

# **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\***

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\****

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

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.

**\* Spyker DA, et al. Clin Pharmacol Ther 2000;67:196-200.**

# ***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**

<b>MEASUREMENTS</b>	<b>RENAL</b>	<b>HEPATIC</b>	<b>DIALYSIS</b>
<b>Blood Flow</b>	+*	+*	+
<b>Afferent Concentration</b>	+	+	+
<b>Efferent Concentration</b>	<b>0</b>	<b>0</b>	+
<b>Eliminated Drug</b>	+	<b>0</b>	+

*\*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 m<sup>2</sup>

#### ***CLEARANCE MARKERS:***

**Inulin**

**Creatinine**

**125I-Iothalamate**

### **RENAL BLOOD FLOW:**

**Normal:** male 1,209 ± 256 mL/min/1.73 m<sup>2</sup>  
female 982 ± 184 mL/min/1.73 m<sup>2</sup>

#### ***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 if renal function is stable, but 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 is biased and tends to underestimate high GFRs and also overestimates low GFRs.**

**Levey AS et al. *Ann Intern Med.* 2006;145-247-254**

**[http://www.nkdep.nih.gov/professionals/gfr\\_calculators/idms\\_con.htm](http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_con.htm)**

# Assessment of Renal Function

- **Cockcroft-Gault equation:**
- **Creatine 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**

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.

# DETLI Approach \*

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

\* **Detli 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\*

\* Reidenberg MM, et al. Clin Pharmacol Ther 1980;28:732-5.

## **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*.**

**\* Physician's Desk Reference. 58th edition, 2004.**

## ***NOMOGRAM* FOR CIMETIDINE DOSING\***

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

**\*From: Atkinson AJ Jr, Craig RM. Therapy of peptic ulcer disease.**

## ***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 =  $GFR \times f_u \times [Drug]$   
( $f_u$  = 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 =  $fU \times GFR$

**LIVER:**  $CL = fU \times Cl_{int}$

### **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 =  $fU \times \text{GFR}$

**LIVER:**  $CL = fU \times \text{Clint}$

### **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**

***Clin. Pharmacol. Ther. 2008;83:898-903***

## CRF – Effects on Drug Metabolism and Transport

Recent Reviews on this topic:

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

	CL <sub>NR</sub> (%)	Enzyme
Captopril	- 50	TPMT
Morphine	- 40	UGT2B7
Procainamide	- 60	NAT-2
Verapamil	- 54	CYP3A4
Metoclopramide	- 66	CYP2D6
Warfarin	- 50	CYP2C9

## 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

## ***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 *DIALYSIS PATIENTS\**

	<i>NORMALS</i>		<i>FUNCTIONALLY ANEPHRIC PATIENTS</i>	
	Fast	Slow	Fast	Slow
<b>T1/2 (hr)</b>	<b>2.6</b>	<b>3.5</b>	<b>12.2</b>	<b>17.0</b>
<b>CLE (L/kg)</b>	<b>809</b>	<b>600</b>	<b>118</b>	<b>94</b>
<b>CLR (L/kg)</b>	<b>426</b>	<b>357</b>	<b>0</b>	<b>0</b>
<b>CLNR (L/kg)</b>	<b>383</b>	<b>243</b>	<b>118</b>	<b>94</b>
<b>Vd(ss) (L/kg)</b>	<b>1.95</b>	<b>1.93</b>	<b>1.41</b>	<b>1.93</b>

\* From: Gibson TP. *Kidney Int* 1977;12:422-9.

## **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**

<b>- HEALTHY SUBJECTS:</b>	<b>6.2 hr</b>
<b>- <i>PREDICTED</i> for DIALYSIS PATIENTS:</b>	<b>42.8 hr *</b>
<b>- <i>MEASURED</i> in DIALYSIS PATIENTS:</b>	<b>41.9 hr *</b>

\* 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\****

	<b>NORMALS</b>	<b>UREMIC PATIENTS</b>
	<b>(N = 4)</b>	<b>(N = 4)</b>
<b>% UNBOUND (fu)</b>	<b>12%</b>	<b>26%</b>
<b>CLH</b>	<b>2.46 L/hr</b>	<b>7.63 L/hr</b>
<b>CLint</b>	<b>20.3 L/hr</b>	<b>29.9 L/hr</b>

**Formulas for intrinsic clearance**

**\*From: Odar-Cederlöf I, Borgå O: Eur J Clin Pharmacol 1974;7:31-7.**

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

Formula

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

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\****

***BASIC OR NEUTRAL  
DRUGS:***

**NORMAL OR  
SLIGHTLY REDUCED**

***ACIDIC DRUGS:***

**REDUCED FOR MOST**

**\* From: Reidenberg MM, Drayer DE: Clin Pharmacokinet  
1984;9(Suppl. 1):18-26.**

## **Effect of Binding Changes on *APPARENT DISTRIBUTION VOLUME*\***

Formula to estimate phenytoin VD

**\* Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.**

## **PHENYTOIN *DISTRIBUTION* IN *DIALYSIS* PATIENTS\***

	<b>NORMALS</b>	<b>UREMIC PATIENTS</b>
<b>% UNBOUND (fu)</b>	<b>12%†</b>	<b>26%</b>
<b>Vd(AREA)</b>	<b>0.64 L/kg</b>	<b>1.40 L/kg</b>

† USUAL VALUE IN NORMAL SUBJECTS ~ 9%

\* From: Odar-Cederlöf I, Borgå O: Eur J Clin Pharmacol 1974;7:31-7.

# **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.

\* **Sheiner LB, et al. J Pharmacokinet Biopharm 1977;5:445-79.**

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

<b>5-hr URINE RECOVERY</b>	<b>&gt; 4 g</b>
<b>[SERUM] 1 hr AFTER DOSE</b>	<b>≥ 0.2 mg/mL</b>
<b>% DOSE ABSORBED</b>	<b>&gt; 42%</b>
<b>ka</b>	<b>&gt; 0.37 hr<sup>-1</sup></b>

**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.

**\* From: Worwag EM et al. Clin Pharmacol Ther 1987;41:351-7.**

# **FUROSEMIDE**

Chemical structure of Furosemide, a loop diuretic.

## **BIOPHARMACEUTIC CLASSIFICATION OF FUROSEMIDE\***

Chart illustrating that furosemide has low permeability for intestinal absorption.

**\* From: Lenneräs. J Pharm Pharmacol 1997;49:627-38.**

## **BIOPHARMACEUTIC DRUG CLASSIFICATION OF FUROSEMIDE \***

### **CLASS IV: LOW SOLUBILITY-LOW PERMEABILITY**

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

\* From: Lenneräs, et al. Pharm Res 1995;12:S396/

# 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*

Sun H, et al (2006)  
Amidon GI, et al (1995)

## ***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**

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 (initiated 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  
Clin. Pharmacol. Ther. 2009;86:475-479**