Effects of Renal Disease on Pharmacokinetics

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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

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Pharmacokinetics in Renal Disease

Dose Adjustments 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.*

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**INFORMATION CONTENT OF DRUG LABELS***

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


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“Renal Dosing” Data in NDAs

- FDA survey of NDAs (2003-2007)
  57% of NDAs included data from studies in patients with *renal impairment.*
  44% of those with renal data included *hemodialysis* information.
  41% of those with renal data included *dose adjustment* recommendations.

Pharmacokinetics in Renal Disease

- **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?

**RENAL CLEARANCE EQUATION**

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

U = URINE CONCENTRATION
V = URINE VOLUME / TIME
P = PLASMA CONCENTRATION
COCKCROFT & GAULT EQUATION

\[
\text{CL}_{\text{Cr}} = \frac{(140 - \text{age})(\text{weight in kg})}{72 (\text{serum Cr in mg/dL})} \\
\text{[reduce estimate by 15% for women]}
\]

Terms in red estimate creatinine synthesis rate.


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
Pharmacokinetics in Renal Disease

• 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 f_u x [Drug]
    (f_u = 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:** $CL = f_u \times CL_{int}$

**NONRESTRICTIVE:**
Clearance *INDEPENDENT* of Protein Binding

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

EXAMPLE: PARA-AMINOHIPPURATE CLEARANCE MEASURES RENAL BLOOD FLOW.

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**INTRINSIC CLEARANCE**

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

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**RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION**

**RESTRICTIVE:**
Clearance *DEPENDS* on Protein Binding

**KIDNEY:** Drug Filtration Rate = $f_u \times GFR$

**LIVER:** $CL = f_u \times CL_{int}$

**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

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

Assessment of Renal Function

*In adults with stable renal function:*
Cockcroft and Gault equation *(estimates creatinine clearance).*
Modification of Diet in Renal Disease (MDRD) Study equation *(estimates GFR).*
CKD-Epidemiology Collaboration Equation *(estimates 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

Estimation of GFR - MDRD

• The MDRD equation* estimates GFR from serum creatinine and is more accurate in reference to the (125)-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

Estimation of GFR–CKD-EPI

• 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

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**

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

\[ \text{CL}_R = \text{RENAL CLEARANCE} \]
\[ \text{CL}_{NR} = \text{NON-RENAL CLEARANCE} \]

**Dettli Approach**

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

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

**NOMOGRAM for CIMETIDINE DOSING**

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?

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*


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 ml/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*


DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT

\[ \bar{C}_{SS} = \frac{DOSE}{\tau} \frac{CL_{E}}{CL_{E}} \]

- MAINTAIN USUAL DOSING INTERVAL BUT REDUCE DOSE IN PROPORTION TO \( \frac{CL_{E}}{CL_{E}} \)
- MAINTAIN USUAL DOSE BUT INCREASE DOSING INTERVAL IN PROPORTION TO \( \frac{CL_{E}}{CL_{E}} \)
- ADJUST BOTH DOSE AND DOSING INTERVAL

Pharmacokinetics in Renal Disease

- 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.

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**PHASE I AND PHASE II METABOLIC REACTIONS**

*PHASE I*

- HYDROXYLATION

*PHASE II*

- GLUCURONIDE CONJUGATION

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**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 70%

N-Acetylprocainamide (NAPA)

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**Procainamide Kinetics in Dialysis Patients**

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Functionally Anephric 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>


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**Procainamide Dosing Nomogram (Fast Acetylators)**

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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

PHENYTOIN  \( \rightarrow \)  \( p \)-HPPH

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 ($f_u$)</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>

$CL_H = f_u \cdot CL_{int}$, So: $CL_{int} = CL_H/f_u$


Effect of PROTEIN BINDING Changes on Phenytoin Plasma Concentration

$$\bar{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

PHENYTOIN > 98% ELIMINATED BY HEPATIC METABOLISM, SO $CL_E = CL_H$

$$\bar{C}_{SS, f_u} = \frac{DOSE/\tau}{f_u \cdot CL_{int}}$$

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

- BOUND [PHENYTOIN]
- FREE [PHENYTOIN]
**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*

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

**Φ** = TISSUE/PLASMA PARTITION RATIO  
**f_u** = FRACTION NOT BOUND TO PLASMA PROTEINS

FOR PHENYTOIN: \( \Phi = 10.4 \)


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**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% ( ^\dagger )</td>
<td>26% ( ^\dagger )</td>
</tr>
<tr>
<td>( V_d ) (AREA)</td>
<td>0.64 L/kg</td>
<td>1.40 L/kg</td>
</tr>
</tbody>
</table>

\( ^\dagger \) Usual Value in Normal Subjects ~ 9%


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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
**IMPAIRED RENAL FUNCTION REDUCES DIGOXIN DISTRIBUTION VOLUME**

\[ V_d = 3.84 \times wt\ (kg) + 3.12 \times CL_{cr}\ (mL/min) \]


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**CRITERIA FOR NORMAL ABSORPTION OF 25 GRAM D-XYLOSE DOSE**

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

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**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>

BIOPHARMACEUTIC CLASSIFICATION of FUROSEMIDE


BIOPHARMACEUTIC 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
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