Pharmacology 659 Online

Drug Absorption, Distribution, Metabolism, and Elimination

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Pharmacokinetics
Pharmacokinetic Concepts

Volume of distribution
A measure of the apparent space in the body available to contain a drug or some other substance.

Clearance
A measure of the ability of the body to eliminate administered drugs and other environmental substances.
Time 0

Amount in blood

0 Time

Blood
Two compartment model
One compartment outflow model
Time

Amount in blood

Extravascular volume

Blood

0 Time

Graph showing the decrease in amount of substance in blood over time after injection.
Multiple compartment models

Model I

Model II

Model III
One Compartment Model

Before Administration  After Distribution Equilibrium
Two Compartment Model

Before Administration  Immediately after Administration  After Distribution Equilibrium
Kinetic model
Apparent Volume of Distribution, $V_d$

\[
V_d = \frac{\text{Amount of drug in the body}}{\text{Concentration measured in plasma}}
\]

\[
V_d = \frac{X}{C_p}
\]

$C_p$ = concentration of drug in plasma, $X$ = amount of drug in body

\[
V_d = \frac{\text{Dose}}{C_p^0}
\]

Dose = amount of drug administered, $C_p^0$ = concentration of drug in plasma at zero time

\[
C_p^0 = \frac{\text{Dose}}{V_d}
\]
Apparent Volume of Distribution

Drug concentration in beaker

Dose = 10 mg
\(C_p^0 = 20 \text{ mg/L}\)
Apparent Volume = 500 ml

With charcoal in beaker

Dose = 10 mg
\(C_p^0 = 2 \text{ mg/L}\)
Apparent Volume = 5000 ml
Volumes of Some Body Compartments into Which Drugs Can Be Distributed

<table>
<thead>
<tr>
<th>Compartment and volume</th>
<th>Examples of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water</strong></td>
<td></td>
</tr>
<tr>
<td>Total body water (0.6 L/kg(^1))</td>
<td>Small, water soluble molecules, e.g. ethanol</td>
</tr>
<tr>
<td><strong>Extracellular water</strong> (0.2 L/kg)</td>
<td>Larger, water-soluble molecules, e.g. gentamicin</td>
</tr>
<tr>
<td><strong>Blood</strong> (0.08 L/kg)</td>
<td></td>
</tr>
<tr>
<td>Plasma (0.04 L/kg)</td>
<td>Molecules bound strongly to plasma proteins and very large molecules, e.g. heparin</td>
</tr>
<tr>
<td><strong>Fat</strong> (0.2 – 0.35 L/kg)</td>
<td></td>
</tr>
<tr>
<td><strong>Bone</strong> (0.07 L/kg)</td>
<td>Highly lipid-soluble molecules, e.g. DDT</td>
</tr>
<tr>
<td></td>
<td>Certain ions, e.g. lead, fluoride</td>
</tr>
</tbody>
</table>

\(^1\) Total body water is highly variable. In a lean, young male it might be 0.7 L/kg and in an obese female it might be 0.5 L/kg
Protein Binding

Albumin
Binds drugs such as phenytoin, salicylates, and disopyramide
Levels might be decreased in many disease states

$\alpha_1$-Acid glycoprotein
Binds quinidine, lidocaine, and propranolol
Increases in acute inflammatory disorder and thus causes major changes in total plasma concentrations of those drugs
<table>
<thead>
<tr>
<th>Drug</th>
<th>V (l/kg)</th>
<th>V (l/70 kg)</th>
<th>% Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>0.16</td>
<td>11.2</td>
<td>91.4</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.63</td>
<td>44.1</td>
<td>90.3</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.55</td>
<td>38.5</td>
<td>51.0</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2.4</td>
<td>168</td>
<td>98.7</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7</td>
<td>490</td>
<td>25.0</td>
</tr>
</tbody>
</table>
Drugs with a very high volume of distribution ($V_d$) have much higher concentrations in extravascular tissues than in the vascular compartment.

Drugs that are completely retained in the vascular compartment have a minimum $V_d$ equal to the blood component in which they are distributed, e.g. 0.04 L/kg body weight or 2.8 L/70 kg for a drug that is restricted to the plasma compartment.
Clearance

\[
\text{CL} = \frac{\text{Rate of elimination}}{C}
\]

\[
\text{CL}_{\text{renal}} = \frac{\text{Rate of elimination}_{\text{renal}}}{C}
\]

\[
\text{CL}_{\text{liver}} = \frac{\text{Rate of elimination}_{\text{liver}}}{C}
\]

\[
\text{CL}_{\text{other}} = \frac{\text{Rate of elimination}_{\text{other}}}{C}
\]

\[
\text{CL}_{\text{systemic}} = \text{CL}_{\text{renal}} + \text{CL}_{\text{liver}} + \text{CL}_{\text{other}}
\]
Zero-order kinetics:

1. A constant amount of the drug is eliminated per unit of time, e.g. ethanol, phenytoin, many drugs in very high concentrations
2. Mechanisms for elimination of the drug are saturated
3. Clearance might be highly variable

First-order kinetics:

1. A constant fraction of the drug is eliminated per unit of time, e.g. most drugs in therapeutic concentrations
2. Absolute rate of elimination of the drug is essentially a linear function of its concentration in plasma
3. Mechanisms for elimination are not saturated
Exponential elimination

\[ t_{1/2} = 2 \text{ hr} \]

\[ K_e = 0.347 \text{ hr}^{-1} \]

\[ C_p^0 = 100 \text{ mg/ml} \]
Concentration vs. Time Graph

- **Conc (μg/ml)**
- **t_{1/2} = 2 hr**
- **Kel = 0.347 hr^{-1}**
- **C_p^0 = 100 mg/ml**
Concentration (mg/ml) vs. $\Delta C/\Delta t$ (mg/(ml.hr))

- $\Delta C/\Delta t$ vs. Concentration ($\mu$g/ml)

**Linear transformation**
The diagram illustrates the relationship between plasma drug concentration and time after administration. The concentration-time curve is linear, indicating a first-order drug elimination process.

Mathematically, the half-life time ($t_{1/2}$) can be calculated using the initial concentration ($C_p^0$) and the rate of drug elimination ($V$) as follows:

$$t_{1/2} = \frac{\ln(2)}{\ln(C_p^0)}$$

The rate of drug elimination ($V$) is given by the dose divided by the initial concentration ($C_p^0$):

$$V = \frac{\text{Dose}}{C_p^0}$$

The diagrams show the concentration-time profiles with the corresponding half-life times ($t_{1/2}$) indicated. The initial concentration ($C_p^0$) is annotated for each graph, with $C_p^0 = 31$ for the right graph and a different value for the left graph.
Half-Life, $t_{1/2}$

Half-Life, $(t_{1/2})$ is the time required to change the amount of drug in the body by one-half during elimination (or during a constant infusion).

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$
Relationship between frequency of dosing and maximum and minimum plasma concentrations when a steady-state plasma level of theophylline, 10 mg/L is desired.

Intravenous infusion of 28 mg/hr
224 mg dose every 8 hours
672 mg dose every 24 hours