Pharmacokinetics
(actions of the body on drugs)

Suggested reading:

Basic and Clinical Pharmacology
(Katzung) Chapter 3
Objectives

• Pharmacokinetics
• Volume Distribution
• Clearance
• Half-life
• Drug Accumulation
• Bioavailability
• Extraction Ratio & First Pass Effect
• Other routes of Administration
• Time course of drug effects
• Target Concentration
• Therapeutic Drug Monitoring
Pharmacokinetics

The pharmacokinetic processes of absorption, distribution and elimination determine how rapidly and for how long the drug will appear at the target organ.
Pharmacokinetics

The standard dose of a drug is based on trials in healthy volunteers and patients with average ability to absorb, distribute and eliminate the drug. This dose will not be suitable for every patient.

Several physiologic (e.g. maturation of organ function) and pathologic processes (e.g. renal failure) dictate dosage adjustment in individuals. These processes affect specific pharmacokinetic parameters.

The 2 basic parameters are:

**CLEARANCE** a measure of the ability of the body to eliminate the drug

**VOLUME OF DISTRIBUTION** a measure of the apparent space in the body available to contain the drug.

These parameters are illustrated on the next page where the volume of compartments into which the drugs diffuse represents the volume of distribution and the size of the outflow “drain” represents the clearance.
Drug Distribution & Elimination

Injected drug rises rapidly to a plateau. No drug elimination.

Injected drug rises rapidly then decays slowly as drug is slowly eliminated (cleared).

Injected drug rises rapidly then decays rapidly as the drug distributes between blood and extravascular space. A plateau level is achieved because there is no drug clearance.

Injected drug rises rapidly then decays rapidly as the drug distributes between blood and extravascular space. [Drug] then decays slowly as drug is slowly cleared.
Volume Distribution

The volume of distribution ($V_d$) relates the amount of drug in the body to the concentration of drug ($C$) in the blood or plasma:

$$V_d = \frac{\text{Amount of drug in body}}{C} = \frac{\text{amount}}{\text{amount per L per 70 kg}} = \frac{L}{70 \text{ kg}}$$  \hspace{1cm} (1)

$V_d$ may be defined with respect to blood, plasma or water (unbound drug) depending on the concentration used in this equation ($C=C_B$, $C_P$ or $C_U$).

$V_d$ is clearly an apparent volume. For example, $V_d$ of digoxin (500 L/70 kg) and chloroquine (13,000 L/70 kg) greatly exceed any physical volume available in the body because:

$V_d$ is the volume necessary to contain the amount of drug homogeneously at the concentration found in the blood, plasma or plasma water.

A high $V_d$ indicates a greater distribution to extravascular tissue than to the vascular compartment (i.e. the distribution is not homogeneous).

A minimum $V_d$ of 2.8 L/70 kg is produced when the drug is restricted to the plasma compartment.
<table>
<thead>
<tr>
<th>Compartment &amp; Volume</th>
<th>Example Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>small H₂O soluble molecules e.g. ethanol</td>
</tr>
<tr>
<td>Total body water (0.6 L/kg)</td>
<td></td>
</tr>
<tr>
<td>Extracellular Water (0.2 L/kg)</td>
<td>Larger H₂O soluble molecules e.g. gentamicin</td>
</tr>
<tr>
<td>Blood (0.08 L/kg)</td>
<td>strongly plasma protein-bound molecules and very large</td>
</tr>
<tr>
<td>plasma (0.04 L/kg)</td>
<td>molecules e.g. heparin</td>
</tr>
<tr>
<td>Fat</td>
<td>highly lipid-soluble molecules e.g. DDT</td>
</tr>
<tr>
<td>(0.2-0.35 L/kg)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>certain ions e.g. Pb and F</td>
</tr>
<tr>
<td>(0.07 L/kg)</td>
<td></td>
</tr>
</tbody>
</table>
Influence of drug binding on volume of distribution

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

- **Vascular compartment**: 2 Units
- **Extravascular compartment**: 18 Units

For Vascular compartment, \[ V_d = \frac{20}{2} = 10 \]

For Extravascular compartment, \[ V_d = \frac{20}{18} = 1.1 \]
Exam-type question

Immediately following oral administration of 300 µg diazepam to a 70 kg man (assume it is fully available orally and is not excreted), plasma [diazepam] was measured to be 3.8 µg/L. The volume distribution of diazepam is:

a. 1,140 L/70 kg
b. 0.013 L/70 kg
c. 79 L/70 kg
d. 303.8 L/70 kg
e. 296.2 L/70 kg
Clearance

Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration:

\[
CL = \frac{Rate\ of\ Elimination}{C} = \frac{amount\ per\ hour}{amount\ per\ L\ per\ 70\ kg} = \frac{L}{h \cdot 70\ kg}
\]

(2)

CL, like \(V_d\) may be defined with respect to blood (CL\(_B\)), plasma (CL\(_P\)) or unbound drug in plasma water (CL\(_U\)).

Clearance is an additive process. Elimination of a drug may involve processes occurring in the liver, kidneys, lungs and other organs. Dividing the rate of clearance at each organ by [drug] presented to it yields the clearance at that organ.

\[
CL_{renal} = \frac{Rate\ of\ Elimination_{kidney}}{C}; \quad CL_{liver} = \frac{Rate\ of\ Elimination_{liver}}{C}
\]

\[
CL_{other} = \frac{Rate\ of\ Elimination_{other}}{C}; \quad CL_{systemic} = CL_{renal} + CL_{liver} + CL_{other}
\]

Other tissues could include the lungs and additional sites of metabolism (e.g. blood or muscle). The two major sites of elimination are the liver and the kidneys. Clearance of unchanged drug in the urine represents renal clearance. In the liver, clearance represents biotransformation of drug (metabolism) or excretion in the bile (or both).
Clearance

For most drugs, CL is constant over the entire range of blood or plasma [drug]. For these drugs,

\[
\text{Rate of Elimination} = CL \cdot C = \frac{L}{h \cdot 70 \text{ kg}} \cdot \frac{\text{amount} \cdot 70\text{ kg}}{L} = \frac{\text{amount}}{h}
\]  

(3)

This is referred to as first order elimination.

Capacity limited

For drugs exhibiting capacity-limited clearance (e.g. ethanol, phenytoin), clearance will vary depending on the [drug] that is achieved. Capacity-limited elimination is known as saturable, dose-dependent, nonlinear and Michaelis-Menten elimination.

Why? For these systems

\[
\text{Rate of Elimination} = \frac{V_{\text{max}}C}{K_m + C}
\]

When C >> K_m, the rate of elimination = V_{\text{max}} and is unaffected by further increases in C. This is known as zero-order elimination - it is independent of C.

If dosing rate exceed the elimination capacity, steady-state cannot be achieved and C continues to rise as long as dosing continues. This is important for aspirin, alcohol and phenytoin. Clearance has no real meaning for drugs with capacity-limited elimination.
Flow-dependent elimination

Some drugs are cleared very readily by the organ of elimination so that at any clinically relevant concentration of drug, most of the drug in the blood perfusing the organ is eliminated on first pass through it.

The elimination of these drugs will depend primarily on the rate of drug delivery to the organ of elimination. These drugs are metabolized so rapidly by the liver that their hepatic clearance is blood-flow-limited.

A table of rapidly, hepatically metabolized drugs

<table>
<thead>
<tr>
<th>Alprenolol</th>
<th>Lidocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Meperidene</td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>Morphine</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Pentazocine</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Propoxyphene</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>
Exam-type question

In fact, diazepam has a clearance of 1.62 L/h/70 kg. If, plasma [diazepam] is 3.8 µg/L immediately following oral administration of 300 µg diazepam to a 70 kg man, the rate of diazepam elimination is:

a. 6.16 µg/h/70 kg
b. 0.43 µg/h/70 kg
c. 2.3 h/70 kg/µg
d. 5.42 µg/h/70 kg
e. indeterminate
Half-life

The half-time (t\(_{1/2}\)) is the time required to change the concentration of a drug by one-half during elimination or during a constant infusion.

In the simplest case, the body may be considered as a single compartment of a size equivalent to the volume of distribution (V\(_d\)). While the organs of elimination can only clear drug from the blood or plasma in direct contact with the organ, this blood or plasma is in equilibrium with the total volume distribution. Thus the time course of drug in the body will depend on both V\(_d\) and the clearance.

\[
t_{1/2} = \frac{0.693 \cdot V_d}{CL} = \frac{L \cdot h \cdot 70\text{kg}}{70\text{kg} \cdot L} = h
\]  

\text{(4)}
The time course of drug accumulation (---) and elimination (---). With constant drug infusion, accumulation achieves 50% steady-state after 1 half-life (1 h), 75% after 2 half-lives and ≈ 90% after 4 half-lives. With elimination, 50% of the drug is lost after 1 half-life (1 h), 75% is lost after 2 half-lives etc. The rule of thumb is that 4 half-lives must elapse before full effects will be seen (i.e. 90% of Δ[] is attained).
Exam-type question

Knowing that diazepam has a clearance of 1.62 L/h/70 kg and its volume of distribution is 79 L/70 kg, calculate the half-life of serum diazepam:

a. 0.02 h
b. 184 h
c. 33.8 h
d. 0.005 h
e. 49.2 h
Drug Accumulation

Repeated dosing causes drug accumulation until dosing stops. This is because in theory, it takes an infinite time to eliminate all of a given dose. In practice, however, this means that if dosing interval is shorter than 4 half-lives, accumulation will be detectable.

Accumulation is inversely proportional to the fraction of the dose lost in each dosing interval.

\[
\text{Fraction lost in one dosing interval} = 1 - \text{fraction remaining}
\]

\[
\text{Accumulation factor} = \frac{1}{1 - \text{fraction remaining}}
\]  \hspace{1cm} (5)

For a drug given every half-life, the accumulation factor is 1/0.5 = 2.

The accumulation factors predicts the ratio:

\[
\frac{\text{steady state } C}{\text{C observed at same time following first dose}}
\]

Thus peak concentration after intermittent doses at steady-state = peak concentration after the first dose * accumulation factor
Bioavailability

The fraction of unchanged drug reaching the systemic circulation following administration via any route. For an IV dose of drug, bioavailability is assumed to be 1.

<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability (%)</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>100 (by definition)</td>
<td>Most rapid onset</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>75 to ≤ 100</td>
<td>Large volumes feasible; painful</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>75 to ≤ 100</td>
<td>Smaller volumes than IM; may be painful</td>
</tr>
<tr>
<td>Oral</td>
<td>5 to ≤ 100</td>
<td>Most convenient; first pass effect may be significant</td>
</tr>
<tr>
<td>Rectal</td>
<td>30 to ≤ 100</td>
<td>Less first pass effect than oral</td>
</tr>
<tr>
<td>Inhalation</td>
<td>5 to ≤ 100</td>
<td>Often very rapid onset</td>
</tr>
<tr>
<td>Transdermal</td>
<td>80 to ≤ 100</td>
<td>Usually very slow absorption; lack of first pass effect; prolonged duration of action</td>
</tr>
</tbody>
</table>
Extent of Absorption

After oral administration, a drug may be incompletely absorbed from the gut e.g. on 70% of digoxin reaches the systemic circulation. This results from lack of absorption in the gut and is largely explained by bacterial metabolism of digoxin.

Other drugs may be too hydrophilic (e.g. atenolol) to cross the lipid bilayer of the cell membrane. Others may be too hydrophobic (lipophilic; e.g. acyclovir) to cross the water layer adjacent to the epithelial cells of the gut.

It has also been recognized that drugs may not be absorbed because of metabolism in the gut wall and reverse transport out of epithelial cells back into the gut lumen. This transport is mediated by a family of carrier proteins (e.g. P-glycoprotein). Over 250 multi-drug resistance carriers family members have been identified by the several genome sequencing projects. These drug exporters are particularly diverse in bacteria and fungi and are significantly upregulated in proliferating cells during chemotherapy. P glycoprotein activity and metabolism can be inhibited by grapefruit juice which serves to increase drug absorption across the gut.
First pass elimination

Following absorption by the gut, the portal blood delivers the drug to the liver prior to entry into the systemic circulation. A drug can be metabolized in the gut wall or even in the portal blood, but most commonly it is the liver that is responsible for metabolism before the drug reaches the systemic circulation. The liver may also excrete the drug into the bile. These processes leading to reduced bioavailability are known collectively as first-pass loss or elimination.

The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction ratio (ER):

\[ ER = \frac{CL_{\text{liver}}}{Q} \]  

where \( Q \) is hepatic blood flow \( \approx 90\text{L/h} \) in a person weighing 70 kg.
Exam-type question
If hepatic blood flow is 90 L/h in a 70 kg person and hepatic clearance of morphine is 60 L/h/70 kg, the first pass extraction ratio is:

a. 150 L/h/70 kg
b. 1.5
c. 0.67
d. 30 L/h/70 kg
e. 5,400 (L/h/70 kg)^2
The systemic availability of the drug (F) can be predicted from the extent of GI absorption (f) and the extraction ratio (ER)

\[ F = f \times (1 - ER) \]  (7)

A drug such as morphine is almost completely absorbed (f = 1) such that loss in the gut is negligible. However, hepatic extraction ratio of morphine is 0.67, so 1 - 0.67 = 0.33.

Thus the bioavailability of morphine is expected to be about 33% which is close to the observed value (24%).

**Rate of Absorption**

Bioavailability is sometimes used to indicate both the extent and rate at which an administered dose reaches the general circulation.

The rate of absorption is determined both by the site of administration and the drug formulation. Both the rate of absorption and the extent of input can affect clinical effectiveness.
In this example, a drug is injected in 3 forms:

A. The drug is rapidly absorbed and completely available.

B. The drug is rapidly absorbed but only 50% available.

C. The drug is absorbed at half the rate of A & B but completely available.

TC is target concentration.
Zero-order drug absorption

The rate of absorption is independent of the amount remaining in the gut (e.g. is determined by rate of gastric emptying or by a controlled release formulation)

First-order drug absorption

The rate of absorption is proportional to the amount in the gut (e.g. the full dose is dissolved in GI fluids).
### Exam-type question

If hepatic blood flow is 90 L/h in a 70 kg person, hepatic clearance of midazolam is 25 L/h/70 kg, and oral availability is 44%, the systemic bioavailability of midazolam is:

- a. 12%
- b. 28%
- c. 0
- d. 32%
- e. 164%
Extraction ratio and First-Pass Effect

Systemic clearance is unaffected by bioavailability. However, clearance markedly affects availability because it determines the extraction ratio.

Therapeutic blood concentrations are attainable by oral administration if larger doses are given. However, drug metabolite concentrations are increased by this approach versus IV administration.

e.g. lidocaine is used to treat cardiac arrhythmias and have a bioavailability of < 40%. However, lidocaine is never given orally because its metabolites are believed to contribute to CNS toxicity.

Drugs with high hepatic ERs include isoniazid, morphine, propranolol, verapamil and tricyclic antidepressants.

These drugs will show marked variations in bioavailability between subjects because of differences in hepatic function and blood flow.

Diseases treated by significant intra- or extra-hepatic circulatory shunting will impact bioavailability of these drugs. For highly extracted drugs, shunting blood past hepatic sites of elimination will substantially increase drug availability. For poorly extracted drugs, shunting past hepatic sites will have little effect on drug availability.
Alternative Administration Routes & First-pass effect

(\textit{Parenteral administration – via non gastrointestinal routes})

There are several clinical reasons for using different routes of administration:

1) Convenience (e.g. oral)
2) Maximize concentration at site of action (and minimize it elsewhere; e.g. topical)
3) Prolong the duration of drug absorption (transdermal)
4) Avoid the first-pass effect.

Hepatic first-pass can be avoided by use of sub-lingual tablets and transdermal preparations and to a lesser extent by use of rectal suppositories. Sublingual and transdermal routes provide direct access to systemic - not portal - veins.
Drugs absorbed from suppositories in the lower rectum enter vessels that empty into the inferior vena cava thus bypassing the liver. However, the upper region of the rectum contains veins that lead to the liver predominate. Thus only 50% of a rectal dose can be assumed to bypass the liver.

Although drugs administered by inhalation bypass the hepatic first-pass effect, the lungs may serve as a site of first-pass loss by excretion and metabolism.
Time course of Drug Effects

The principles of pharmacokinetics and pharmacodynamics provide a framework for understanding the time course of drug effects.

In the simplest case, drug effects are proportional to [drug]. However, this does not mean that effects simply parallel the course of concentrations. Consider the Angiotensin Converting Enzyme (ACE) inhibitor, enalapril.

Here we plot conc of enalapril (ng/mL) remaining in the blood following a single oral dose (half-time for elimination is 3 hr). Because EC$_{50}$ for the action of enalapril is 1 ng/mL, its inhibitory action does not mirror its elimination. Remember, inhibition $\approx C*I_{\text{max}}/(EC_{50}+C)$.

Even though C at 24 h is < 1% of its peak, this C $\approx 0.5$ EC$_{50}$.
Time course of Drug Effects – some rules of thumb

When [] are in the range between $EC_{50}/4$ and $4 EC_{50}$, the time course of effect is essentially a linear function in time - 13% of the effect is lost every half-life.

At [] below $EC_{50}/4$, the time course of effect is a linear function in [drug] and the effect will follow the exponential decline in [drug]. It is only when [drug] is low relative to $EC_{50}$ that the concept of a half-life of effect has any meaning.

Time course of Drug Effects – Delayed Effects

Changes in drug effects are often delayed in relation to changes in drug concentration. This may reflect the time required to distribute the drug from plasma to the target site. This distribution delay is pharmacokinetic and may account for delays of a few minutes (e.g. plasma to CNS delays).
Time course of Drug Effects – Delayed effects (cont)

A more common reason for more prolonged delay effects is the slow turnover of a physiologic agent that is involved in the expression of drug action.

e.g. warfarin acts as an anticoagulant by inhibiting hepatic vitamin K epoxidase. This inhibitory action occurs rapidly and closely mirrors plasma [warfarin]. However, the clinical effect reflects the decrease in serum prothrombin complex of clotting factors. Vitamin K epoxidase inhibition decreases the synthesis of these clotting factors but the complex has a long half-life (14 hr) and it is this half-life that determines the rate of expression of the clinical effect.
Time course of Drug Effects – Cumulative Effects

Some drug effects are related to a cumulative action rather than to a rapidly reversible event.

The renal toxicity of aminoglycoside antibiotics is greater when administered as a constant infusion versus intermittent dosing. The accumulation of aminoglycoside in the renal cortex is thought to cause renal damage.

While both dosing schemes produce the same average $[\text{drug}]_{\text{steady-state}}$, the intermittent dosing scheme produces much higher peak concs which saturate an uptake system into the cortex. Total aminoglycoside uptake is thus less with the intermittent dosing scheme.

The difference in toxicity is the predictable result of different patterns of concentration and the saturable uptake system.
Designing a rational dosage regimen - Target Concentration Approach

A rational dosage regimen assumes that there is a target concentration that will produce the desired therapeutic effect. By considering pharmacokinetic factors that determine the dose-concentration relationships, it is possible to individualize the dose regimen to achieve the target concentration.

The table shown at the end of this handout indicates concentration ranges necessary for effective treatment. The initial TC should be chosen from the lower end of the range.

Maintenance dose

Drugs are administered in such a way as to maintain a steady-state of drug in the body - enough is given in each dose to replace the drug eliminated since the preceding dose. Calculating the maintenance dose is thus a primary goal.
Clearance is the most important pharmacokinetic parameter in considerations of steady-state dose regimens.

At steady state (SS), the dosing rate (rate in) must equal the rate of elimination (rate out). Substitution of target concentration (TC) for $C$ predicts the maintenance dosing rate:

$$Dosing\ rate_{SS} = Rate\ of\ elimination_{SS}$$
$$= CL \times TC$$  \hspace{1cm} (8)

Thus if the TC is known, the clearance in that patient will determine dosing rate.

If the route of administration has a bioavailability $< 100\%$, the dosing rate must be modified. For oral dosing:

$$Dosing\ rate_{oral} = \frac{Dosing\ rate_{SS}}{F_{oral}}$$  \hspace{1cm} (9)
If intermittent doses are given, the maintenance dose is calculated from:

\[ \text{Maintenance dose} = \text{Dosing rate} \times \text{Dosing interval} \]  

**Maintenance dose calculation example**

A target plasma [theophylline] of 10 mg/L is required to relieve acute bronchial asthma. Assuming the patient is healthy in all other regards, we may use the mean theophylline clearance of 2.8 L/h/70 kg (see PK table). Since the drug is administered IV, \(F = 1\).

\[
\text{Dosing rate} = CL \times TC \\
= 2.8 \text{ L/h/70 kg} \times 10 \text{ mg/L} \\
= 28 \text{ mg/h/70 kg}
\]

Following relief of the asthma attack, the physician might want to maintain this level using oral theophylline. According to the PK table, \(F_{\text{oral}} = 0.96\). When dosing every 12 h, each maintenance dose would be:

\[
\text{Maintenance dose} = \frac{\text{Dosing rate} \times \text{Dosing interval}}{F_{\text{oral}}} \\
= \frac{28 \text{ mg/h} \times 12 \text{ h}}{0.96} \\
= 350 \text{ mg}
\]
If the dosing interval were shorter or longer, the maintenance doses shown above would be used. A capsule size close to the ideal dose would be prescribed at the indicated interval.

In practice, F could be omitted because it is so close to 1.

Note that the volume of distribution and half-life need not be known in order to calculate the average plasma concentration expected for a given dosing rate or to predict the dosing rate for a desired target concentration.

PK parameters need are: TC, CL, dosing interval and F

<table>
<thead>
<tr>
<th>Dosing Rate mg/h/70 kg</th>
<th>F</th>
<th>Dosing Interval hours</th>
<th>Maintenance Dose mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>0.96</td>
<td>4</td>
<td>117</td>
</tr>
<tr>
<td>28</td>
<td>0.96</td>
<td>8</td>
<td>233</td>
</tr>
<tr>
<td>28</td>
<td>0.96</td>
<td>12</td>
<td>350</td>
</tr>
<tr>
<td>28</td>
<td>0.96</td>
<td>24</td>
<td>700</td>
</tr>
</tbody>
</table>
Relation between dosing frequency & minimum plasma levels when a steady-state theophylline of 10 mg/L is desired. The smooth red line shows the [drug] achieved with an intravenous infusion of 28 mg/hour. The doses for 8-hourly oral administration (black) are 233 mg; for 24-hourly oral administration are 700 mg. In each instance, the mean steady-state theophylline is 10 mg/L.
Computation of dosing rate and average $[\text{ss}]_{ss}$ are independent of any specific PK model. In contrast calculations of maximum and minimum concentrations (see last figure) do require PK assumptions.

The accumulation factor calculation assumes a one-compartment body model.

Peak $[]$ prediction assumes absorption rate $>$ elimination rate

In a clinical situation, these assumptions are reasonable for calculation of minimum and maximum $[]$s.
### Loading Dose

When the time needed to achieve steady-state is great, it may be desirable to administer a loading dose that raises \([\text{drug}]_{\text{plasma}}\) to the TC. In theory only the amount of loading dose need be computed.

\(V_d\) relates the total amount of drug in the body to concentration in plasma \((C_p)\). Thus substituting TC for \(C_p\), we obtain:

\[
\text{Loading dose} = \text{amount in body following loading dose} = V_d \times TC
\]  

(11)

For theophylline, the loading dose would be

\[
V_d \ (35 \text{ L}) \times \text{TC} \ (10 \text{ mg/L}) \]

\[= 350 \text{ mg for a 70 kg person.}\]
To this point, we have ignored the fact that drugs show complex, multicompartment pharmacokinetics. While this assumption is reasonable in most cases, in some instances this cannot be ignored - especially with respect to loading doses.

If the rate of absorption is rapid relative to distribution (e.g. as is the case with IV bolus injection), the initial $[\text{drug}]_{\text{serum}}$ resulting from an appropriate loading dose – calculated using the apparent $V_{d}$ – can be initially many times greater than desired. Severe transient toxicity might occur!

This is especially true of lidocaine (an anti-arrhythmic) where instantaneous toxicity can occur.

While the *amount* of loading dose may be correct, the *rate of administration* can be crucial in preventing excessive $[\text{drug}]$. Slow administration of an IV drug over several minutes is prudent practice. For example, IV administration of theophylline should be over a 20 minute interval to avoid $\text{high} [\text{theophylline}]_{\text{plasma}}$ during the distribution phase.
These basic principles can be used to interpret clinical [drug] measurements on the basis of 3 PK variables:

- absorption, clearance, volume distribution

and 2 pharmacodynamic variables:

- maximum efficacy in the target tissue, potency

Diseases may modify all of these parameters and the ability to predict the effect of disease states on pharmacokinetic parameters is important in adjusting dosage.

**A. Absorption**

Compliance failure (over- or under-dosage) can be detected by [drug] measurements in which deviations from expected values are obtained.

If compliance is adequate, absorption abnormalities in the small bowel frequently accounts for low [drug]. Also variations in metabolism during absorption affect bioavailability.
B. Clearance
Clearance abnormalities may be expected when there is major impairment of the kidney, liver or heart. Drug clearance may be a useful indicator of the functional consequences of heart, liver or kidney failure.

C. Volume of distribution
Apparent volume of distribution is a balance between binding to tissues which increases $V_d$ and binding to plasma proteins which increases plasma concentrations and makes $V_d$ smaller.

Older people have a reduction in skeletal muscle mass and thus bind less (and therefore have a lower $V_d$ for) digoxin. $V_d$ may be overestimated in obese patients if based on body weight and the drug does not enter fatty tissues well e.g. digoxin.

Theophylline has a $V_d$ similar to that of total body water. Adipose has a similar water content to other tissues. Thus $V_d$ for theophylline is proportionate to body weight even in obese patients.

Accumulation of fluid (edema, ascites) markedly increases $V_d$ of hydrophilic drugs (e.g. gentamicin) that normally have a small $V_d$. 
D. **Half-life**
Differences between clearance and half-life are useful in understanding the basis of the effect of disease on drug disposition. e.g. $t_{1/2}$ diazepam increases with age. However, clearance of diazepam does not change with age. The increase in $t_{1/2}$ results from increased $V_d$. Metabolic processes giving rise to $CL_{diazepam}$ are unchanged.

**Pharmacodynamic variables**

A. **Efficacy**
All pharmacological responses saturate at $E_{max}$ when $[\text{drug}] \gg EC_{50}$. Recognizing that saturation has been achieved avoids administration of further, ineffectual (and possibly toxic) doses of drug.

B. **Potency**
$EC_{50}$ is that $[\text{drug}]$ where the effect is 50% $E_{max}$. Failure of response due to diminished potency/sensitivity can be detected by measuring $[\text{drug}]$ in a patient who is not improving but who is receiving normal dosage.
Reduced sensitivity can result from abnormal physiology:  
*e.g.* hyperkalemia inhibits *digoxin binding to Na,KATPase* and thus diminishes responsiveness to *digoxin.*

or from drug antagonism:  
*e.g.* *Ca channel blockers impair cardiac inotropic response to digoxin.*

---

### The Target Concentration Strategy (TCS)

Concentration links pharmacokinetics to pharmacodynamics. TCS is a process for optimizing dosage in an individual on the basis of a measured surrogate response such as [drug]. The steps are:

1. **Chose TC**
2. **Predict** $V_d$ and CL from standard population values with adjustments for mass & renal function
3. **Give loading or maintenance dose calculated from TC, $V_d$ and CL**
4. **Measure patient’s response and [drug]**
5. **Revise $V_d$ and/or CL based on measured [drug]**
6. **Repeat steps 3-5, adjusting predicted dose to achieve TC**
Interpretation of [Drug] measurements

Clearance.

Clearance is the single most important factor determining [drug].

Factors influencing clearance are:
1. Dose
2. Blood flow
3. Intrinsic function of liver and kidneys

Changes in protein binding may fool one into suspecting a change in clearance when in fact drug elimination is unchanged.

E.g. drugs such as salicylates are extensively bound to albumin. Albumin levels are low in some disease states resulting in lower \([\text{salicylate}]_{\text{plasma}}\) and thus increased \(V_d\).

\[
t_{1/2} = \frac{0.693 \cdot V_d}{CL} = \frac{L \cdot h \cdot 70\,kg}{70\,kg \cdot L} = h
\]

(4)

Thus increased \(V_d\) will increase \(t_{1/2}\) without a change in CL.
Adjustments for individual patients

Volume of distribution

$V_d$ is calculated for an individual using body weight. If a patient is obese, drugs that do not penetrate fat (e.g. disoxin, tobramycin) should have their volumes calculated from ideal body weight as shown below:

Ideal body wt (kg)  
= 52+1.9 kg/in height over 5 ft (men)  
= 49+1.7 kg/in height over 5 ft (women)

Patients with edema, ascites or pleural effusions offer larger $V_d$ to aminoglycoside antibiotics (e.g. tobramycin) than is predicted by body weight. The correction is:

1. Subtract estimate of wt of excess fluid accumulation
2. Use this new wt to compute $V_d$
3. Increase $V_d$ by adding 1 L for each kg of excess fluid.

This is important owing to the relatively small $V_d$ of water-soluble drugs.
Adjustments for individual patients

Clearance

Renal disease or reduced cardiac output often reduce the clearance of drugs that depend on renal function. Altered clearance by liver is much less common but can occur.

The dose in a patient with renal impairment may be calculated as:

\[
\text{corrected dose} = \text{average dose} \times \frac{\text{patient's creatine clearance}}{100 \text{ mL/min}}
\]

where 100 mL/min is the normal creatine clearance.

This simplified approach ignores nonrenal routes of clearance. If a drug is cleared by renal and nonrenal routes, this equation should be applied to the part of the dose that is cleared by the kidney.

e.g. if a drug is 50% cleared by the liver and 50% by the kidney and the normal dose is 200 mg/d, the corrected dose in a patient with a creatine clearance of 20 mL/min will be:

\[
dose = 100 \text{ mg/d} + 100 \text{ mg/d} \times \frac{20 \text{ mL/min}}{100 \text{ mL/min}}
\]

\[
dose = 100 \text{ mg/d} + 20 \text{ mg/d} = 120 \text{ mg/d}
\]
Summary

• Pharmacokinetics
  the action of the body on drugs

• Volume distribution
  $V_d =$ amount of drug in body/plasma [drug]

• Clearance
  $CL = \frac{\text{rate of drug elimination}}{\text{plasma [drug]}}$

• Half-life
  $t_{1/2} = \frac{0.693 \times V_d}{CL}$

• Drug Accumulation
  Accumulation Factor = $\frac{1}{1 - \text{Fraction remaining}}$

• Bioavailability
  Fraction of drug reaching systemic circulation following administration by any route

• Extraction Ratio & First Pass Effect
  $ER = \frac{CL_{liver}}{Q}$

• Other routes of Administration
  Parenteral routes bypass hepatic portal circulation (sublingual, transdermal, IM, subcut., IV, inhalation, rectal)
• **Target Concentration (TC)**

  Concentration (range) of drug required to produce the desired therapeutic effect

• **Time course of drug effects**


- \( Dosing \ rate_{ss} = CL \times TC \)
- \( Dosing \ rate_{oral} = \frac{CL \times TC}{F_{oral}} \)

  \( Maintenance \ Dose = dosing \ rate \times dosing \ interval \)

  \( loading \ dose = \frac{V_{d} \times TC}{CL} \)

• **Therapeutic Drug Monitoring**

  Ideal wt (kg) = 52 + 1.9 kg/in height over 5 ft (men) = 49 + 1.7 kg/in height over 5 ft (women)

  In patients with renal impairment:

  \( corrected \ dose = \frac{patient's \ creatine \ clearance}{100 \ mL/min} \times \text{average dose} \)
### Table 3-1. Pharmacokinetic and pharmacodynamic parameters for selected drugs.
(See Speight & Holford, 1997, for a more comprehensive listing.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Availability (F) (%)</th>
<th>Urinary Excretion (%)</th>
<th>Bound in Plasma (%)</th>
<th>Clearance (L/h/70 kg)</th>
<th>Volume of Distribution (L/76 kg)</th>
<th>Half-Life (h)</th>
<th>Target Concentrations</th>
<th>Toxic Concentrations</th>
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<td>0.6 mg/L</td>
<td>...</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>100</td>
<td>2</td>
<td>93</td>
<td>0.462</td>
<td>9.1</td>
<td>14</td>
<td>75 mg/L</td>
<td>&gt;150 mg/L</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>...</td>
<td>79</td>
<td>30</td>
<td>5.88</td>
<td>27</td>
<td>5.6</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Verapamil</td>
<td>22</td>
<td>3</td>
<td>90</td>
<td>63</td>
<td>350</td>
<td>4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Warfarin</td>
<td>93</td>
<td>3</td>
<td>99</td>
<td>0.192</td>
<td>9.8</td>
<td>37</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>63</td>
<td>18</td>
<td>25</td>
<td>61.8</td>
<td>98</td>
<td>1.1</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

¹Convert to mL/min by multiplying the number given by 16.6.
²Varies with concentration.
³Target area under the concentration time curve after a single dose.
⁴Can be estimated from measured Cₘ using CL = Vₘₐₓ/(Kₘ + Cₘ). Vₘₐₓ = 415 mg/d, Kₘ = 5 mg/L. See text.
⁵Varies because of concentration-dependent clearance.