Elimination
Metabolism and Excretion

Outline

1. Total Body Clearance
   - Concept
   - Mass balance
   - Additivity

2. Hepatic Clearance
   - Hepatic clearance and extraction ratio
   - Factor influence hepatic clearance
   - Examples
   - Bioavailability and first pass effect

3. Renal Clearance
   - Nephron Function and Renal Clearance
   - Components of renal clearance
   - Examples

1. Total Body Clearance Concept

   • A parameter relating rate of drug elimination to the blood or plasma drug concentration.

   \[
   \text{Clearance}(CL) = \frac{\text{Rate of Elimination}}{C}
   \]
1.2. Mass Balance and Rate Extraction

Organ extraction rate
= rate of drug in - rate of drug out

1.2. Mass Balance and Rate Extraction

- Assumptions
  - Instant mixing, not considering time to distribution equilibrium
  - It reaches distribution equilibrium
  - It is reasonable assumption for liver and kidney with high perfusion rate and rapid equilibrating rate

1.2. Mass Balance and Rate Extraction

Rate of presentation = \( QC_A \)
Rate of extraction = \( Q(C_A - C_V) \)

Extraction ratio \( (E) \) = \( \frac{\text{Rate of extraction}}{\text{Rate of presentation}} = \frac{(C_A - C_V)}{C_A} \)

- \( E \) ranges from zero (no drug is eliminated) and 1.0 (no drug escapes past the organ).
- \( C_A \): Blood drug concentration in artery
- \( C_V \): Blood drug concentration in vein

1.3. Total Body Clearance

\[ \text{Clearance (CL)} = \frac{Q(C_A - C_V)}{C_A} \]

\[ \text{Clearance (CL)} = QE \]
1.4. Total Body Clearance Using Blood or Plasma Drug Concentration

- When estimate extraction ratio, total body clearance using blood drug concentration has to be used.
- But plasma drug concentration are often determined.
- Blood clearance: total body clearance using blood drug concentration
- Plasma clearance: total body clearance using plasma drug concentration
- Appendix G (Blood to plasma concentration ratio)

\[
\frac{\text{Plasma Clearance}}{\text{Blood Clearance}} = \frac{\text{Blood Conc}(C_B)}{\text{Plasma Conc}(C_p)} \quad \frac{\text{CL}_p}{\text{CL}_B} = \frac{C_B}{C_p}
\]

1.4. Total Body Clearance Using Blood Drug Concentration (Blood Clearance)

- Maximum Blood Clearance Value
  - Maximum $E = 1$
  - Maximum $\text{CL}_B = Q$
    - $Q_{\text{liver}} = 1.35 \text{ L/min}$
    - $Q_{\text{kidney}} = 1.1 \text{ L/min}$

1.4. Total Body Clearance Using Blood Drug Concentration (Blood Clearance)

- Volume of blood from which all the drug would appear to be removed per unit time
  - Unit: ml / min, L/hr

1.5. CL and V based on drug concentration in blood, plasma, and unbound

- Rate of elimination
  \[= \text{CL}. C = \text{CL}_b . C_b = \text{CL}_u . C_u\]

- Amount in the body
  \[= V. C = V_b . C_b = V_u . C_u\]
1.6. Additivity of Total Body Clearance

- Total clearance is the sum of the clearances by each of the eliminating organs.
- For a drug eliminated by both renal excretion and hepatic metabolism, then

\[
\text{Rate of elimination} = \text{Rate of renal excretion} + \text{Rate of hepatic metabolism}
\]

\[
\text{Total clearance} = \text{Renal clearance} + \text{Hepatic clearance}
\]

2. Hepatic Clearance

- Factors in this fig
  - Perfusion rate
  - Drug Binding
    - Drug to RBC
    - Drug Binding to plasma protein
  - Drug metabolism by hepatocytes
    - Drug secretion to bile

2.1. Hepatic Clearance (CL) and Extraction Ratio (E)

**Extraction by the Liver**

\[
E = \frac{(C_A - C_v)}{C_A} = \frac{100 - 50}{100} = 0.5
\]

\[
\text{CL} = Q \times E = 1350 \times 0.5 = 675 \text{ mL/min}
\]

(hepatic blood flow \( Q = 1350 \text{ ml/min} \))

<table>
<thead>
<tr>
<th>( C_A )</th>
<th>( C_v )</th>
<th>Extraction ratio (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>100</td>
<td>99</td>
<td>0.01</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>0.99</td>
</tr>
</tbody>
</table>
2.2. Factors Influence Hepatic Clearance

- Hepatic Blood Clearance ($CL_b$) = $Q_H \cdot E_H$
  - All terms are in blood, not in plasma
- Depends on:
  - Blood Perfusion
  - Protein binding
  - Enzyme activity

\[ CL_b = \frac{Q_H \cdot fu_b \cdot CL_{int}}{Q_H + fu_b \cdot CL_{int}} \]
\[ E_H = \frac{fu_b \cdot CL_{int}}{Q_H + fu_b \cdot CL_{int}} \]
\[ CL_b = Q_H \cdot E_H \]
- $Q_H$: hepatic blood flow
- $fu_b$: fraction unbound in BLOOD.
- $CL_{int}$: intrinsic clearance, which relates to metabolism to unbound drug

2.2.1. Perfusion and Hepatic Clearance

- High extraction ratio ($E > 0.7 - 1$):
  - $CL$ is determined by $Q$
  - $E$ will not change with blood flow ($E \approx 1$)
- Intermediate ($E = 0.3 - 0.7$)
  - See equation
- Low E ($E < 0.3$)
  - Concentration in artery and vein is similar
  - $Q$ change will not alter tissue drug concentration
  - $Q$ change will not alter rate of elimination
  - $Q$ change will not alter CL
  - $E$ will change with $Q$ (when CL is constant)
2.2.1. Perfusion and Hepatic Clearance

<table>
<thead>
<tr>
<th>Sensitivity of CL to changes in blood flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug with</td>
</tr>
<tr>
<td>High extraction ratio $E_i = 1$</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Low extraction ratio</td>
</tr>
<tr>
<td>↓</td>
</tr>
</tbody>
</table>

Symbols: ↑ increase, ↓ decrease, ↔ little or no change.

2.2.2. Binding Within Blood and Hepatic Clearance

• High E drug
  – Liver will remove all drugs regardless binding to RBC or protein
  – Binding will not change E
  – Binding will not change CL

• Low E drug
  – Plasma protein binding will change CL
    • Only unbound across membrane for elimination
  – Rate of elimination = $CL_u \cdot C_u$
    – $CL_u$: clearance based on unbound concentration
    – $C_u$: unbound concentration
  – Divided by $C$, then
  – Hepatic clearance (CL) = $CL_u \cdot fu$

2.2.3. Enzymatic Activity and Hepatic Clearance

• High E
  – Perfusion rate limited
  – Hepatic enzymatic activity is high
  – Change of enzyme activity cause little change in CL

• Low E
  – Enzyme activity limited
  – Clearance correlate to enzymatic activity
  – Inhibition or induction of enzyme will change clearance
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2.2.3. Enzymatic Activity and Hepatic Clearance

- $K_m$: the Michaelis-Menten constant, affinity for the enzyme,
- $V_m$ (Vmax):
  - Maximum rate of metabolism,
- When $Cu = K_m$,
  - Rate of metabolism = 50% of $V_m$,
  - this is a convenient way of defining $K_m$.

\[
\text{rate of metabolism} = \frac{V_m \cdot C_u}{K_m + C_u}
\]

\[
\text{unbound \cdot metabolic \cdot clearance} = \frac{V_m}{K_m + C_u}
\]

2.2.4. Example 1: Perfusion and CL

2.2.4. Example 2: Fraction Unbound and Extraction Ratio
2.2.4. Example 3

- **EX 1**: Drug A has a plasma clearance of 1350 ml/min (100% liver metabolism) and a blood/plasma conc ratio of 0.92. Is the drug's elimination rate limited by protein binding or by hepatic blood flow? (Assuming a hepatic blood flow of 1500 ml/min)

\[
\frac{CLp}{CL_B} = \frac{C_B}{Cp}
\]

- \(CL_B = CLp \cdot \frac{Cp}{C_B}\) = __________?
- \(E = CL_B/Q = \) ________________?
- Elimination rate is determined by ?

2.2.4. Example 4.

- Predict the effect of liver blood flow increase on the CL of the 2 drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>V (L)</th>
<th>Clearance (L/hr)</th>
<th>Fraction Excreted Unchanged</th>
<th>Extraction ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.97</td>
<td>26</td>
<td>6</td>
<td>0.60</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>430</td>
<td>77</td>
<td>0.05</td>
<td>0.95</td>
</tr>
</tbody>
</table>

2.3. Bioavailability and First-Pass Effect

- Maximum oral bioavailability \((F) = 1 - E_H\)
  - \(F = Fa \cdot Fg \cdot Fh\)
  - \(Fa = 100\%\) (assume complete absorption)
  - \(Fg = 100\%\) (assume no gut metabolism)

\[
F_H = 1 - E_H = 1 - \frac{fu_b \cdot CL_{int}}{Q_H + fu_b \cdot CL_{int}}
\]

\[
F_H = \frac{Q_H}{Q_H + fu_b \cdot CL_{int}}
\]
2.4. Biliary excretion and enterohepatic cycling

- Biliary clearance
  \[ \text{Biliary clearance} = \frac{\text{bile flow} \times \text{concentration in bile}}{\text{concentration in plasma}} \]
- Bile flow = 0.5 - 0.8 ml/min
- Enterohepatic circulation

Hepatic Clearance Summary

- Total Body Clearance
  - Concept: \( \text{Clearance (CL)} = \frac{Q(C_t - C_p)}{C_t} \)
  - Mass balance
  - Blood and plasma clearance
  - Additivity
- Hepatic Clearance
  - Hepatic clearance and extraction ratio
    - High E and Low E \( \text{Clearance (CL)} = QE \)
  - Factor influence hepatic clearance
    - Perfusion (High E and Low E)
    - Binding (High E and Low E)
    - Enzymatic activity (High E and Low E)
  - Bioavailability and first pass effect

3. Renal Clearance

- Rate of excretion = \( CL_R \cdot C \)
- \( CL_R = \frac{\text{rate of excretion}}{\text{plasma C}} \)
- Factors influence \( CL_R \)
  - Plasma C
  - Plasma protein binding
  - Urine flow
  - Urine pH
3.1. Nephron Function and Renal Clearance

3.2. Components of Renal clearance

- Glomerular filtration
  - (unbound drug blood → urine)
- Active secretion
  - (blood → urine, transporters)
- Reabsorption
  - (active vs. passive) (urine → blood)

3.1. Nephron Function and Renal Clearance

3.2. Components of Renal clearance

- Rate of Excretion
  = Rate of filtration + Rate of Active secretion − Rate of Reabsorption

- $CL_R = \frac{(Rate\ of\ Excretion)}{C}$

$$CL_R = f_uGFR + \frac{Active\ Secretion\ Rate}{C} - \frac{Reabsorption\ Rate}{C}$$
3.2.1. Glomerular Filtration

- Renal blood flow (Q) = 1.1 L/ml (20% cardiac output 5L/min)
  - 10% filtered at glomerulus
- Molecular weight cut off for glomerular filtration
  - 6000 -20,000 Da: > 70% filtered
  - 32,000 Da : 33% filtered
  - cut off: 35,000 Da
  - Albumin (69,000 Da): 0.1% filtered
  - Only unbound drug (Cu) can be filtered

Renal Extraction Ratio by GFR

- Extraction ratio
  = rate of extraction / rate of presentation
  = GFR. Cu / (renal Q_R . C_b)
- If small molecule not bound to protein (fu = 1)
  - Cu = C_b
  - Extraction ratio = GFR / Q_R = 120 (ml/min) /1100 (ml/min) = 0.11

Marker of GFR

- Creatinine
  - Mw: 113
  - Endogenous GFR marker
  - Muscle breakdown product
  - Not bound to protein
  - Distributed in TBW (V = 42 L)
  - Only renal elimination by glomerular filtration
  - CL = 120 ml/min

- Inulin
  - Mw: 5000
  - Exogenous GFR marker
  - Not bound to protein
  - Distributed in extracellular water (V = 15 L)
  - Only eliminated by glomerular filtration
  - CL = 120 ml/min

3.2.1. Glomerular Filtration

- Rate of filtration = GFR . Cu = fu. GFR. C
  - GFR: glomerular filtration rate (120 ml/min)
- CL_{filtration} = rate of filtration / C = fu. GFR
3.2.2. Active Secretion

- Active transport process applies
  - Saturation
  - Substrate specificity
  - Inhibition and competition
- Renal excretion rate = CLR . C
- Renal filtration rate = fu. GFR. C
- If CLR . C > fu. GFR. C, or CLR > fu. GFR
  - then it suggests active secretion occurs

3.2.3. Reabsorption

- If CLR < fu . GFR, it suggests reabsorption
  - Secretion may still occurs, but less than reabsorption
- Reabsorption process
  - All principles and factors govern drug movement across membrane apply
    - Active transport
    - Passive diffusion
    - Paracellular
    - Endocytosis

3.3. Renal Clearance: Example 1 - reabsorption

- Methamphetamine
  - Weak base, pKa = 10
  - When urine pH is not controlled (pH 4.5-7.5), 16% dose is excreted
  - When urine pH is alkalinated by sodium bicarbonate, 1-2% of dose excreted
  - When urine pH is acidified by ammonium chloride, 70-80% dose is excreted
  - Why?
Clinical application—overdose of Meth?

• Treat symptom
  – Sudden increase in blood pressure; Increased body temperature; Tremor; Muscle twitching; Confusion; Rapid breathing; Hallucinations; Panic; Muscle pain; Muscle weakness; Aggressive behavior; Tiredness; Nausea; Vomiting; Abdominal pain; Diarrhea; Irregular heart rhythm; Light-headedness; Fainting; Sweating; Seeing spots in vision; Convulsions

• Other method?

3.3. Renal Clearance: Example 2. - reabsorption

• Salicylic acid
  – Weak acid, pKa 3
  – High urine pH increase renal clearance
  – Why?

3.3. Renal Clearance: Example 3 Crystalluria

• Drug precipitate as function of pH
• Sulfonamide:
  – Weak acid,
  – Precipitate under low pH
  – Drink high volume of water
  – Alkalinize urine
• HIV protease inhibitor (Indinavir)
  – Weak base
  – Acidify urine

3.4. Detoxifying overdose by forced diuresis and urine pH control—Clinical application

• Renal excretion must be a major elimination route (fe > 0.5)
• Compounds must be extensively reabsorbed from renal tubule
• Reabsorption is pH sensitive
  – weak acid pKa 3-7.5
  – Weak base pKa 3-6
Renal Clearance Summary

• Nephron Function and Renal Clearance
• Components of renal clearance
  – Glomerular filtration
  – Active secretion
  – Reabsorption
• Detoxifying overdose by forced diuresis and urine pH control---Clinical application