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

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.

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**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 CURRENT DRUG LABELS**

<table>
<thead>
<tr>
<th>CORE INFORMATION CATEGORY</th>
<th>Inclusion of Desirable Data Elements MEAN (95% CI)</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>

**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*
**RENAI 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 mL/min/1.73 m²
- 256 mL/min/1.73 m²
- 982 mL/min/1.73 m²
- 184 mL/min/1.73 m²

**CLEARANCE MARKER:**
- Para-Aminohippuric Acid

**GOALS of Renal Disease Effects Lecture**

- How is renal function assessed?

*If renal function is stable*, commonly estimated from the *Cockcroft and Gault equation* for creatinine clearance, or the *Modification of Diet in Renal Disease (MDRD) Study equation* for estimating GFR.
**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 tends to underestimate high GFRs and also overestimates low GFRs.
- Not validated in the elderly population


**Assessment of Renal Function**

- Cockcroft-Gault equation:
  - Creatinine Clearance: ml/min

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

**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:**

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

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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**

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

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

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

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**NOMOGRAM FOR CIMETIDINE DOSING**


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**Key ASSUMPTIONS of Dettli Method**

- CL\text{NR} remains \textit{CONSTANT} when renal function is impaired.
- CL\text{R} declines in \textit{LINEAR FASHION} with CL\text{CR}
  - \textit{Intact Nephron} Hypothesis
  - Some drugs ↓ \textit{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.

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 pharmacist. 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\(_E\) < 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.


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**NOMOGRAM FOR CIMETIDINE DOSING**

![NOMOGRAM FOR CIMETIDINE DOSING](image)


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**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 \(1/\text{CL}_E\)
- MAINTAIN USUAL DOSE BUT INCREASE DOSING INTERVAL in proportion to \(1/\text{CL}_E\)
- 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
    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 - Procaïnamide
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

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**RENA L 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?**

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**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

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>CLNR (%)</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**
**GOALS of Renal Disease Effects Lecture**

- **EFFECT OF RENAL DISEASE ON DRUG METABOLISM**

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

**PROCAINAMIDE ACETYLATION**
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>$V_{d(0)}$ (L/kg)</td>
<td>1.95</td>
<td>1.93</td>
</tr>
</tbody>
</table>


Procainamide Dosing Nomogram
(FAST ACETYLATORS)

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 → p-HPPH

CYP2C9: Major, CYP2C19: Minor

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**Effect of Renal Disease on PHENYTOIN PROTEIN BINDING**

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**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>$Cl_{ul}$</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</td>
</tr>
</tbody>
</table>

$Cl_{ul} = f_u \cdot Cl_{int}$, So: $Cl_{int} = Cl_{ul}/f_u$

Effect of PROTEIN BINDING Changes on Phenytoin Plasma Concentration

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

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

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

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 NORMAL OR NORMAL OR DRUGS: SLIGHTLY REDUCED

ACIDIC DRUGS: REDUCED FOR MOST


Effect of Binding Changes on APPARENT DISTRIBUTION VOLUME*

\[ V_d = ECF + \phi_f u TBW - ECF \]

\[ \Phi = \text{TISSUE/PLASMA PARTITION RATIO} \]

\[ u = \text{FRACTION NOT Bound TO PLASMA PROTEINS} \]

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 (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*

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

**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_s**: > 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>


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**FUROSEMIDE**

![Furosemide Structure](image)
**Biopharmaceutical Classification of Furosemide**

In vitro – in vivo correlation poor
- good bioavailability not expected


**Biopharmaceutical Drug Classification of Furosemide**

CLASS IV:
LOW SOLUBILITY-LOW PERMEABILITY


**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

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**BASIC “FULL” STUDY DESIGN**

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**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 (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.

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