# 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

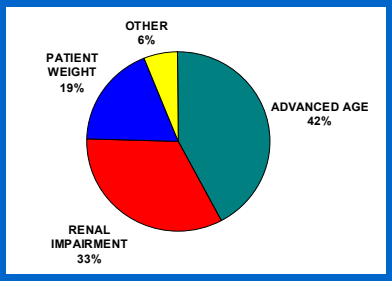
- ***DOSE ADJUSTMENT*** **in Patients with Renal Impairment**

  **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.

## 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*

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

* 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

| MEASUREMENTS | RENAL | HEPATIC | DIALYSIS |
|---|---|---|---|
| Blood Flow | +* | +* | + |
| Afferent Concentration | + | + | + |
| Efferent Concentration | 0 | 0 | + |
| Eliminated Drug | + | 0 | + |

**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 $m^2$
*CLEARANCE MARKERS*:
Inulin
Creatinine
$^{125}$I-Iothalamate

**RENAL BLOOD FLOW:**
Normal: ♂ 1,209 ± 256 mL/min/1.73 $m^2$
♀ 982 ± 184 mL/min/1.73 $m^2$
*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 is now the preferred approach.

## 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.

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

*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

Continuous Infusion:

$$C_{SS} = \frac{I}{CL_E}$$

Intermittent Dosing:

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

## *ADDITIVITY* OF CLEARANCES

$$CL_E = CL_R + CL_{NR}$$

$CL_R$ = RENAL CLEARANCE

$CL_{NR}$ = NON-RENAL CLEARANCE

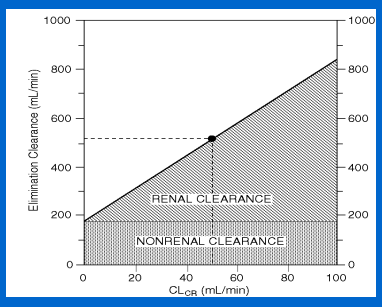
## DETTLI Approach*

$$CL_R = \alpha CL_{Cr}$$

$$CL_E = CL_R + CL_{NR}$$

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

## *NOMOGRAM* FOR CIMETIDINE DOSING*




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

## 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*

* 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.)

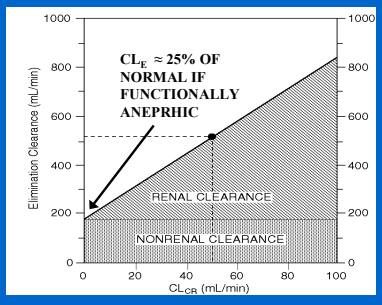
Three days later the patient was noted to be confused. The nephrology team reevaluated the patient and agreed to *discontinue cimetidine* as suggested by the attending internist/clinical pharmacologist. Two days later the patient was alert and was discharged from the hospital to resume outpatient hemodialysis therapy.

## *LABELING* FOR CIMETIDINE*

- ***DOSAGE ADJUSTMENT***
  1/2 normal dose if $CL_{Cr}$ < 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*.

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

## *NOMOGRAM* FOR CIMETIDINE DOSING*




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

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

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

- MAINTAIN USUAL DOSING INTERVAL BUT *REDUCE DOSE* IN PROPORTION TO $\downarrow CL_E$
- MAINTAIN USUAL DOSE BUT *INCREASE DOSING INTERVAL* IN PROPORTION TO $\downarrow CL_E$
- *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 – Procainamide |
| Metabolites: | Glucuronides, Hippurates, etc. |

## *RESTRICTIVE* VS. *NONRESTRICTIVE* ELIMINATION

**RESTRICTIVE:**

Clearance *DEPENDS* on Protein Binding.

KIDNEY: Drug Filtration Rate = $f_U \bullet$ GFR
LIVER: $CL = f_U \bullet Cl_{int}$

**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 = $f_U$ • GFR
LIVER: CL = $f_U$ • $Cl_{int}$

**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 |

## *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

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, JJL 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

| | $CL_{NR}$ (%) | 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:

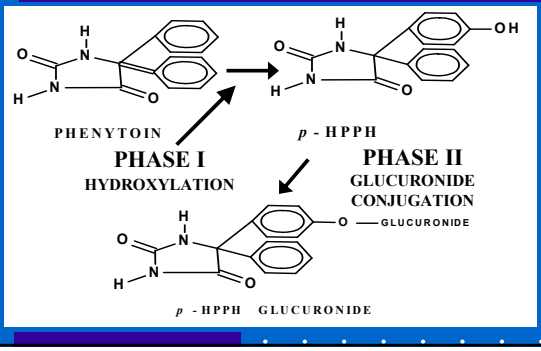
| | | |
|---|---|---|
| Propranolol | +300 % | CYP2D6 |
| Erythromycin | +100 % | CYP3A4 |
| Propoxyphene | +100 % | CYP3A4 |
| Dyhydrocodeine | +70 % | CYP2D6 |

## Effects of Uremic Toxins

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

Inhibition of drug metabolism and transport reversed by hemodialysis

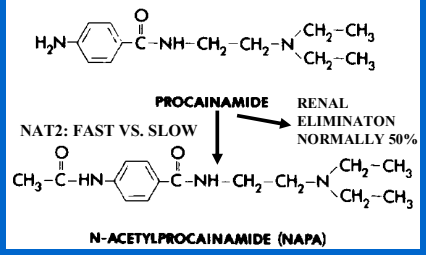
## *PHASE I AND PHASE II* METABOLIC REACTIONS




## GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON *DRUG METABOLISM*
- *EXAMPLES:*
  - PROCAINAMIDE - Acetylation
  - PHENYTOIN - Hydroxylation

## PROCAINAMIDE *ACETYLATION*

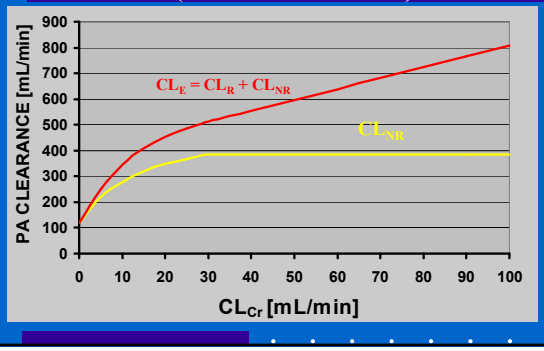



## Procainamide Kinetics in *DIALYSIS PATIENTS**

| | *NORMALS* | | *FUNCTIONALLY ANEPHRIC PATIENTS* | |
|---|---|---|---|---|
| | Fast | Slow | Fast | Slow |
| $T_{1/2}$ (hr) | 2.6 | 3.5 | 12.2 | 17.0 |
| $CL_E$ (L/kg) | 809 | 600 | 118 | 94 |
| $CL_R$ (L/kg) | 426 | 357 | 0 | 0 |
| $CL_{NR}$ (L/kg) | 383 | 243 | 118 | 94 |
| $V_{d(ss)}$ (L/kg) | 1.95 | 1.93 | 1.41 | 1.93 |

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

## Procainamide Dosing Nomogram *(FAST ACETYLATORS)*

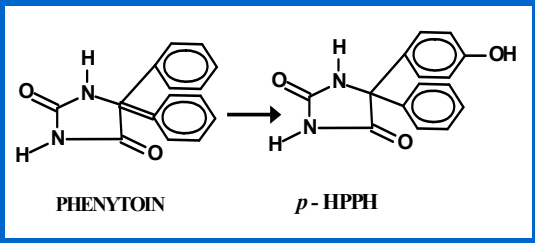


## NAPA ELIMINATION HALF LIFE IN *FUNCTIONALLY ANEPHRIC* PATIENTS

- HEALTHY SUBJECTS: 6.2 hr
- *PREDICTED* for DIALYSIS PATIENTS: 42.8 hr *
- *MEASURED* in DIALYSIS PATIENTS: 41.9 hr *

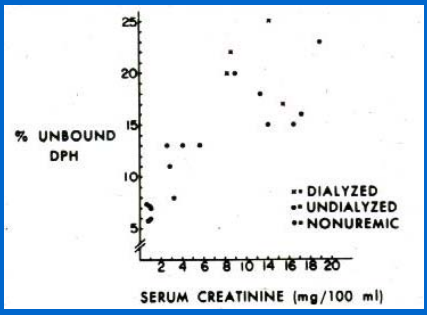
* See Study Problem at end of Chapter 5.

## PHENYTOIN *HYDROXYLATION* BY P450




CYP2C9: Major, CYP2C19: Minor

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



## PHENYTOIN
### *KINETICS IN DIALYSIS PATIENTS**

| | NORMALS (N = 4) | UREMIC PATIENTS (N = 4) | |
|---|---|---|---|
| % UNBOUND ($f_u$) | 12% | 26% | |
| $CL_H$ | 2.46 L/hr | 7.63 L/hr | |
| $CL_{int}$ | 20.3 L/hr | 29.9 L/hr | NS |

$$CL_H = f_u \bullet Cl_{int}, \quad \text{So: } Cl_{int} = CL_H/f_u$$

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

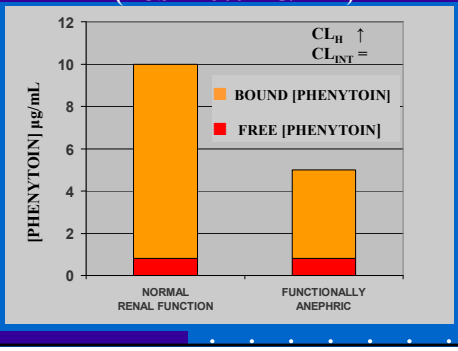
## Effect of *PROTEIN BINDING Changes* on Phenytoin Plasma Concentration

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

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

$$\bar{C}_{ss,\,u}/f_u = \frac{DOSE / \tau}{f_u\ CL_{INT}}$$

## *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 |

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

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

$$V_d = ECF + \phi f_u(TBW - ECF)$$

Φ = TISSUE/PLASMA PARTITION RATIO

$f_u$ = FRACTION NOT BOUND TO PLASMA PROTEINS

FOR PHENYTOIN: Φ = 10.4

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

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

| | NORMALS | UREMIC PATIENTS |
|---|---|---|
| % UNBOUND ($f_u$) | 12%† | 26% |
| $V_{d(AREA)}$ | 0.64 L/kg | 1.40 L/kg |

† 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**

$$V_d = 3.84 \bullet wt\ (kg) + 3.12\ CL_{Cr}\ (mL/min)$$

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

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

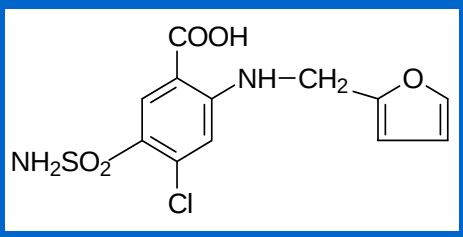
| | |
|---|---|
| 5-hr URINE RECOVERY | > 4 g |
| [SERUM] 1 hr AFTER DOSE | ≥ 0.2 mg/mL |
| % DOSE ABSORBED | > 42% |
| $k_a$ | > 0.37 $hr^{-1}$ |

## EFFECT OF RENAL DISEASE ON D-XYLOSE *ABSORPTION**

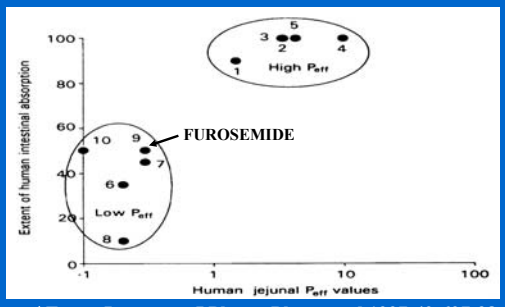
| PATIENT GROUP | $k_a$ ($hr^{-1}$) | $k_o$ ($hr^{-1}$) | % DOSE ABSORBED |
|---|---|---|---|
| NORMALS | 1.03 ± 0.33 | 0.49 ± 0.35 | 69.4 ± 13.6 |
| MODERATE | 0.64 ± 0.28 | 0.19 ± 0.15 | 77.4 ± 14.8 |
| DIALYSIS | 0.56 ± 0.42 | 0.67 ± 0.61 | 48.6 ± 13.3 |

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

## FUROSEMIDE




## BIOPHARMACEUTIC CLASSIFICATION OF FUROSEMIDE*




* 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

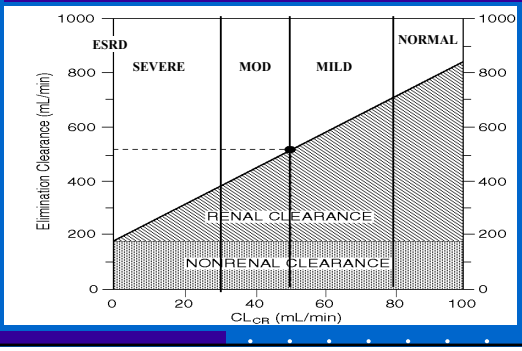
Sun H, et al (2006)
Amidon GI, et al (1995)

## FDA *GUIDANCE FOR INDUSTRY*

*PHARMACOKINETICS IN PATIENTS WITH IMPAIRED RENAL FUNCTION* – Study Design, Data Analysis, and Impact on Dosing and Labeling

AVAILABLE AT:
http://www.fda.gov/cder/guidance/index.htm

## BASIC "FULL" STUDY DESIGN



## 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***.

http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4351b1-01-FDA.pdf

(document pages 57-73)