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)
  - Filtration of low molecular weight substances
- Proximal Tubule
  - Active secretion of weak electrolyte drugs (acids), reabsorption of water
- Distal Tubule
  - Passive reabsorption of lipid soluble drug and water
- Loop of Henle
  - Reabsorption of water
- 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
  
  \[ \text{CL}_{\text{PAH}} \approx \text{renal blood flow} \approx 425 - 650 \text{ ml/min} \]

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 alkalized 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

\[
\text{Renal Clearance} = \frac{\text{filtration rate}}{C_p} + \frac{\text{secretion rate}}{C_p} - \frac{\text{reabsorption rate}}{C_p}
\]

- 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

\[
\text{Renal Clearance} = \frac{\text{Rate of Excretion}}{\text{Plasma Concentration}} = \frac{\Delta U/\Delta t}{C_{p,\text{midpoint}}}
\]
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…

- Renal Excretion
- Metabolism
- Drug in Blood
- Absorption
- Drug in Intestine
- Enzymatic breakdown of conjugate
- Conjugate in Intestine
- Conjugate in Bile
- Dumped from Gall Bladder
- Excretion in Feces

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
  - \([\text{Saliva}] = [\text{Plasma}]_{\text{unbound}}\)
  - Drug monitoring
  - PK studies with special populations

Renal Disease Considerations

- With larger values of \(\text{fe}\) 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)
- \(^{99m}\text{Tc DTPA}\) injected and measured by external scintigraphy over 6 minutes
- Normal creatinine clearance = 120 - 130 ml/min

**Calculation**

Cockcroft - Gault Equation

For Male

\[
CL_{Cr} = \frac{[140 - \text{age(yr)}] \times \text{body weight(kg)}}{72 \times \text{CS}_{Cr}}
\]

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 $\frac{C_p_{\text{min}}}{C_p_{\text{max}}}$
  Equations

\[
\ln \frac{C_p}{C_p_{\text{max}}} = \ln \frac{C_p_{\text{min}}}{C_p_{\text{max}}} = \ln \frac{C_p_{\text{min}}}{C_p} + \ln \frac{C_p}{C_p_{\text{max}}}
\]

Example $\text{k}_{\text{nr}}$ and $b$ Values

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<thead>
<tr>
<th></th>
<th>$\text{k}_{\text{nr}}$</th>
<th>$b$</th>
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</thead>
<tbody>
<tr>
<td>Kanamycin</td>
<td>0.01</td>
<td>0.0024</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>0.03</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.008</td>
<td>0.00072</td>
</tr>
</tbody>
</table>
Example Calculation

\( \text{CL}_{cr} = 10 \text{ ml/min} & 120 \text{ ml/min} \)

\( \text{For Kanamycin} \)

\( \text{kel}_{\text{patient}} = \text{knr} + b \cdot \text{CL}_{cr} \)

\[
= 0.01 + 0.0024 \times 10 \\
= 0.01 + 0.024 = 0.034 \text{ hr}^{-1}
\]

\( \text{cf}: \text{kel} = 0.01 + 0.0024 \times 120 = 0.298 \text{ hr}^{-1} \)

\( \text{fe} = 0.97 \)

---

Example Calculation

\( \text{CL}_{cr} = 10 \text{ ml/min} & 120 \text{ ml/min} \)

\( \text{For Sulfadiazine} \)

\( \text{kel}_{\text{patient}} = \text{knr} + b \cdot \text{CL}_{cr} \)

\[
= 0.03 + 0.0005 \times 10 \\
= 0.03 + 0.005 = 0.035 \text{ hr}^{-1}
\]

\( \text{cf}: \text{kel} = 0.03 + 0.0005 \times 120 = 0.09 \text{ hr}^{-1} \)

\( \text{fe} = 0.67 \)

---

Example Calculation

\( \text{CL}_{cr} = 10 \text{ ml/min} & 120 \text{ ml/min} \)

\( \text{For Tetracycline} \)

\( \text{kel}_{\text{patient}} = \text{knr} + b \cdot \text{CL}_{cr} \)

\[
= 0.008 + 0.00072 \times 10 \\
= 0.008 + 0.0072 = 0.0152 \text{ hr}^{-1}
\]

\( \text{cf}: \text{kel} = 0.008 + 0.00072 \times 120 = 0.0944 \text{ hr}^{-1} \)

\( \text{fe} = 0.92 \)
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: \(C_p\) and \(C_{p\text{min}}\)
- Equation:

\[
C_p = \frac{F \cdot \text{Dose}}{V \cdot kel \cdot \tau} = \frac{1 \times 250}{13.3 \times 0.3 \times 6} = 10.4 \text{ mg/L}
\]

if \(ka >> kel\)

\[
C_{p\text{min}} = \frac{F \cdot \text{Dose}}{V \cdot R \left[\frac{1}{1-R}\right]} = 3.7 \text{ mg/L}
\]

\(R = e^{-0.3 \times 6} = 0.165\)

\(\overline{C_p}\) in Patient

With \(kel = 0.034 \text{ hr}^{-1}\)

\[
\overline{C_p} = \frac{F \cdot \text{Dose}}{V \cdot kel \cdot \tau} = \frac{1 \times 250}{13.3 \times 0.034 \times 6} = 92 \text{ mg/L}
\]

- Much too high
  - PDR < 35 mg/L

Graphical Result

\[
\overline{C_p} = 10.4 \text{ mg/L}
\]

\(C_{p\text{min}} = 3.7 \text{ mg/L}\)
Dosage Regimen for Patient

- Change the dose (reduce)
- Change the dosing interval (increase)
- Change the dose and the dosing interval (reduce/increase)
- Using the equation:

\[ \frac{C_p}{V \cdot \text{kel} \cdot \tau} = F \cdot \text{Dose} \]

Altered Dose

Aiming for \( C_p = 10.4 \text{ mg/L} \)

\[ \text{Dose} = \frac{C_p \cdot V \cdot \text{kel} \cdot \tau}{F} = \frac{10.4 \times 13.3 \times 0.034 \times 6}{1} = 28.2 \text{ mg} \]

- 28.2 mg rather than 250 mg
- If \( k_a \gg \text{kel}; R = 0.815 \); \( C_{p_{\text{min}}} = 9.3 \text{ mg/L} \)
- Regimen: 28 mg q6h

Altered Interval

Aiming for \( C_p = 10.4 \text{ mg/L} \)

\[ \tau = \frac{\text{Dose} \cdot F}{C_p \cdot V \cdot \text{kel}} = \frac{250 \times 1}{10.4 \times 13.3 \times 0.034} = 53 \text{ hours} \]

- 53 hr rather than 6 hr
- If \( k_a \gg \text{kel}; R = 0.165 \); \( C_{p_{\text{min}}} = 3.7 \text{ mg/L} \)
- Regimen: 250 mg q53h
Altered Dose and Interval

Aiming for $C_p = 10.4$ mg/L

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

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

Graphical Answer

Another Approach

using $C_{p_{min}}$ and $C_{p_{max}}$ Information
- Define $C_{p_{min}}$ and $C_{p_{max}}$ 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\textsubscript{cr} of 2.3 mg/100 ml. Required \( C_{p_{\text{max}}}/C_{p_{\text{min}}}/ \leq 6 \text{ mg/L} \) and \( C_{p_{\text{min}}} \leq 1 \text{ mg/L} \). \( V, km \) 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. \( C_{p_{\text{max}}} = 6 \text{ mg/L} \) and \( C_{p_{\text{min}}} = 1 \text{ mg/L} \)
b. \( CL_{cr} = \frac{(140 - 65) \times 75}{72 \times 2.3} = 34 \text{ ml/min} \)
c. \( kel = km + b \times CL_{cr} = 0.02 + 0.0028 \times 34 = 0.115 \text{ hr}^{-1} \)

calculation...
d. \( R = 1/6 = 0.1667 = e^{kel\tau} \)
\( ln(0.1667) = -1.792 = -0.115 \times \tau \)
thus \( \tau = 15.6 \text{ hr} \)
e. Use a longer interval to keep \( C_{p_{\text{min}}} \) below 1 mg/ml, i.e. \( \tau = 18 \text{ hr} \)
f. New \( R \) value = \( e^{0.115 \times 18} = 0.1262 \)
Calculate Maintenance Dose

Using \( C_{\text{p}}_{\text{max}} = 6 \, \text{mg/L} \)

g. Maintenance Dose = \( C_{\text{p}}_{\text{max}} \cdot V \cdot (1 - R) \)

\[
= 6 \times 75 \times 0.28 \times (1 - 0.1262)
\]

\[= 110 \, \text{mg} \]

Thus use 100 mg q18h

\[
C_{\text{p}}_{\text{max}} = \frac{\text{Dose}}{V \cdot (1 - R)} \approx \frac{100}{75 \times 0.28 \times (1 - 0.1262)} = 5.45 \, \text{mg/L}
\]

\[
C_{\text{p}}_{\text{min}} = C_{\text{p}}_{\text{max}} \cdot R = 5.45 \times 0.1262 = 0.69 \, \text{mg/L}
\]

Calculate Loading Dose

- Loading Dose = \( C_{\text{p}}_{\text{max}} \cdot V = 6 \times 75 \times 0.28 \)

\[= 126 \, \text{mg} \]

- 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