

Pharmacokinetics Overview

Disclaimer: This handout and the associated lectures are intended as a very superficial overview of pharmacokinetics.

Summary of Important Terms and Concepts

- Absorption, peak levels, loading dose, volume of distribution
- Bioavailability
- Elimination by 1st order kinetics, exponential decay, half life, clearance
- Steady state, drug accumulation, maximum and minimum drug levels with intermittent dosing
- Importance of half lives in TDM consults
- Distribution phase
- Non-linear or Zero-order pharmacokinetics
- Plasma protein binding
- Varying goals of TDM, peaks vs. troughs, etc.

Three Critical Equations

$$1) []_{\text{bolus}} = \text{dose} / V_d$$

$$2) []_{\text{steady state}} = \text{rate}_{\text{in}} / \text{Cl}$$

$$3) \text{Cl} = (0.693 * V_d) / t_{1/2}$$

From the above three equations, it is clear that the critical data to obtain for TDM/pharmacokinetic consultation is the **dosage**, **V_d** and either the **Cl** or **t_{1/2}** of the drug. Note that V_d and Cl usually given in weight-based units; hence, it is also necessary to find out the patient's weight. Of course, knowledge of the references ranges for efficacy and toxicity of the drug is critical as well.

References

- 1) *Basic Clinical Pharmacokinetics*, 3rd edition by Michael E Winters (1994).
- 2) Chapter 11, *Pharmacokinetics and Toxicokinetics* in Goldfrank's Textbook of Toxicology.
- 3) Chapter 26, *Therapeutic Drug Monitoring* in Tietz's Textbook of Clinical Chemistry.

Absorption and Peak Levels

After a single, “instantaneous”, intravenous administration of a drug, the resulting peak **plasma concentration** ($[]$) can be related to the dose by the **volume of distribution** (V_d).

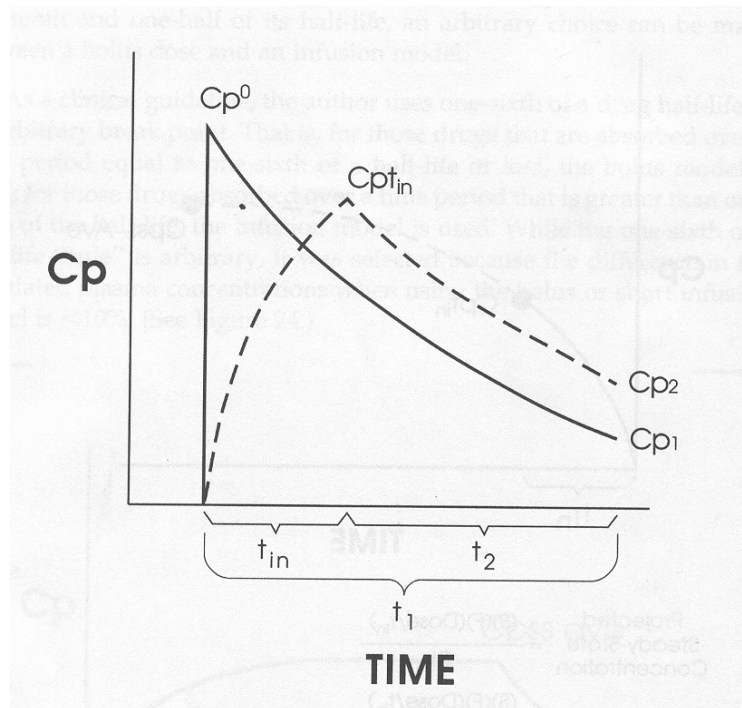
$$[]_{\text{inst.,peak}} = \text{dose} / V_d$$

Think of V_d s as the volume of water required to dilute the drug to an equivalent concentration. For example, if a drug is limited to the plasma volume (like Ab-derived medications), then the V_d is the patient’s plasma volume. However, most often V_d s do *not* correspond to “real” body volumes in this way. Instead, because of drug binding to lipids and proteins in body tissues, V_d s more typically represent theoretical volumes.

V_d s may relate to plasma volume, blood volume, total extracellular water, total body water, etc., but are almost always modified by tissue binding.

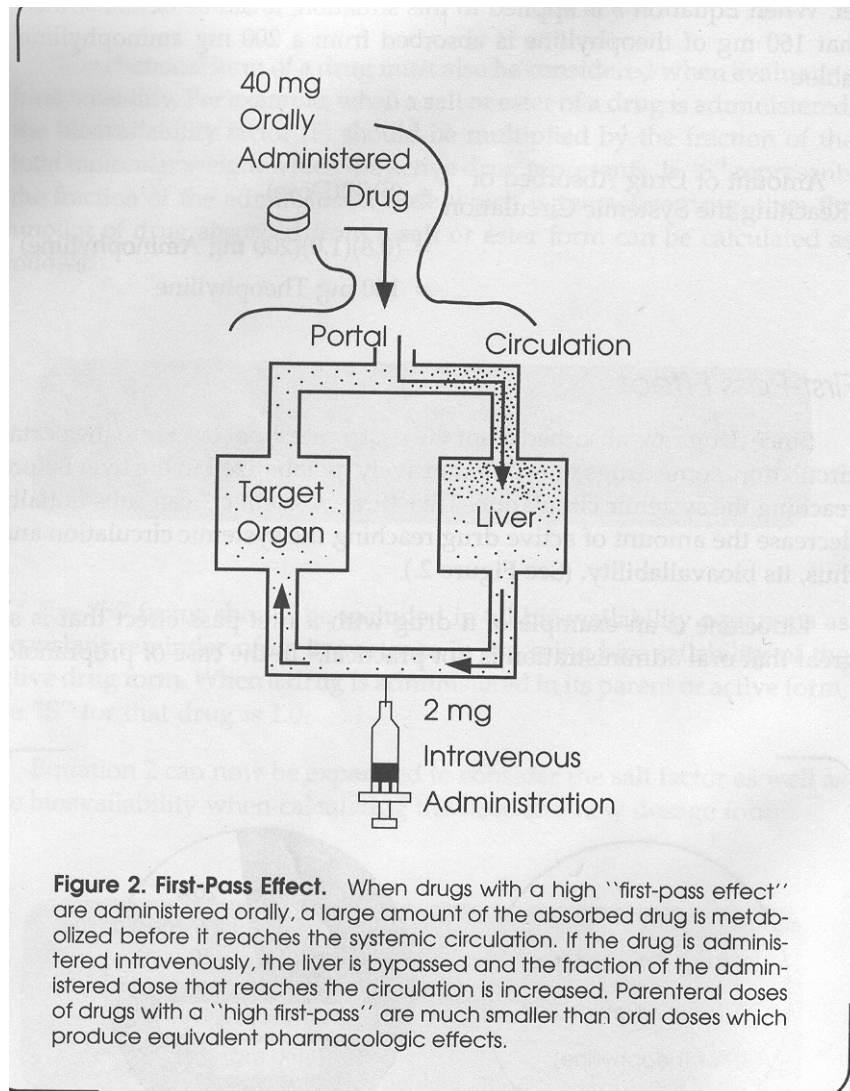
V_d s are used to calculate loading doses of medications with long half-lives. These are then followed by appropriate maintenance doses (see steady state calculations).

In reality, non-instantaneous absorption and distribution of the drug leads to peak plasma levels lower than the theoretical instantaneous peak value above. Although absorption of many drugs follows a logarithmic curve and could be described mathematically, many reasons for variability exist (gastric pH, physical factors: e.g. concretions & bezoars, delayed gastric emptying, pylorospasm, etc.) and this is not routinely considered.



Bioavailability

Bioavailability reflects loss or deactivation of administered medication and is route-dependent. For example, poor absorption and “first-pass” hepatic metabolism are important with oral administration but not IV. Intramuscular and subcutaneously administered medications have separate issues.



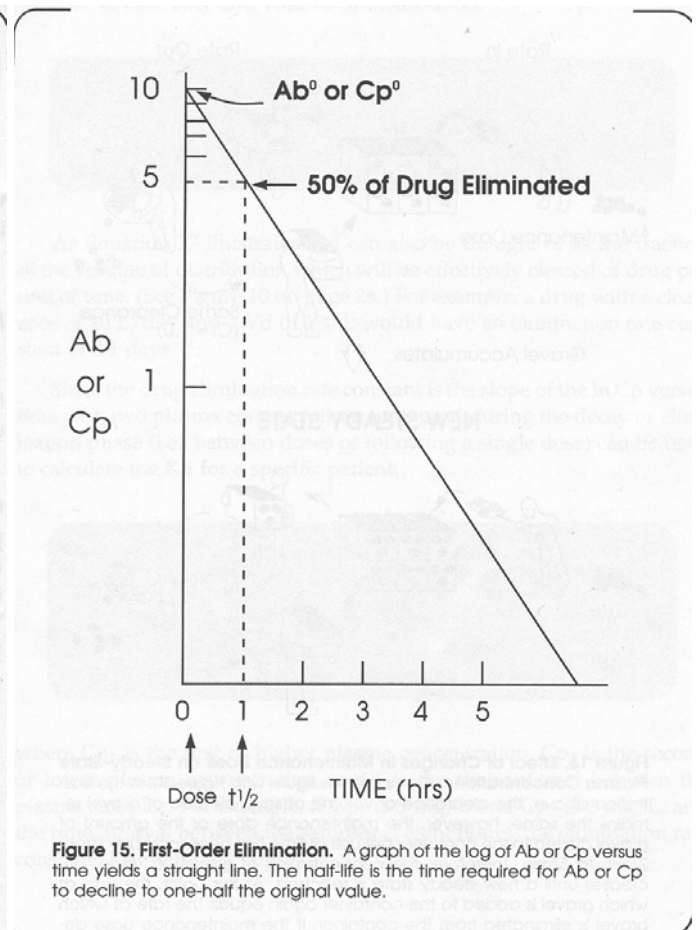
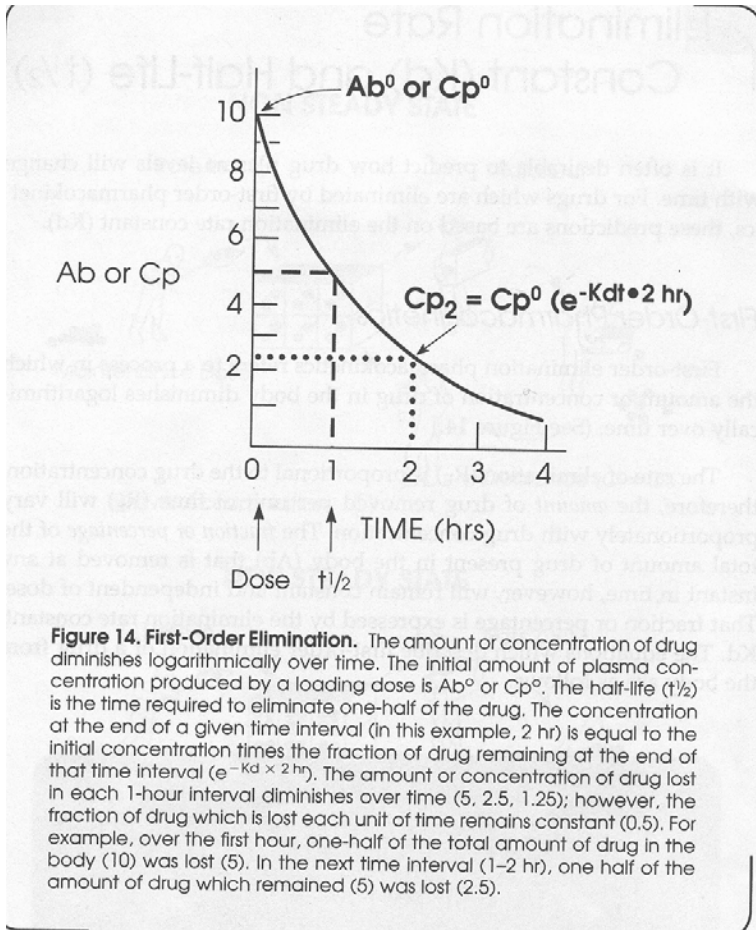
Elimination of a Single Dose

A majority of drugs are “eliminated” by **first-order kinetics**, which can be characterized by a single **exponential decay curve**.

$$d[]/dt = k * []_t$$

$$[]_t = []_0 \exp(-kt)$$

$$\ln([]_t) = \ln([]_0) - kt$$



When plotted as a semi-log, the logarithm of the plasma drug concentration ($\ln C$) is linear with time. Exponential decay curves are characterized by half-lives ($t_{1/2}$), where the exponential rate constant, k , can be related to the **half life**: $k = 0.693 / t_{1/2}$.

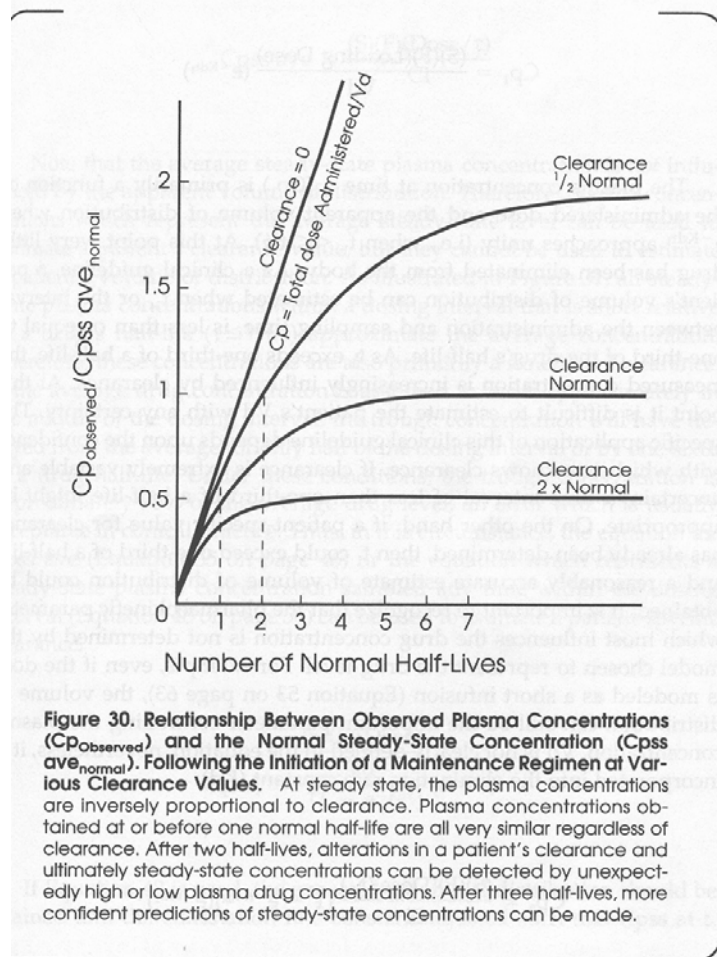
First order kinetics basically means that the rate of drug elimination linearly depends on drug concentration (hence, sometimes hear about linear vs. non-linear pharmacokinetics). When the drug concentration increases, a proportional increase in the elimination rate occurs. Therefore, after a single dose of a drug the rate of elimination is fastest initially but then slows as the drug level decreases. This is clearly seen in the exponential decay curves above and is encapsulated in the concept of a half life.

“Linear” pharmacokinetics implies that steady state drug levels are proportional dose; i.e. if you double the dose you will double the steady state plasma level of the dose.

Clearance

Clearance (CI) is an alternative and equivalent way to describe first order pharmacokinetics. Think of clearance as a way to describe the rate of drug elimination, which can be related to the instantaneous drug concentration in plasma. The definition of clearance is the volume of plasma “cleared” of drug per unit of time.

$$\text{Rate}_{\text{out}} = \text{CI} * []$$



Think about how this idea implies first order kinetics. As the concentration of drug decreases, the rate of elimination decreases proportionately. Clearance is constant as long as first order kinetics is maintained. On the right, we see how the steady state drug concentration doubles when clearance halves and vice versa.

Clearance is related to the exponential rate constant, above, by $\text{CI} = k * V_d$. However, more frequently one needs to relate clearance to half life or vice-versa:

$$\text{CI} = (0.693 * V_d) / t_{1/2}$$

Note that only the “free” drug (not bound to protein) is cleared. Protein-bound drug is sequestered from the mechanism of elimination and doesn't count. Without going into this in detail, let me just stress that it is important to know if the clearance you are using has been defined for free drug in plasma or total drug. Most often it has been defined for total drug since this is most commonly measured.

Steady State Drug Levels

When a drug is administered continuously, it **accumulates** in the body. Because of first order kinetics, the rate of drug elimination increases as the plasma concentration increases. Eventually, the rate of elimination matches the rate of drug administration and a **steady state** is achieved where the average plasma concentration of the drug is constant.

Hence, steady state implies that $\text{Rate}_{\text{out}} = \text{Rate}_{\text{in}}$. Because the rate of elimination depends on the clearance and the plasma drug concentration (previous page), an equation can be derived relating the average concentration of the drug at steady state to the average rate of drug administration:

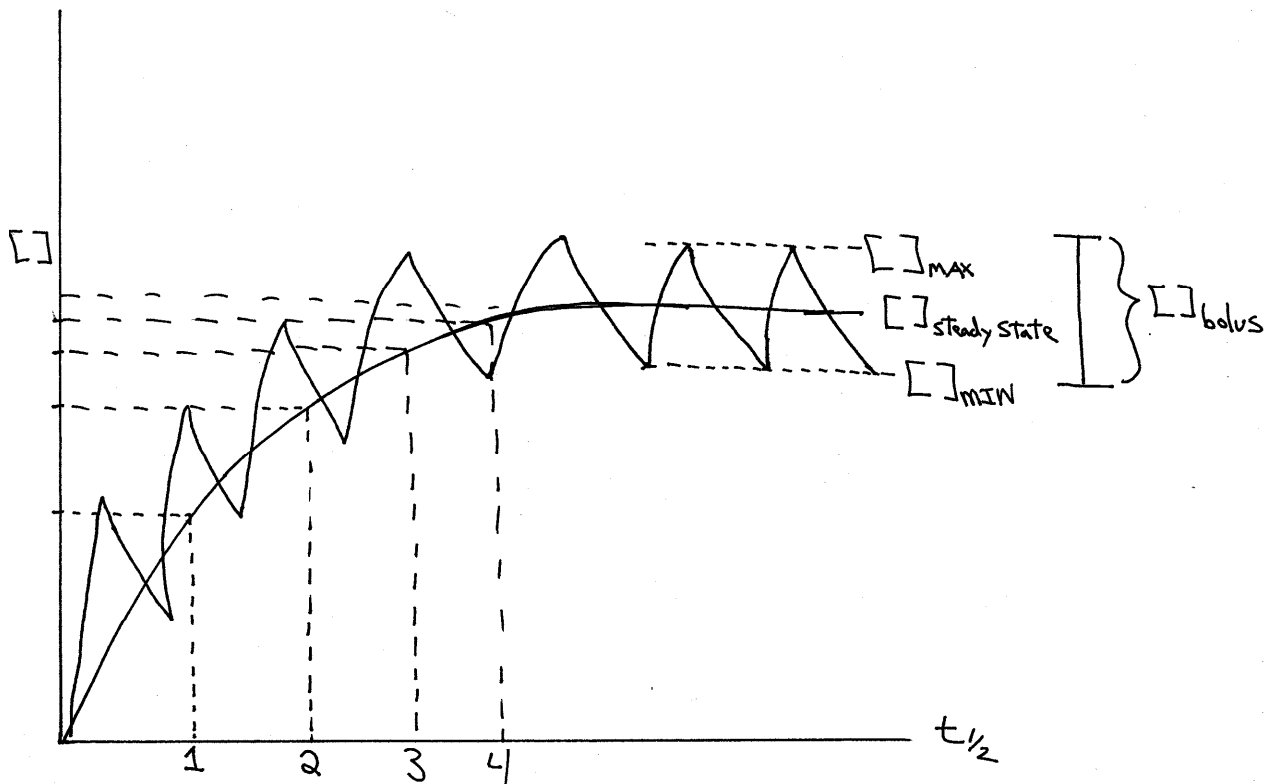
$$[]_{\text{steady state}} = \text{Rate}_{\text{in}} / \text{Cl}$$

For intermittent dosing, calculating concentrations becomes much more complex and a “saw tooth” pattern of drug concentrations can be seen. The maximum and minimum drug levels are most relevant during intermittent dosing and can be related to complex equations not detailed here. Instead, a very rough but useful approach can be utilized to approximate these values. This method assumes that $[]_{\text{steady state}}$ occurs about halfway between the maximum and minimum drug concentrations and also that drug absorption is instantaneous.

$$[]_{\text{bolus}} = (\text{single dose}) / Vd$$

$$[]_{\text{max}} = []_{\text{steady state}} + \frac{1}{2} * []_{\text{bolus}}$$

$$[]_{\text{min}} = []_{\text{steady state}} - \frac{1}{2} * []_{\text{bolus}}$$



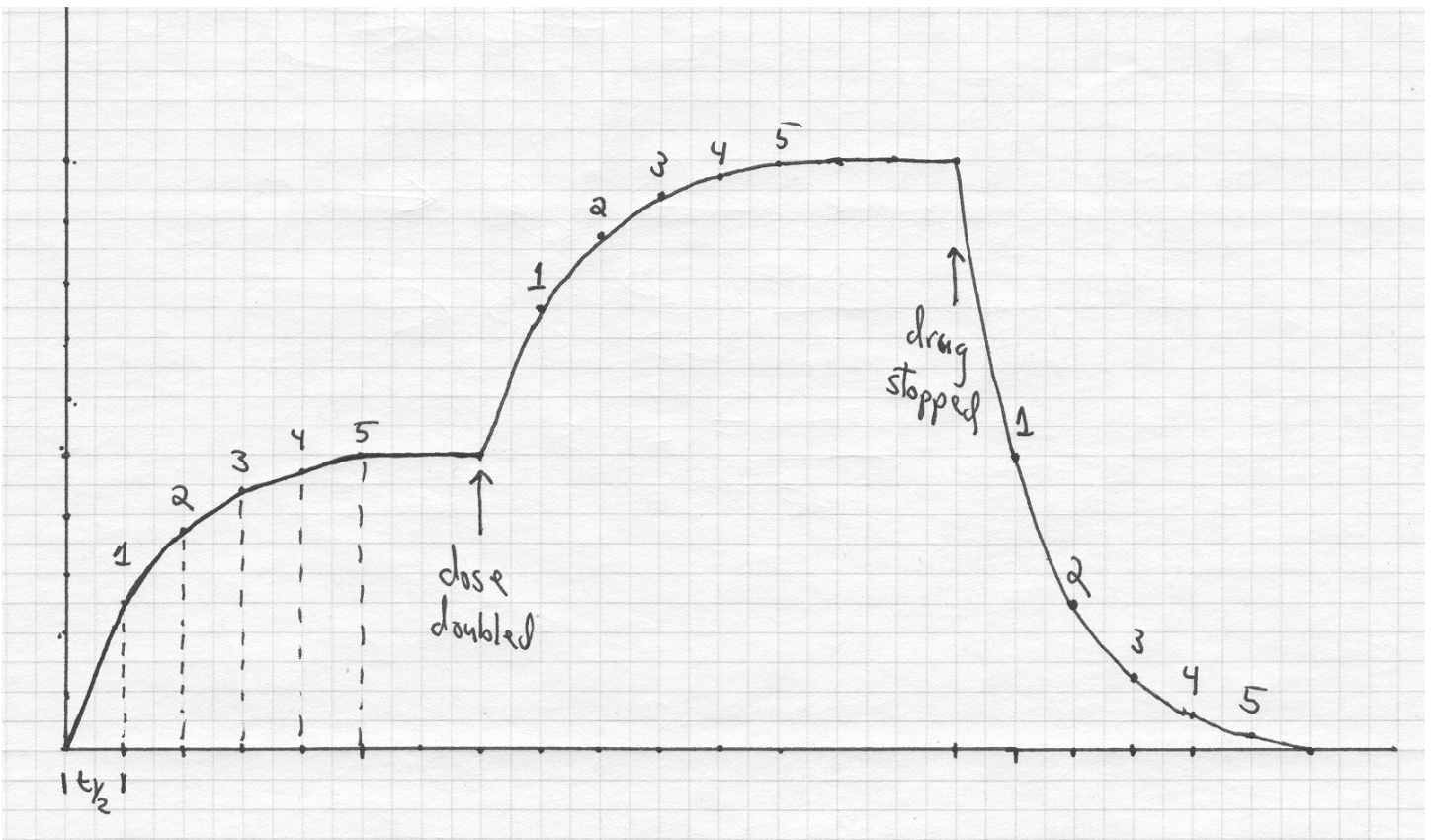
Importance of Half Lives

“When investigating a TDM issue, the most important fact to know up about a drug is its half life.”

Half life is the key for knowing

- (1) When a new medication is started, how long until the patient reaches steady state?
- (2) When a patient stops taking a medication, how long until it is gone?
- (3) When dosage is changed, how long until a new steady state is achieved?

- 1 * $t_{1/2} = 50\%$
- 2 * $t_{1/2} = 75\%$
- 3 * $t_{1/2} = 87.5\%$
- 4 * $t_{1/2} = 93.75\%$
- 5 * $t_{1/2} = 96.875\%$

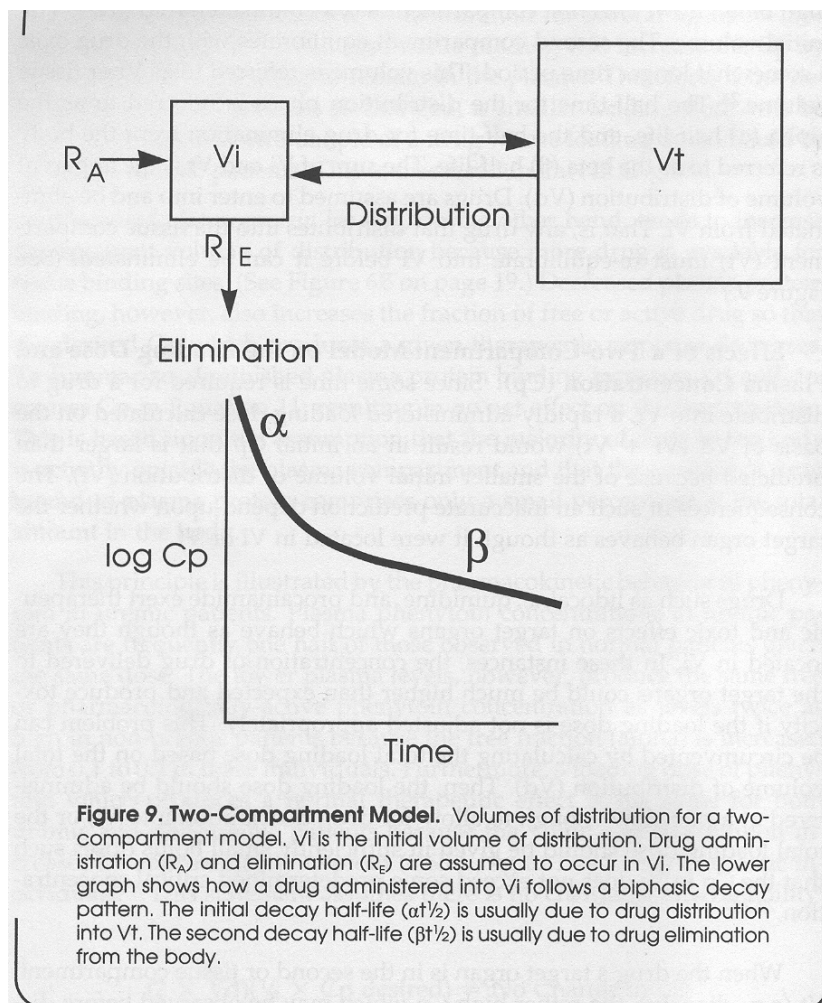


Distribution Phase

Many drugs demonstrate a **distribution phase** in their kinetic profile. After injection or absorption, most drugs rapidly equilibrate into an initial volume (such as plasma or extracellular water), from which they subsequently “distribute” into their final volume of distribution. Hence, kinetic profiles of plasma drug concentrations often display two phases of decay: an initial distribution phase followed by the true kinetic profile for drug elimination.

The distribution phase complicates therapeutic drug monitoring in the following ways

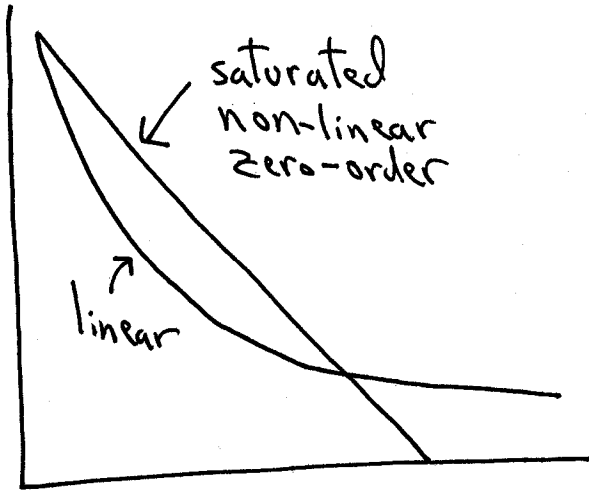
- 1) Peak plasma drug levels drawn too early do not always reflect physiologically relevant drug concentrations. Best known example of this problem is for digoxin, which distributes from a smaller volume ($\sim 1/10$ final V_d) into its final V_d over a few hours. Distribution is essentially complete by four hours (distribution phase half life of 0.5 – 1.0 hours). Drug levels collected before distribution is complete are often in the toxic range, but don't reflect true digoxin toxicity because the drug level at its site of action is much less.
- 2) Be cautious when looking up V_d s and make sure they reflect the physiologically relevant volume.
- 3) When determining an elimination half life, it is important to not use time points before distribution phase has completed.
- 4) When drugs have very long distribution phases, distinguishing distribution from elimination is very difficult. As well, correlating plasma drug levels with either efficacy or toxicity can be difficult. This is true for cyclosporine, for example.



Non-linear Pharmacokinetics

First-order kinetics, covered above, are often called linear pharmacokinetics because the rate of drug elimination is directly proportional to drug concentration (rate = $Cl \cdot [C]$ and $d[C]/dt = -k \cdot [C]$). However, any drug elimination process (e.g. enzymatic metabolism or glomerular filtration) will be “saturated” when the substrate (i.e. the drug) concentration is greatly increased relative to the “active” sites for the process. At that point, the rate of drug elimination becomes constant and independent of drug concentration and called non-linear or zero-order pharmacokinetics.

$$d[C]/dt = -k \quad [C] = [C]_{\text{initial}} - kt$$



Whereas linear pharmacokinetics displays an exponential decrease of drug concentration with time, non-linear pharmacokinetics displays a linear or constant decrease of drug with time. Tricky, eh?

So, whereas linear kinetics are characterized by a constant “half life”, non-linear kinetics are characterized by a constant loss of drug per unit time. An example is ethanol which is eliminated at a fixed 0.15 g/kg/hr (where g refers to the ethanol and kg refers to the patient’s weight; for a 70 kg person ethanol is eliminated at ~ 10.5 g/hr).

The major complication saturated elimination is unpredictability when drugs *transition* from linear to non-linear pharmacokinetics. A clear example of this problem occurs for phenytoin.

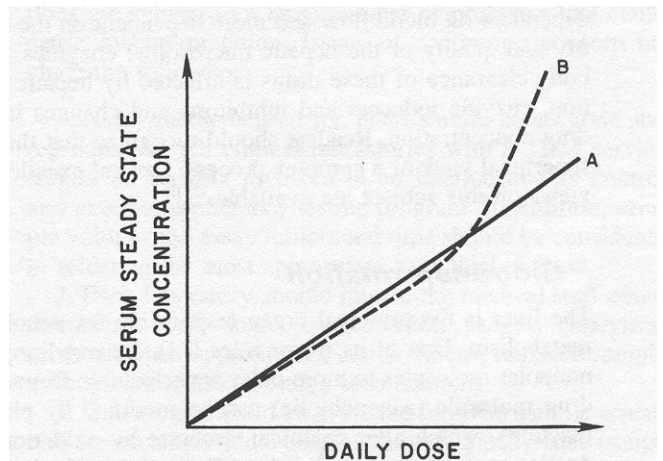
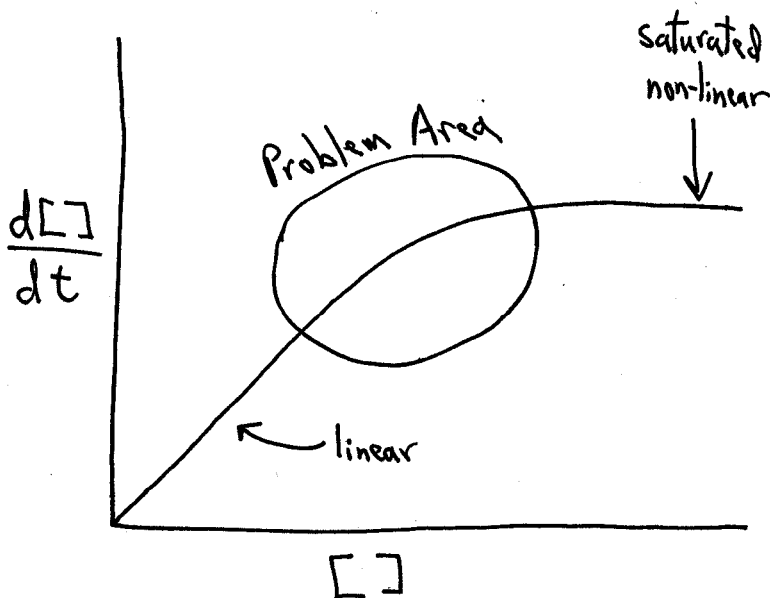


FIGURE 26-10. Dose-response curves. Line A illustrates the linear relationship between serum drug concentration and total daily dose of a drug that displays first-order kinetics. Line B illustrates the dose-response relationship for a drug that displays capacity-limited kinetics because of a saturable enzyme or transport mechanism; in this situation, serum concentration becomes independent of total daily dose, and the relationship of drug concentration to dose becomes nonlinear. (Adapted from Pippenger, C. Practical pharmacokinetic applications. Syva Monitor, January, 1977, pp. 1-4. Syva Co., San Jose, CA.)