOSING*

DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT

\[ \bar{C}_{ss} = \frac{\text{DOSE}}{\tau} \frac{1}{\text{CL}_E} \]

• MAINTAIN USUAL DOSING INTERVAL BUT **REDUCE DOSE** IN PROPORTION TO \( \downarrow \text{CL}_E \)

• MAINTAIN USUAL DOSE BUT **INCREASE DOSING INTERVAL** IN PROPORTION TO \( \downarrow \text{CL}_E \)

• **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 = $f_U \times GFR$

**LIVER**: $CL = f_U \times C_{l_{int}}$

NONRESTRICTIVE:
Clearance *INDEPENDENT* of Protein Binding

**KIDNEY**: $CL = Q$ (renal blood flow)

*EXAMPLE*: PARA-AMINOhippurate Clearance Measures Renal Blood Flow.
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:** \( CL = f_U \) \( \cdot \) \( C_{l_{int}} \)

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, $CL_{Cr}$ 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.

*Clin. Pharmacol. Ther. 2009;86:553-556*
### Effect of CRF on Non-Renal Drug Clearance in Humans

<table>
<thead>
<tr>
<th>Drug</th>
<th>CL\textsubscript{NR} (%)</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>-50</td>
<td>TPMT</td>
</tr>
<tr>
<td>Morphine</td>
<td>-40</td>
<td>UGT2B7</td>
</tr>
<tr>
<td>Procainamide</td>
<td>-60</td>
<td>NAT-2</td>
</tr>
<tr>
<td>Verapamil</td>
<td>-54</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>-66</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Warfarin</td>
<td>-50</td>
<td>CYP2C9</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
- Dyhydrocodeine +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

PHASE I

HYDROXYLATION

PHASE II

GLUCURONIDE CONJUGATION

$\text{PHENYTOIN}$

$\text{PHENYTOIN}$

$p$ - HPPH

GLUCURONIDE

$p$ - HPPH

GLUCURONIDE
GOALS of Renal Disease Effects Lecture

• EFFECT OF RENAL DISEASE ON DRUG METABOLISM

• EXAMPLES:
  PROCAINAMIDE - Acetylation
  PHENYTOIN - Hydroxylation
PROCAINAMIDE ACETYLATION

NAT2: FAST VS. SLOW

RENAL ELIMINATION
NORMALLY 50%

N-ACETYLPROCAINAMIDE (NAPA)
**Procainamide Kinetics in DIALYSIS PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>NORMALS</th>
<th>FUNCTIONALLY ANEPRHIC PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>2.6</td>
<td>3.5</td>
</tr>
<tr>
<td>$CL_E$ (L/kg)</td>
<td>809</td>
<td>600</td>
</tr>
<tr>
<td>$CL_R$ (L/kg)</td>
<td>426</td>
<td>357</td>
</tr>
<tr>
<td>$CL_{NR}$ (L/kg)</td>
<td>383</td>
<td>243</td>
</tr>
<tr>
<td>$V_{d(ss)}$ (L/kg)</td>
<td>1.95</td>
<td>1.93</td>
</tr>
</tbody>
</table>

Procainamide Dosing Nomogram

(FAST ACETYLATORS)

\[ \text{CL}_F = \text{CL}_R + \text{CL}_{NR} \]
### NAPA Elimination Half Life in Functionally Anephric Patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Subjects</td>
<td>6.2 hr</td>
</tr>
<tr>
<td>Predicted for Dialysis Patients</td>
<td>42.8 hr</td>
</tr>
<tr>
<td>Measured in Dialysis Patients</td>
<td>41.9 hr</td>
</tr>
</tbody>
</table>

* See Study Problem at end of Chapter 5.
PHENYTOIN *HYDROXYLATION* BY P450

CYP2C9: Major, CYP2C19: Minor
Effect of Renal Disease on **PHENYTOIN PROTEIN BINDING**

![Graph showing effect of renal disease on phenytoin protein binding](image)
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 (f_u)</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>CL_H</td>
<td>2.46 L/hr</td>
<td>7.63 L/hr</td>
</tr>
<tr>
<td>CL_int</td>
<td>20.3 L/hr</td>
<td>29.9 L/hr NS</td>
</tr>
</tbody>
</table>

\[ \text{CL}_H = f_u \cdot \text{CL}_{\text{int}}, \quad \text{So: CL}_{\text{int}} = \frac{\text{CL}_H}{f_u} \]

Effect of *PROTEIN BINDING* Changes on **Phenytoin** Plasma Concentration

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

**PHENYTOIN > 98% ELIMINATED BY HEPATIC METABOLISM, SO** \( CL_E = CL_H \)

\[ \overline{C}_{ss,u} / f_u = \frac{DOSE / \tau}{f_u \cdot CL_{INT}} \]
FREE AND TOTAL PHENYTOIN LEVELS (DOSE = 300 MG/DAY)
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
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**

*BASIC OR NEUTRAL DRUGS:* NORMAL OR SLIGHTLY REDUCED

*ACIDIC DRUGS:* REDUCED FOR MOST

Effect of Binding Changes on APPARENT DISTRIBUTION VOLUME*

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

\( \Phi = \text{TISSUE/PLASMA PARTITION RATIO} \)

\( f_u = \text{FRACTION NOT BOUND TO PLASMA PROTEINS} \)

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\textsubscript{u})</td>
<td>12% †</td>
<td>26%</td>
</tr>
<tr>
<td>V\textsubscript{d(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*

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

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

\[
\begin{align*}
\text{COOH} & \quad \text{NH-CH}_2-\text{CH}_2-\text{SO}_2-\text{NH} \\
\text{NH}_2\text{SO}_2 & \quad \text{Cl}
\end{align*}
\]
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

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
BASIC "FULL" STUDY DESIGN

Elimination Clearance (mL/min)

CL_{CR} (mL/min)

ESRD

SEVERE

MOD

MILD

NORMAL

RENAL CLEARANCE

NONRENAAL CLEARANCE
FDA GUIDANCE FOR INDUSTRY

• 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