Effects of Renal Disease on Pharmacokinetics
October 15, 2009

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

'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
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*

Pie chart showing Advanced age (42%), Renal impairment (33%), Patient Weight (19%), and Other (6%).

*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>

Chart showing that as of year 2000 desirable data on drug metabolism, pharmacokinetics and dose adjustment were included in only 23%, 42%, and 37% of drug labels, respectively.

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
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

Clearance is urinary excretion rate divided by 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:
    male  1,209 ± 256 mL/min/1.73 m2
    female  982 ± 184 mL/min/1.73 m2

  CLEARANCE MARKER:
    Para-Aminohippuric Acid
GOALS of Renal Disease Effects Lecture

How is renal function assessed?
Commonly estimated from the Cockcroft and Gault equation for creatinine clearance if renal function is stable, but the Modification of Diet in Renal Disease (MDRD) Study equation for estimating GFR has been used also.
Estimation of GFR

- The MDRD equation to estimate GFR from serum creatinine is the most accurate compared to the (125)I-iothalamate standard.

- However, it is biased and tends to underestimate high GFRs and also overestimates low GFRs.


http://www.nkdep.nih.gov/profesionals/gfr_calculators/idms_con.htm
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

Equations for Continuous Infusion and Intermittent Dosing.

The steady-state concentration is directly related to dosing rate and inversely related to elimination clearance.
Photograph of Professor Luzius Dettli holding a microphone and standing in front of a chalkboard.
ADDITIVITY OF CLEARANCES

Formula showing that total elimination clearance equals the sum of renal and nonrenal clearances.
DETTLI Approach

Formulas indicating that renal clearance of drugs is proportional to creatinine clearance.

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

Chart showing elimination clearance as the sum of nonrenal clearance and renal clearance for cimetidine.

Renal clearance varies as a function of creatinine clearance.
Key *ASSUMPTIONS* of Dettli Method

- CLNR remains *CONSTANT* when renal function is impaired.
- CLR declines in *LINEAR FASHION* with CLCR

*Intact Nephron* Hypothesis
- Some drugs ↓ *SECRETION* > *GFR* with aging*

CIMETIDINE Case History

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.
CIMETIDINE Case History (cont.)

*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”.*
CIMETIDINE Case History (cont.)

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 CLCr < 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***

Chart showing that $\text{CLE} \approx 25\% \text{ OF NORMAL IF FUNCTIONALLY ANEPRHIC}$

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

Formula for steady-state concentration with intermittent dosing.

- MAINTAIN USUAL DOSING INTERVAL BUT *REDUCE DOSE IN PROPORTION TO ↓CLE*

- MAINTAIN USUAL DOSE BUT *INCREASE DOSING INTERVAL IN PROPORTION TO ↓CLE*

- *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
  Drug Filtration Rate = GFR x fu x [Drug]
  (fu = 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 = fU x GFR
**LIVER:** CL = fU x Clint

**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 = fU x GFR
LIVER: CL = fU x Clint

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, CLCr 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

Recent Reviews on this topic:

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

Recent Reviews on this topic:

AW Dreisbach, JKL Lertora
The effect of chronic renal failure on drug metabolism and transport

*Expert Opin. Drug Metab. Toxicol.*
2008;4:1065-1074
## 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:

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Change</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>+300 %</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>+100 %</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>+100 %</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Dydrocodeine</td>
<td>+70 %</td>
<td>CYP2D6</td>
</tr>
</tbody>
</table>
Effects of Uremic Toxins

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

Inhibition of drug metabolism and transport reversed by hemodialysis
**PHASE I AND PHASE II METABOLIC REACTIONS**

Chemical structures of Phenytoin Phase I hydroxylation and Phase II Glucuronide Conjugation.
GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON DRUG METABOLISM

- EXAMPLES:
  PROCAINAMIDE - Acetylation
  PHENYTOIN - Hydroxylation
PROCAINAMIDE ACETYLATION

Chemical structure of procainamide acetylation to NAPA.
Procainamide Kinetics in

*FUNCTIONALLY NORMALS

<table>
<thead>
<tr>
<th>Functionally Normal</th>
<th>Fast</th>
<th>Slow</th>
<th>Functionally Anephric</th>
<th>Fast</th>
<th>Slow</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 (hr)</td>
<td>2.6</td>
<td>3.5</td>
<td>12.2</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>CLE (L/kg)</td>
<td>809</td>
<td>600</td>
<td>118</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>CLR (L/kg)</td>
<td>426</td>
<td>357</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CLNR (L/kg)</td>
<td>383</td>
<td>243</td>
<td>118</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Vd(ss) (L/kg)</td>
<td>1.95</td>
<td>1.93</td>
<td>1.41</td>
<td>1.93</td>
<td></td>
</tr>
</tbody>
</table>

Procainamide Dosing Nomogram

*FAST ACETYLATORS*

Chart showing PA renal and nonrenal clearance (mL/min) with increasing levels of Clcr[mL/min]
NAPA ELIMINATION HALF LIFE IN
FUNCTIONALLY ANEPHRIC 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

Chemical structure of phenytoin hydroxylation

CYP2C9: Major, CYP2C19: Minor
Effect of Renal Disease on

PHENYTOIN PROTEIN BINDING

Chart showing increasing % of unbound DPH with increasing serum Creatinine (mg/100 ml).
PHENYTOIN

KINETICS IN DIALYSIS PATIENTS*

<table>
<thead>
<tr>
<th></th>
<th>NORMALS</th>
<th>UREMIC PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 4)</td>
<td>(N = 4)</td>
</tr>
<tr>
<td>% UNBOUND (fu)</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>CLH</td>
<td>2.46 L/hr</td>
<td>7.63 L/hr</td>
</tr>
<tr>
<td>CLint</td>
<td>20.3 L/hr</td>
<td>29.9 L/hr</td>
</tr>
</tbody>
</table>

Formulas for intrinsic clearance

Effect of PROTEIN BINDING Changes on Phenytoin Plasma Concentration

Formula

PHENYTOIN > 98% ELIMINATED BY HEPATIC METABOLISM, SO CLE = CLh

Formula
FREE AND TOTAL PHENYTOIN LEVELS
(DOSE = 300 MG/DAY)

Chart illustrating these levels.

The free fraction of phenytoin is increased but the free drug concentration is the same in functionally anephric patients.
**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

- ISSUE 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*

Formula to estimate phenytoin VD

PHENYTOIN *DISTRIBUTION IN DIALYSIS PATIENTS*

<table>
<thead>
<tr>
<th></th>
<th>NORMALS</th>
<th>UREMIC PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>% UNBOUND (fu)</td>
<td>12%†</td>
<td>26%</td>
</tr>
<tr>
<td>Vd(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*

Formula to estimate digoxin VD as a function of creatinine clearance.

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%

ka                          > 0.37 hr⁻¹
EFFECT OF RENAL DISEASE 
ON D-XYLOSE ABSORPTION*

Chart comparing normals, moderates and dialysis patients showing the % of dose absorbed for each group. Absorption is impaired in dialysis patients.

FUROSEMIDE

Chemical structure of Furosemide, a loop diuretic.
BIOPHARMACEUTIC CLASSIFICATION
OF FUROSEMIDE*

Chart illustrating that furosemide has low permeability for intestinal absorption.

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

AVAILABLE AT: http://www.fda.gov/cder/guidance/index.htm
BASIC “FULL” STUDY DESIGN

Chart showing reductions in creatinine clearance with increasing severity of renal disease.
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
FDA GUIDANCE FOR INDUSTRY

- A revision of this guidance document is currently under way (2008).
- A concept paper/draft guidance has been posted by the FDA regarding revised recommendations for PK studies in patients with impaired renal function.

(document pages 57-73)