Routes of Excretion

Objectives

- To describe various routes of excretion
- To understand renal clearance and its relationship with renal excretion
- To understand the effect of renal disease on drug elimination
- To calculate suitable dosage regimen for patient with impaired renal function

Renal Excretion

- Major Organ for Excretion of Drugs is the Kidney
- Functional Unit is the Nephron
  - Bowman's Capsule
  - Proximal Tubule
  - Loop of Henle
  - Distal Tubule
  - Collecting Duct

A Nephron

Bowman's Capsule (Glomerular)

Proximal Tubule

Distal Tubule

Loop of Henle

Collecting Duct

Nephron

- Bowman's Capsule
  - Filtration of low molecular weight substances
- Proximal Tubule
  - Active secretion of weak electrolyte drugs (acids), reabsorption of water
- Loop of Henle
  - Reabsorption of water
- Distal Tubule
  - Passive reabsorption of lipid soluble drug and water

Glomerular Filtration

- Low molecular weight compounds (< 60,000 dalton) filtered from blood
- Tight protein binding will reduce filtration as would incorporation into red blood cells will reduce filtration
- Glomerular Filtration Rate (GFR) 110 to 130 ml/min ≈ 180 L/day
- Inulin is filtered and not secreted or reabsorbed in tubule
- 90% of water reabsorbed: Urine output ≈ 1 - 2 L/day

Tubular Secretion

- In proximal tubule
  - Reabsorption of water
  - Active secretion of some weak electrolytes, especially weak acids
  - Active process, can be inhibited
    - e.g. penicillins and probenecid (also increased distribution)
    - e.g. cephalosporins
  - p-aminohippuric acid (PAH) extensively secreted thus CL_{PAH} ≈ renal blood flow ≈ 425 - 650 ml/min

Tubular Reabsorption

- Distal Tubule
  - Passive excretion and reabsorption of lipid soluble drug
  - Concentration high because of reabsorbed water
  - Lipid soluble (non ionized form) may be extensively reabsorbed

Tubular Reabsorption…

- Weak acids or bases - ionization depends on pH of filtrate and pKa of drug
  - e.g. urine acidic - weak acids reabsorbed (more in the unionized form)
  - e.g. urine acidic - weak bases not reabsorbed, excretion enhanced
- Urine pH can vary from 4.5 to 8 depending on diet or drugs
  - e.g. meat will reduce pH
  - e.g. Bicarb will increase pH

Drug Overdose Treatment

- Possible to increase excretion by adjusting urinary pH
  - e.g. pentobarbital (and other barbiturates) are weak acids and excretion can be increased with alkalinized urine (sodium bicarb)
- Can be predicted using Henderson-Hasselbalch equation

Renal Clearance

- Can be used to quantitate renal excretion
- Used to study mechanism for renal excretion
  - GFR ≈ 120 ml/min
  - Renal Blood Flow ≈ 650 ml/min
- Components of renal clearance include:
  - Filtration, secretion, reabsorption rate

$$\text{Renal Clearance} = \frac{\text{filtration rate} + \text{secretion rate} - \text{reabsorption rate}}{Cp}$$

Renal Clearance…

- Values may range from
  - 0 ml/min (e.g. glucose)
  - to 650 ml/min (e.g. PAH)
- Can be calculated from kel and V after PK analysis
- Can be calculated from Excretion Rate and Cp as in Lab #3 PHAR 4634

$$\text{Renal Clearance} = \frac{\text{Rate of Excretion}}{\text{Plasma Concentration}} = \frac{\Delta U / \Delta t}{Cp_{midpoint}}$$

Hemodialysis

‘artificial kidney’

- Used to remove toxic waste material from the blood, normally removed by functioning kidneys
- Blood flow is exteriorized and diverted across semi-permeable membrane
  - Small molecules (including many drugs) are removed from the blood

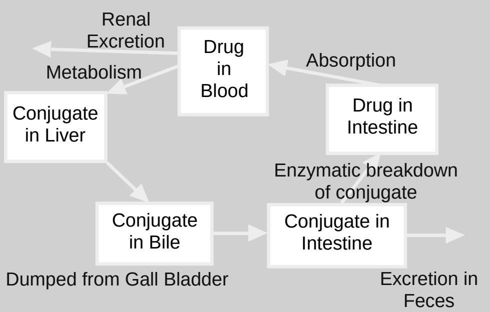
Hemodialysis…

- An important route of excretion for patients with poor renal function
- Drug will be removed:
  - when water solubility it high
  - if there is little protein binding
  - if they are small (< 500 dalton)
  - if they have a small apparent volume of distribution

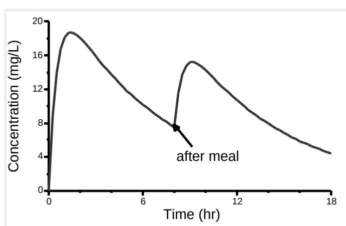
Biliary Excretion

- Liver secretes 0.25 to 1 L/day of bile
- Drugs (and/or metabolites) excreted if > 300 dalton: optimal at 500 dalton
  - smaller drugs may be ‘bigger’ as metabolites, especially conjugates
- Drugs excreted in bile include:
  - Cromoglycate
  - Morphine, Indomethacin, Chloramphenicol as metabolite
- Maybe active secretion with bile/plasma ratio as high as 50/1

Biliary Excretion…



Biliary Excretion…



Pulmonary Excretion

- Lung is a major organ of excretion for gaseous and volatile drugs
  - gaseous anesthetics
  - alcohol - breathalyzer test

Salivary Excretion

- Not really excretion - drug excreted in saliva is probably swallowed
  - Salivary recycling
- Excretion dependent on pH and protein binding
  - $[\text{Saliva}] \approx [\text{Plasma}]_{\text{unbound}}$
  - Drug monitoring
  - PK studies with special populations

Renal Disease Considerations

- With larger values of fe renal disease will have considerable effect on overall elimination
- Good markers of renal disease include creatinine clearance and inulin clearance
- Good correlation between the clearance of many drugs and creatinine (or inulin) clearance

Creatinine Clearance

- Creatinine is produced in the body by muscle metabolism
- Production dependent on age, weight and sex
- Elimination is mainly (> 90%) by glomerular filtration
  - small percentage by secretion
- Inulin clearance measurement involves administration of compound

Measurement

- Creatinine Clearance can be determined from
  - a timed urine collection and
  - plasma concentration at midpoint time

$$\text{Creatinine Clearance} = \frac{\text{Rate of Excretion into Urine}}{\text{Serum Creatinine}}$$

- Serum creatinine as mg/100 ml and creatinine clearance as ml/min

Glomerular Filtration Rate

- Normal inulin clearance ≈ 124 ml/min (male) and ≈ 109 ml/min (female)
- ^{99m}Tc DTPA injected and measured by external scintigraphy over 6 minutes
- Normal creatinine clearance ≈ 120 - 130 ml/min

Calculation

Cockcroft - Gault Equation

For Male

$$CL_{Cr} = \frac{[140 - \text{age(yr)}] \bullet \text{body weight(kg)}}{72 \bullet Cs_{Cr}}$$

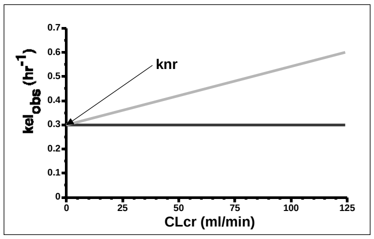
For Female

Use the male value x 0.85

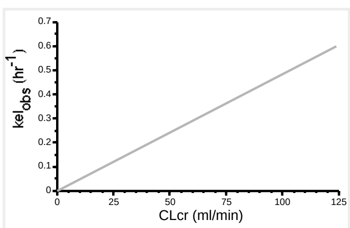
- Can use lean body weight (for body weight)

Estimation of kel

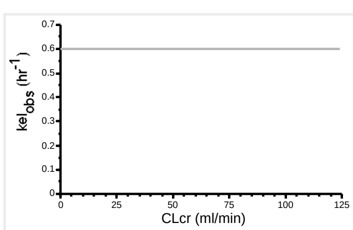
Dettli Plot (fe = 0.3 - 0.7)



Dettli Plot (fe = 1)



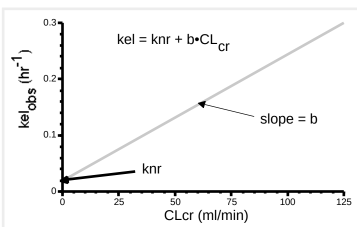
Dettli Plot (fe = 0)



Calculation of kel and Regimen

- Estimate Creatinine Clearance
- Estimate kel from Dettli Plot
- Calculate Regimen from $\overline{Cp}$ or Cp_{min}/Cp_{max} Equations

Calculation of kel



Example knr and b Values

	knr	b
Kanamycin	0.01	0.0024
Sulfadiazine	0.03	0.0005
Tetracycline	0.008	0.00072

Example Calculation

CL_{cr} = 10 ml/min & 120 ml/min

- For Kanamycin
- $kel_{patient}$ = knr + b•CL_{cr}
  = 0.01 + 0.0024 x 10
  = 0.01 + 0.024 = 0.034 hr^{-1}
- cf: kel = 0.01 + 0.0024 x 120 = 0.298 hr^{-1}
- fe = 0.97

Example Calculation

CL_{cr} = 10 ml/min & 120 ml/min

- For Sulfadiazine
- $kel_{patient}$ = knr + b•CL_{cr}
  = 0.03 + 0.0005 x 10
  = 0.03 + 0.005 = 0.035 hr^{-1}
- Cf: kel = 0.03 + 0.0005 x 120 = 0.09 hr^{-1}
- fe = 0.67

Example Calculation

CL_{cr} = 10 ml/min & 120 ml/min

- For Tetracycline
- $kel_{patient}$ = knr + b•CL_{cr}
  = 0.008 + 0.00072 x 10
  = 0.008 + 0.0072 = 0.0152 hr^{-1}
- Cf: kel = 0.008 + 0.00072 x 120
  = 0.0944 hr^{-1}
- fe = 0.92

Average Plasma Concentration

Example Calculation

- Data: Kanamycin; Normal renal function; 250 mg IM q6h; F = 1; V = 13.3 L; kel = 0.30 hr^{-1}
- Question: $\overline{Cp}$ and Cp_{min}
- Equation:

$$\overline{Cp} = \frac{F \bullet Dose}{v \bullet kel \bullet \tau} = \frac{1x250}{13.3x0.3x6} = 10.4 \text{ mg/L}$$

if ka >> kel

$$Cp_{min} = \frac{F \bullet Dose}{V} \bullet \left[\frac{R}{1-R}\right] = 3.7 \text{ mg/L}$$

$$R = e^{-0.3 \bullet 6} = 0.165$$

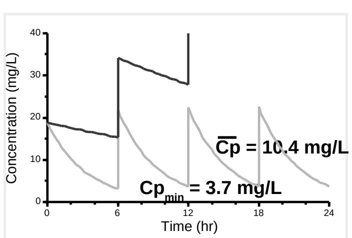
$\overline{Cp}$ in Patient

With kel = 0.034 hr^{-1}

$$\overline{Cp} = \frac{F \bullet Dose}{V \bullet kel \bullet \tau} = \frac{1x250}{13.3x0.034x6} = 92 \text{ mg/L}$$

- Much too high
  - PDR < 35 mg/L

Graphical Result



Dosage Regimen for Patient

- Change the dose (reduce)
- Change the dosing interval (increase)
- Change the dose and the dosing interval (reduce/increase)
- Using the $\overline{Cp}$ Equation:

$$\overline{Cp} = \frac{F \cdot Dose}{V \cdot kel \cdot \tau}$$

Altered Dose

Aiming for $\overline{Cp}$ = 10.4 mg/L

$$Dose = \frac{\overline{Cp} \cdot V \cdot kel \cdot \tau}{F} = \frac{10.4x13.3x0.034x6}{1} = 28.2 \text{ mg}$$

- 28.2 mg rather than 250 mg
- If ka >> kel; R = 0.815; Cp_{min} = 9.3 mg/L
- Regimen: 28 mg q6h

Altered Interval

Aiming for $\overline{Cp}$ = 10.4 mg/L

$$\tau = \frac{Dose \cdot F}{\overline{Cp} \cdot V \cdot kel} = \frac{250x1}{10.4x13.3x0.034} = 53 \text{ hours}$$

- 53 hr rather than 6 hr
- If ka >> kel; R = 0.165; Cp_{min} = 3.7 mg/L
- Regimen: 250 mg q53h

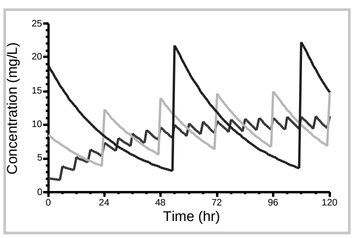
Altered Dose and Interval

Aiming for $\overline{Cp}$ = 10.4 mg/L

$$\text{Dose} = \frac{\overline{Cp} \cdot V \cdot kel \cdot \tau}{F} = \frac{10.4 \text{x} 13.3 \text{x} 0.034 \text{x} 24}{1} = 113 \text{ mg}$$

- 113 mg q24hr versus 250 mg q6h
- If ka >> kel; R = 0.442; Cp_{min} = 6.7 mg/L
- Regimen: 113 mg q24h

Graphical Answer



Another Approach

using Cp_{min} and Cp_{max} Information

- Define Cp_{min} and Cp_{max} based on drug, patient's clinical state
- Determine CL_{cr} from Cockcroft-Gault eqn
- Determine kel from Dettli Plot
- Calculate Tau and Round to convenient value
- Recalculate R
- Calculate Maintenance and Loading Dose

Example Calculation

- Data: 75 kg, 65 yr male patient with $Serum_{cr}$ of 2.3 mg/100 ml. Required $Cp_{max} \leq 6$ mg/L and $Cp_{min} \leq 1$ mg/L. V, km and b values are 0.28 L/kg, 0.02 hr^{-1} and 0.0028 $min.ml^{-1}.hr^{-1}$, respectively for gentamicin
- Question: Calculate an appropriate dosing regimen for gentamicin treatment

Calculation

a. $Cp_{max} = 6$ mg/L and $Cp_{min} = 1$ mg/L

b. $$CL_{cr} = \frac{[140 - 65] x 75}{72 x 2.3} = 34 \text{ ml/min}$$

c. $kel = km + b \cdot CL_{cr} = 0.02 + 0.0028 \times 34$
$= 0.115\ hr^{-1}$

Calculation…

d. $R = 1/6 = 0.1667 = e^{-kel \cdot \tau}$
$\ln(0.1667) = -1.792 = -0.115 \times \tau$
thus $\tau = 15.6$ hr

e. Use a longer interval to keep Cp_{min} below 1 mg/ml, i.e. $\tau = 18$ hr

f. New R value = $e^{0.115 \times 18} = 0.1262$

Calculate Maintenance Dose

using Cp_{max} = 6 mg/L

g. Maintenance Dose = $Cp_{max} \cdot V \cdot (1 - R)$

= 6 x 75 x 0.28 x (1 - 0.1262)

= 110 mg

Thus use 100 mg q18h

$$Cp_{max} = \frac{Dose}{V \cdot (1 - R)} = \frac{100}{75 x 0.28 x (1 - 0.1262)} = 5.45 \text{ mg/L}$$

$$Cp_{min} = Cp_{max} \cdot R = 5.45 x 0.1262 = 0.69 \text{ mg/L}$$

Calculate Loading Dose

- Loading Dose = $Cp_{max} \cdot V$ = 6 x 75 x 0.28 = 126 mg
- Use 125 mg
- Regimen 125 mg then 100 mg q18h

Objectives

- To describe various routes of excretion
- To understand renal clearance and its relationship with renal excretion
- To understand the effect of renal disease on drug elimination
- To calculate suitable dosage regimen for patient with impaired renal function