Basic Clinical Pharmacokinetics

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More Information

- http://hodsdon.com/wiki
  - Look towards the bottom of the “Medicine” page
- *Basic Clinical Pharmacokinetics* (3rd Edition) by Michael E. Winter, Lippincott Publishing.
- *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy* by David Golan, *et al*., Lippincott Publishing.
- *Tietz Textbook of Clinical Chemistry (*4th Edition), edited by Carl A. Burtis *et al*., Chapters 33 & 34.

Important Concepts

- Absorption
  - peak levels, loading dose, volume of distribution, bioavailability.
- Elimination by 1st order kinetics
  - linear pharmacokinetics, exponential decay, half-life, clearance.
- Steady state drug levels
  - drug accumulation, maintenance dose, maximum and minimum drug levels with intermittent dosing.
- Complications
  - distribution phase, non-linear or zero-order pharmacokinetics, plasma protein binding.
- Varying goals for therapeutic drug monitoring (TDM)
  - use of peak versus trough drug levels.

Only Three Critical Equations

1) $[drug]_{peak} = dose / V_d$
   - Relates the peak drug level to a single dose and the volume of distribution (V_d).

2) $[drug]_{steady\ state} = rate_{in} / Cl$
   - Relates the steady state drug level to the “infusion rate” and the clearance (Cl) for a drug eliminated by 1st order or linear pharmacokinetics.

3) $Cl = (0.693 * V_d) / t_{1/2}$
   - Relates clearance (Cl) to half-life ($t_{1/2}$) and the volume of distribution (V_d).
   - For future reference, $Cl = k * V_d$, where k is the exponential rate constant for elimination and $k = 0.693 / t_{1/2} = 1 / \tau_c$.

Critical Clinical Data

- For the drug:
  - Rate of absorption, distribution and V_d.
  - Clearance (Cl) and/or half-life ($t_{1/2}$).
  - Relative roles of hepatic metabolism and renal elimination.
  - Reference range and recommended indices for TDM.
- For the patient:
  - Weight.
  - Drug dosing including time since any previous change in dosing and any previous drug levels.
  - Clinical status including liver and renal function and signs of drug toxicity.

Volume of Distribution (V_d) and Peak Drug 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 (Vd):

$[drug]_{peak}$ = dose / V_d.

Most common use is to calculate an appropriate loading dose for drugs with long half-lives, which are then followed maintenance doses based o the drug clearance.

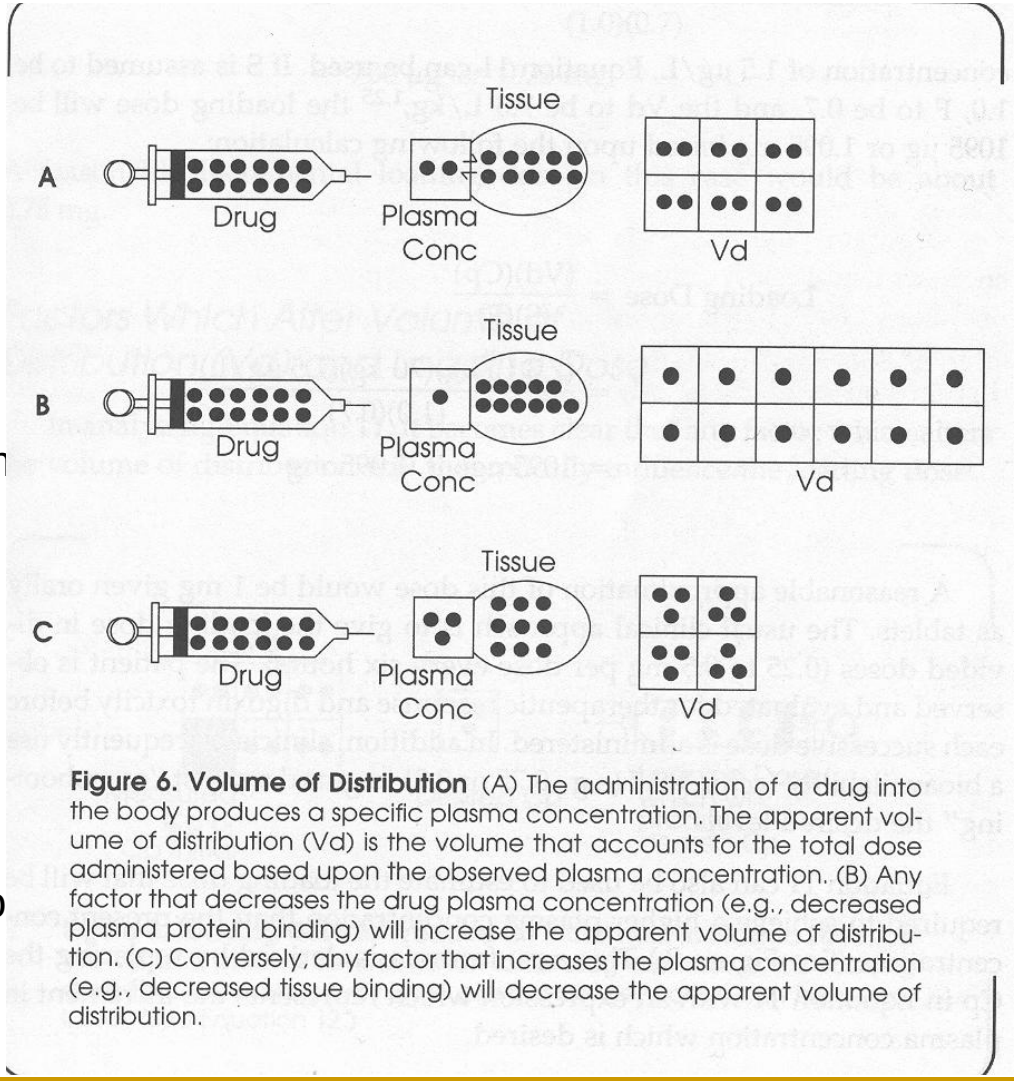
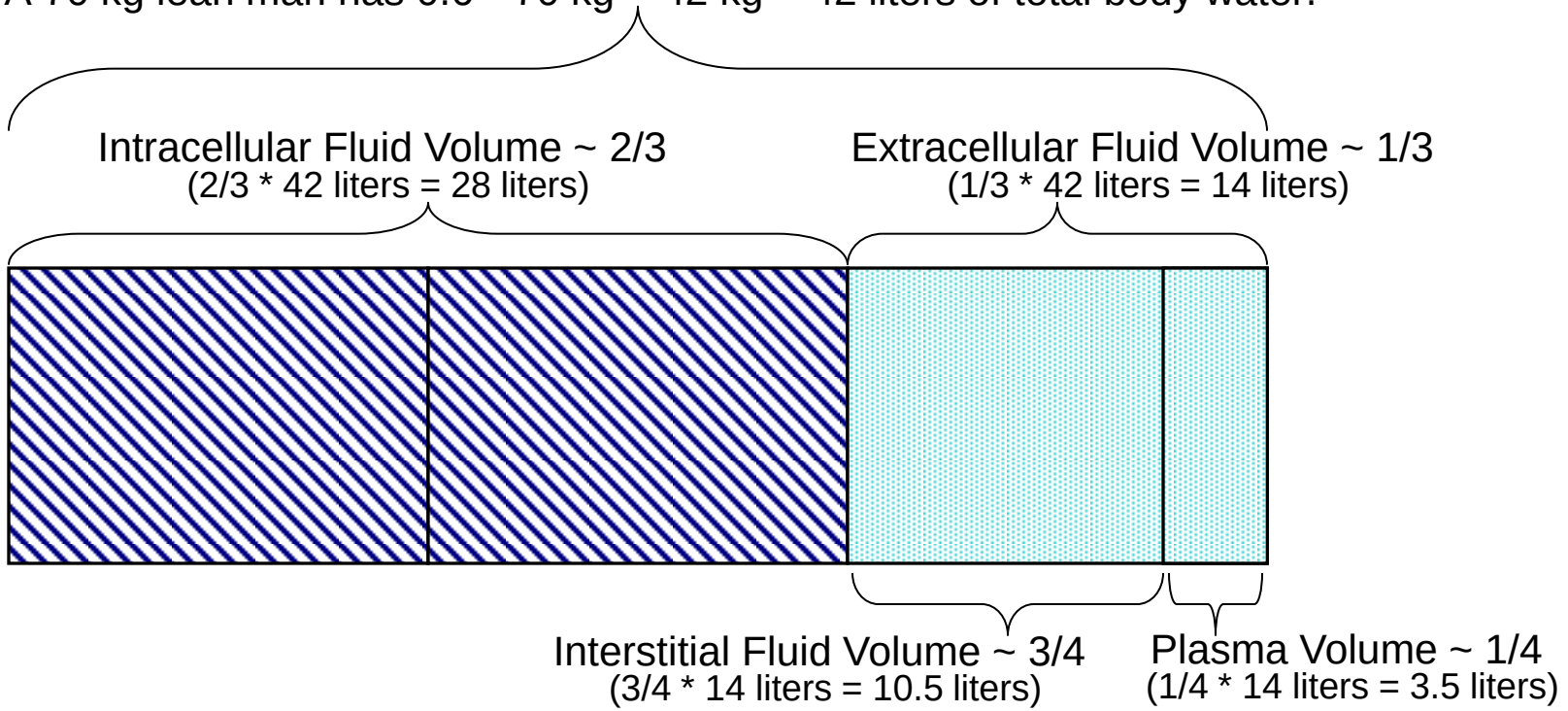


Figure 6. Volume of Distribution (A) The administration of a drug into the body produces a specific plasma concentration. The apparent volume of distribution (Vd) is the volume that accounts for the total dose administered based upon the observed plasma concentration. (B) Any factor that decreases the drug plasma concentration (e.g., decreased plasma protein binding) will increase the apparent volume of distribution. (C) Conversely, any factor that increases the plasma concentration (e.g., decreased tissue binding) will decrease the apparent volume of distribution.

Human Body Fluid Volumes

The human body is 50 – 70% “aqueous” volume by weight (1 L ~ 1 kg)

A 70 kg lean man has 0.6 * 70 kg = 42 kg = 42 liters of total body water.



Human Blood Volume is ~ 7% of body weight: 0.07 * 70 kg = 4.9 liters (round off to 5 L).

The “hematocrit” defines the cellular fraction of blood, normal ~ 40%.

Therefore, plasma volume is about 0.40 * 5 liters ~ 3 liters.

However, V_ds are theoretical volumes and unfortunately do not generally correspond to these "real" volumes.

- If it wasn't for tissue/protein binding, then V_ds could be related to real body volumes,
  - e.g. plasma volume, blood volume, total extracellular water, total body water, etc.
  - For example, an IgG-based medication might be expected to distribute within total extracellular water, assuming minimal tissue or cell surface binding.
  - On the other hand, a conjugated IgG (such as digibind) or an IgM might be limited to plasma volume.
  - Small water-soluble molecules with minimal tissue binding, such as acetone, approximately distribute within total body water.
- However, most drugs bind extensively to proteins and tissue components resulting in much larger "apparent" V_ds.

Bioavailability

- Bioavailability reflects loss or deactivation of administered medication and is route-dependent.
- Best dealt with by simply lowering the effective dose in the pharmacokinetic equations.
- For example, poor absorption and “first-pass” hepatic metabolism are important with oral administration but not IV.
- Note that a change in hepatic function may result in a change in bioavailability.
- Intramuscular and subcutaneously administered medications have separate issues.

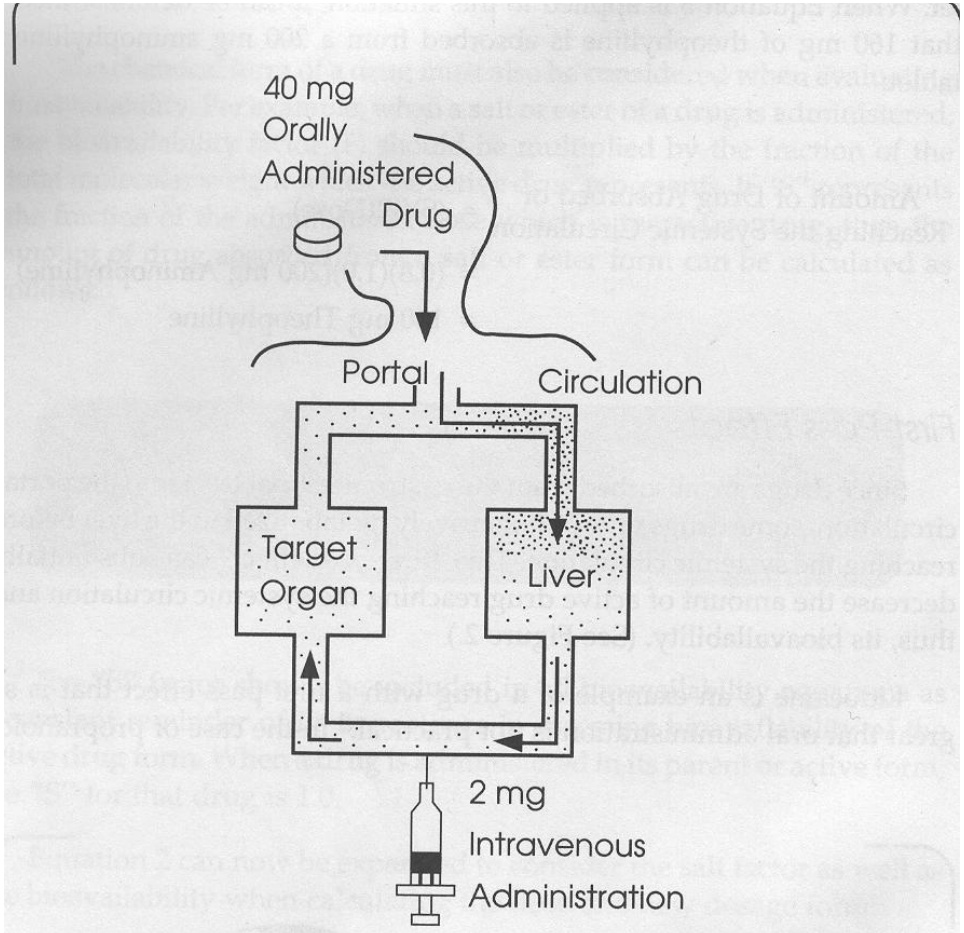
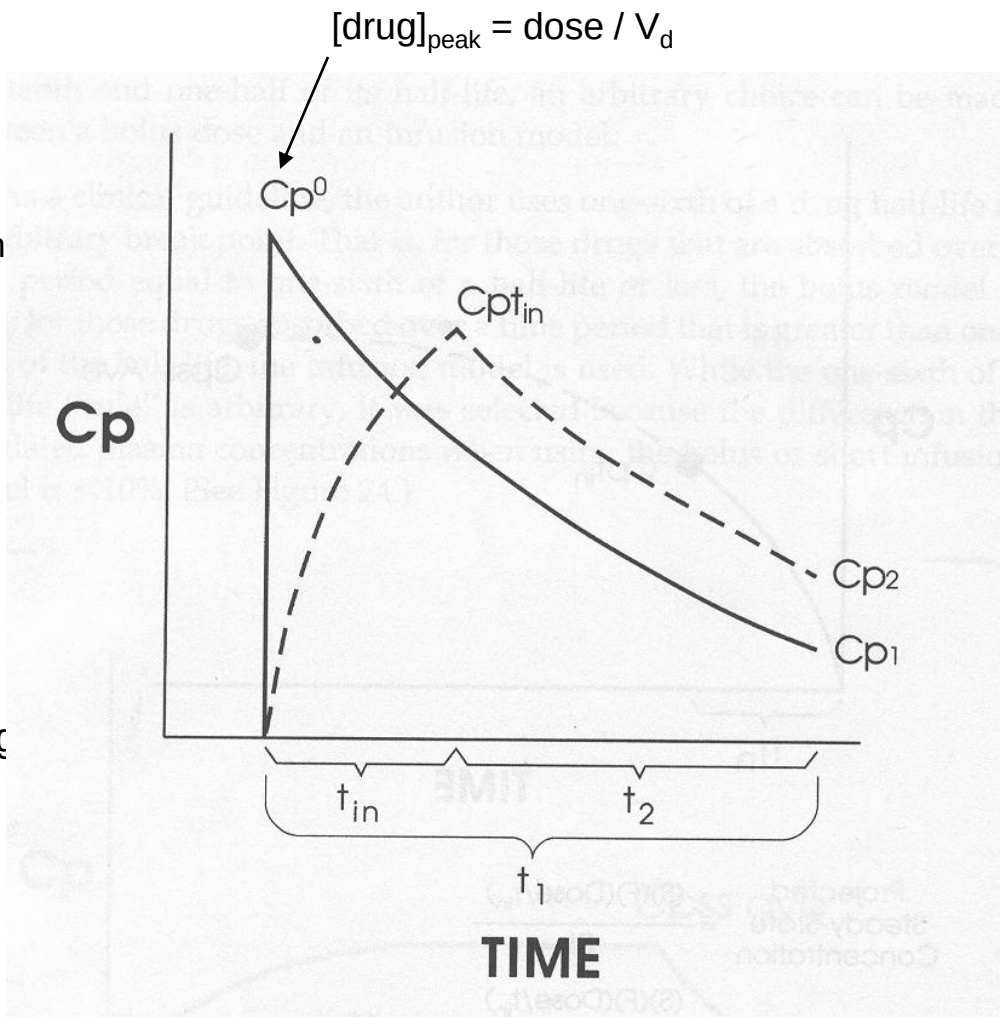


Figure 2. First-Pass Effect. When drugs with a high ``first-pass effect'' are administered orally, a large amount of the absorbed drug is metabolized before it reaches the systemic circulation. If the drug is administered intravenously, the liver is bypassed and the fraction of the administered dose that reaches the circulation is increased. Parenteral doses of drugs with a ``high first-pass'' are much smaller than oral doses which produce equivalent pharmacologic effects.

P.O. Medications must be Absorbed.

- Absorption is generally a first-order process and can be characterized by an exponential equation:
  - $[drug]_t = ([drug]_{peak})(1 - e^{-kt})$
  - assumes NO elimination during absorption
  - (need to expand on chalkboard)
- However, absorption rates are often highly variable (affected by stomach/intestine pH, presence of food, rate of gastric emptying, etc.).
- In overdoses, absorption is generally delayed due to formation of concretions, gastric irritation, delayed gastric emptying, etc.
- In reality, ongoing metabolism of the drug during absorption leads to
  - **lower** and **later** peak levels (Cpt_{in})
  - and **delayed** elimination or higher trough levels (Cp_2) for repeated dosing.



1st Order or Linear Pharmacokinetics

- Implies that the ***rate*** of drug elimination depends linearly on drug concentration:

$$\frac{d\,[drug\;\;]}{dt} = k * [drug\;\;]_t$$

- Plasma drug concentrations decay ***exponentially***.
- And are characterized by a constant ***half-life*** ($k = 0.693 / t_{1/2}$).
- "Linear" pharmacokinetics implies that steady state drug levels are directly proportional to the administered dose.
  - i.e. if you double the dose you will double the steady state plasma level of the dose.

1st Order or Linear Pharmacokinetics

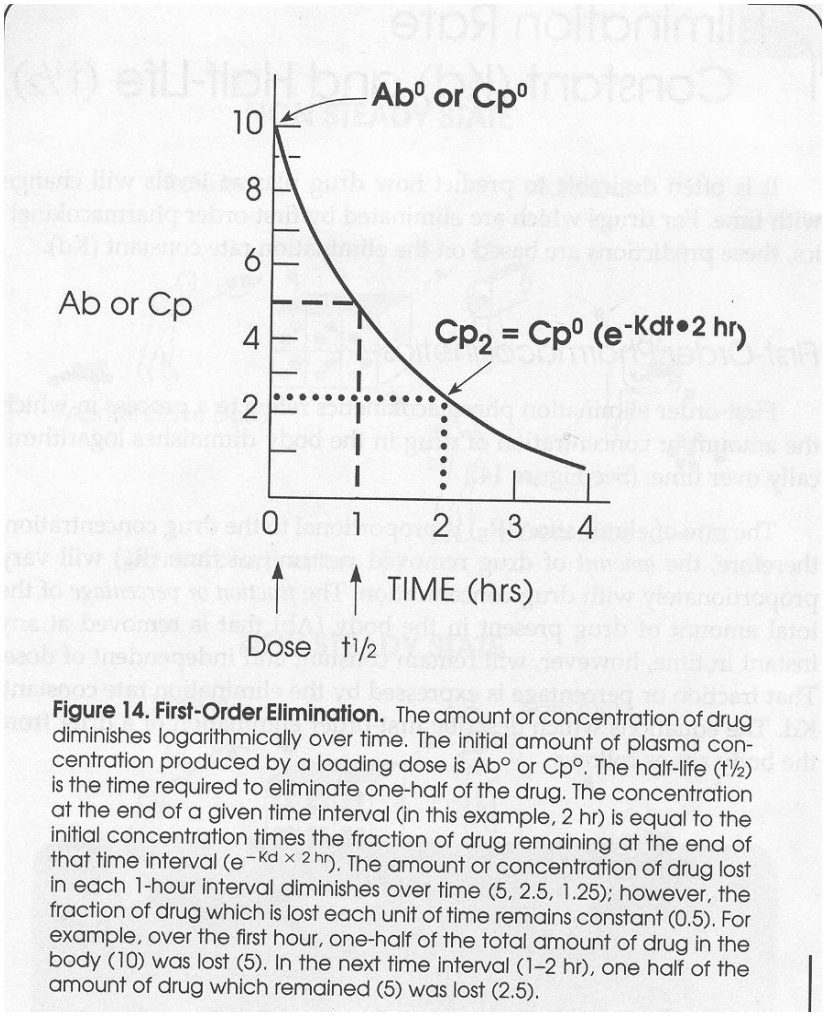


Figure 14. First-Order Elimination. The amount or concentration of drug diminishes logarithmically over time. The initial amount of plasma concentration produced by a loading dose is Ab° or Cp°. The half-life ($t_{1/2}$) is the time required to eliminate one-half of the drug. The concentration at the end of a given time interval (in this example, 2 hr) is equal to the initial concentration times the fraction of drug remaining at the end of that time interval ($e^{-Kd \times 2\,hr}$). The amount or concentration of drug lost in each 1-hour interval diminishes over time (5, 2.5, 1.25); however, the fraction of drug which is lost each unit of time remains constant (0.5). For example, over the first hour, one-half of the total amount of drug in the body (10) was lost (5). In the next time interval (1–2 hr), one half of the amount of drug which remained (5) was lost (2.5).

$$[drug]_t = [drug]_0 e^{-kt}$$

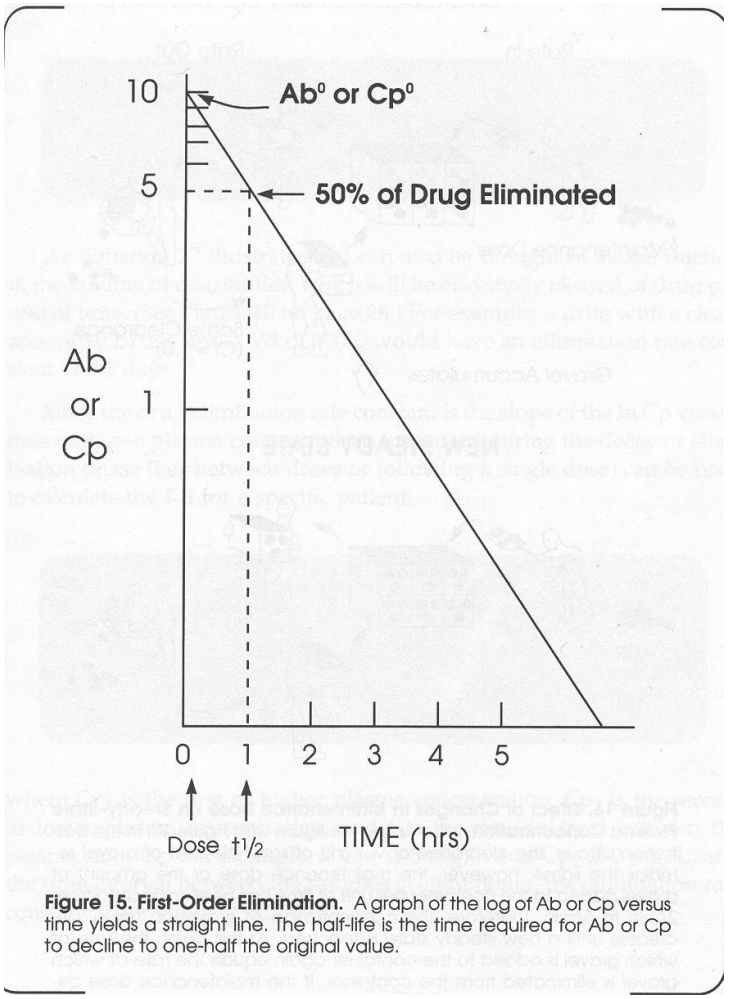


Figure 15. First-Order Elimination. A graph of the log of Ab or Cp versus time yields a straight line. The half-life is the time required for Ab or Cp to decline to one-half the original value.

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

Clearance

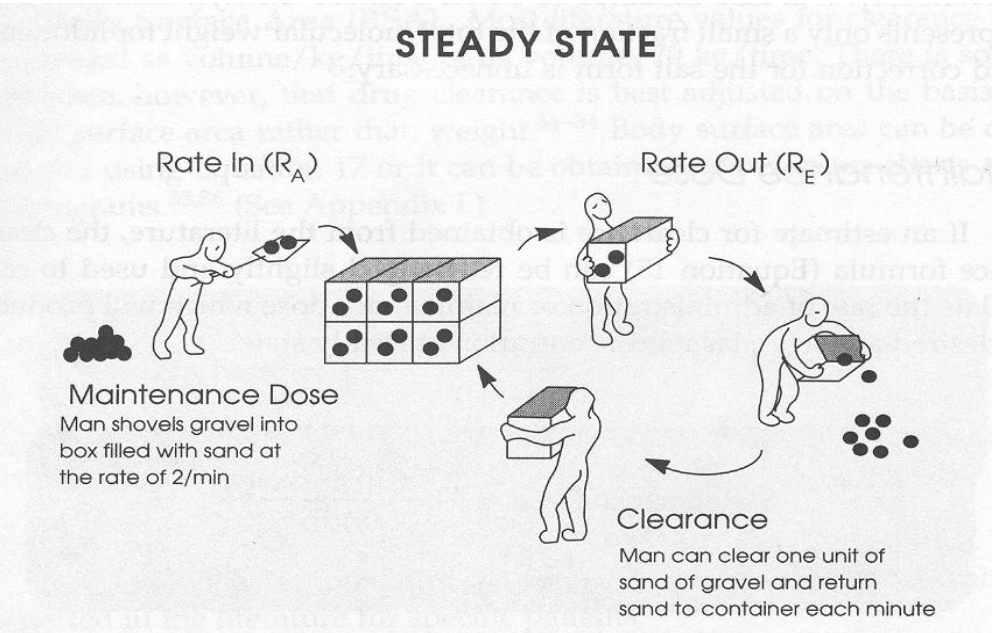


Figure 10. Steady State, Maintenance Dose, Clearance, Elimination Rate Constant. At steady state, the rate of drug administration (R_A) is equal to the rate of drug elimination (R_E), and the concentration of drug remains constant. In this example, the man on the left is able to shovel gravel or ``drug'' into a container of sand at the rate of 2/min. The man on the right is able to remove one unit of sand containing gravel or ``drug'' from the container, dump the gravel, and return the sand to the container each minute. The *amount* of gravel or drug removed per unit of time (rate of elimination) will be determined by the concentration of gravel per unit of sand as well as the clearance (volume of sand cleared of gravel). The elimination rate constant (Kd) can be thought of as the fraction of the total volume cleared per unit of time. In this case, Kd would be equal to ⅙ or 0.17^{-1}.

- **Clearance (Cl)** is an alternative and equivalent way to describe first order pharmacokinetics.
- Think of clearance as a description of the drug elimination rate, which can be related to the instantaneous drug concentration in plasma.
- $Rate_{out} = Cl * [drug]_t$
- The definition of clearance is the apparent “volume” of plasma “cleared” of drug per unit of time.

Clearance

- Think about how the idea of **clearance** implies first order pharmacokinetics (rate = Cl * $[drug]_t$).
  - As the concentration of drug decreases, the rate of elimination decreases proportionately.
  - Like the half-life, clearance is constant as long as first order kinetics is maintained.

- Clearance is related to the exponential rate constant by
  - **Cl = k * Vd**.
  - However, more frequently one needs to relate clearance to half life or vice-versa: **$Cl = (0.693 * V_d) / t_{1/2}$**

- It is important to know if the clearance you are using has been defined for the amount of **free** or **total** drug in plasma. Strictly speaking, only the free drug is cleared. However, since clearance relates to a “theoretical” volume, it can be defined for either.
  - Most often it has been defined for total drug since this is most commonly measured.

Don't Get Confused…

$Rate_{elimination} = d\,[drug]_t / dt = k * [drug]_t$

$Rate_{out} = Cl * [drug]_t$

$Rate_{out}$ is expressed as an "amount of drug" lost per unit time.

$Rate_{elimination}$ is expressed as a "concentration of drug" lost per unit time.

This is why the volume of distrubution relates clearance to the exponential rate constant for elimination, $Cl = k * V_d$.

Therefore, it follows that $Rate_{out} = V_d * Rate_{elimination}$.

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 $\mathbf{Rate_{out} = Rate_{in}}$.
- Because the rate of elimination depends on the clearance and the plasma drug concentration, an equation can be derived relating the average concentration of the drug at steady state to the average rate of drug administration:
  - $\mathbf{[drug]_{steady\ state} = Rate_{in} / Cl}$

Steady State Drug Levels

$[drug]_{steady\ state} = Rate_{in}/Cl$

Notice the “linear” dependence of the steady state drug level on variations on the clearance.

This is how a continuous I.V. infusion would appear.

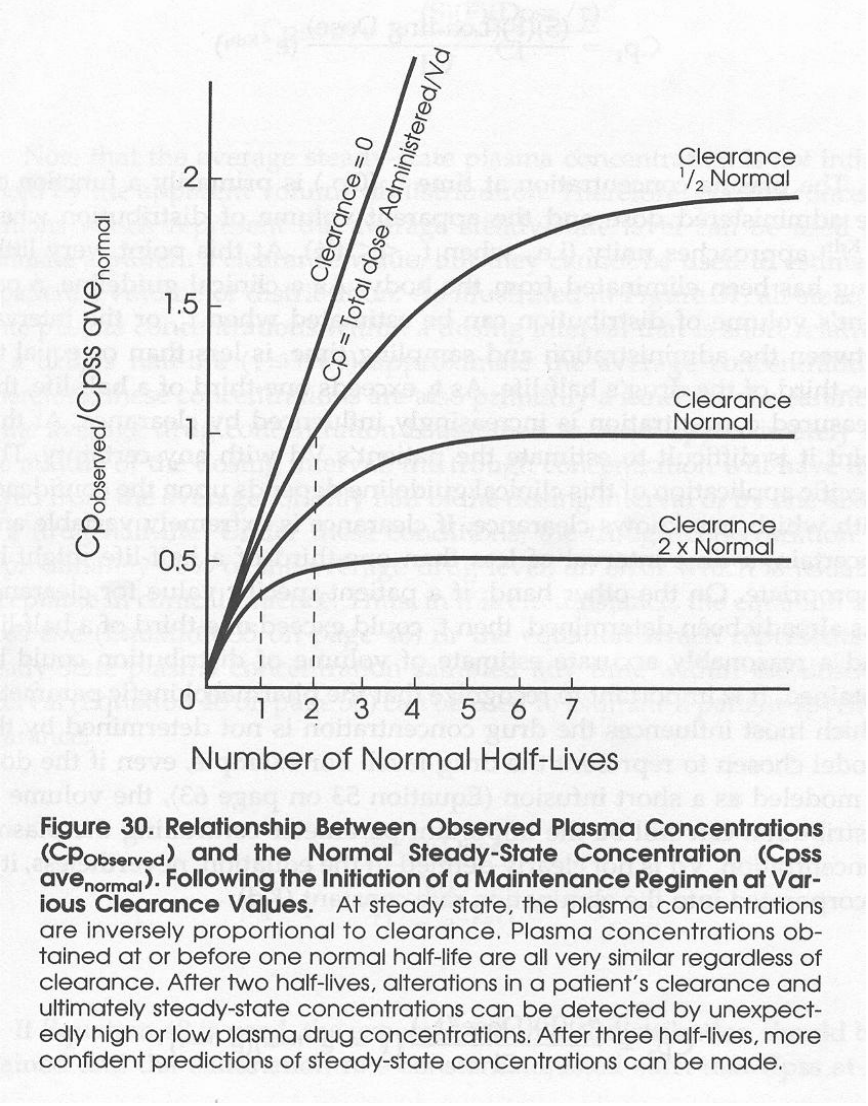


Figure 30. Relationship Between Observed Plasma Concentrations ($Cp_{Observed}$) and the Normal Steady-State Concentration ($Cpss\ ave_{normal}$). Following the Initiation of a Maintenance Regimen at Various Clearance Values. At steady state, the plasma concentrations are inversely proportional to clearance. Plasma concentrations obtained at or before one normal half-life are all very similar regardless of clearance. After two half-lives, alterations in a patient's clearance and ultimately steady-state concentrations can be detected by unexpectedly high or low plasma drug concentrations. After three half-lives, more confident predictions of steady-state concentrations can be made.

Intermittent Dosing

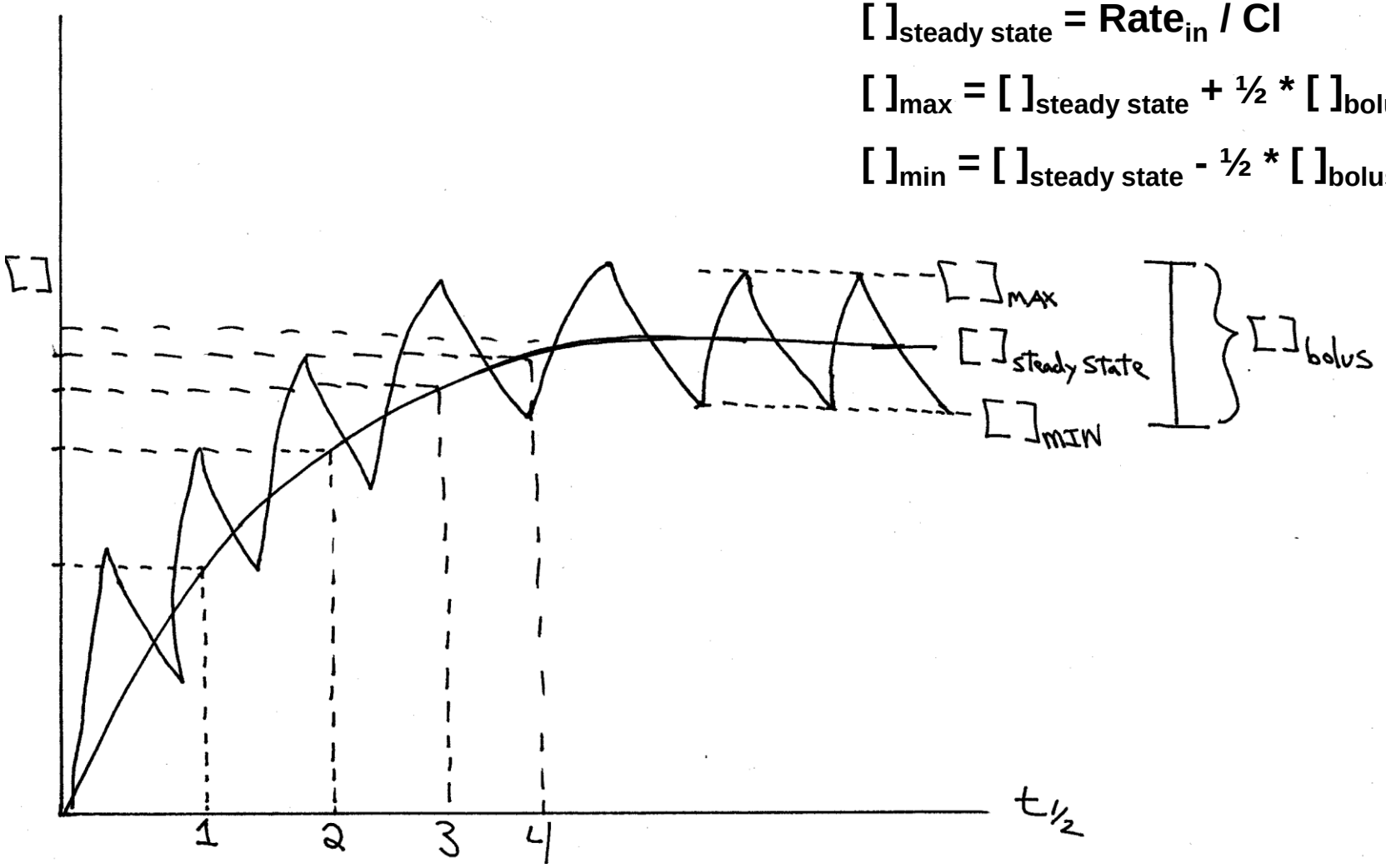
Approximations!

$[\,]_{bolus}$ = (single dose) / V_d

$[\,]_{steady\ state}$ = $Rate_{in}$ / Cl

$[\,]_{max}$ = $[\,]_{steady\ state}$ + ½ * $[\,]_{bolus}$

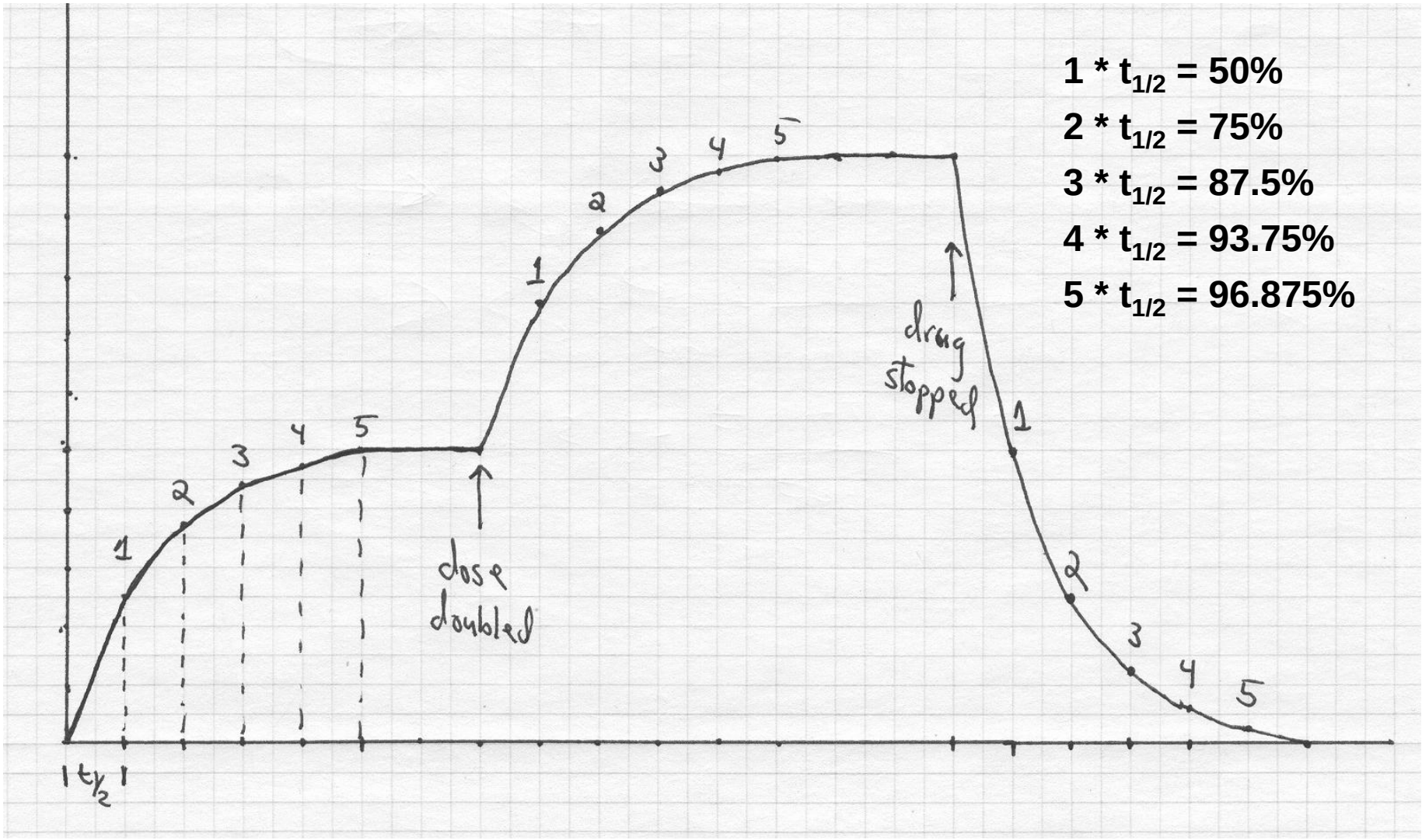
$[\,]_{min}$ = $[\,]_{steady\ state}$ - ½ * $[\,]_{bolus}$



Critical Importance of the Half-life!

- Half life is the key for knowing
  - When a new medication is started, how long until the patient reaches steady state?
  - When a patient stops taking a medication, how long until it is gone?
  - When a drug dosage is changed, how long until a new steady state is achieved?

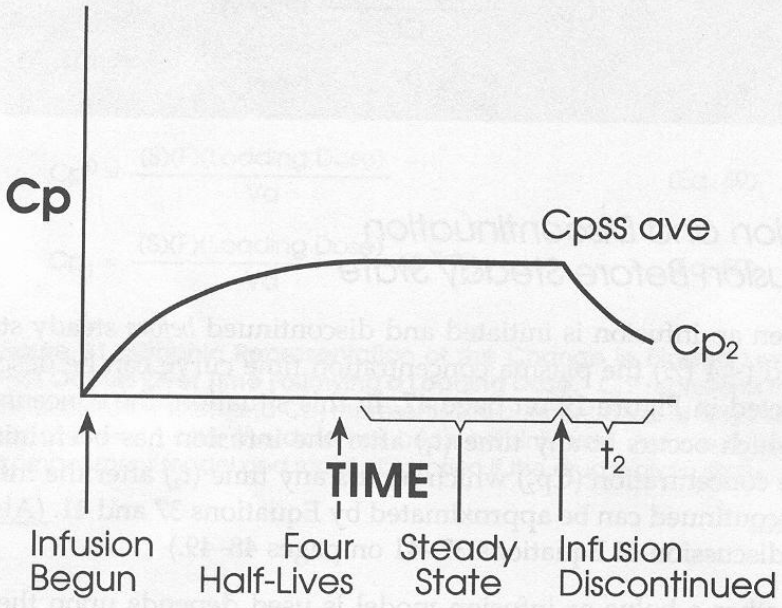
Critical Importance of the Half-life!



Notes on the "Fancy Equations"

- Everything is just a 1st order, exponential process characterized by either a
  - rate constant (k),
  - a time constant (τ),
  - or a half-life ($t_{1/2}$),
  - $k = 1/\tau = 0.693 / t_{1/2}$
- Exponential decay: $[drug]_t = [drug]_{t=0} * e^{-kt}$.
- Exponential growth: $[drug]_t = [drug]_{t=\infty} * (1 - e^{-kt})$.

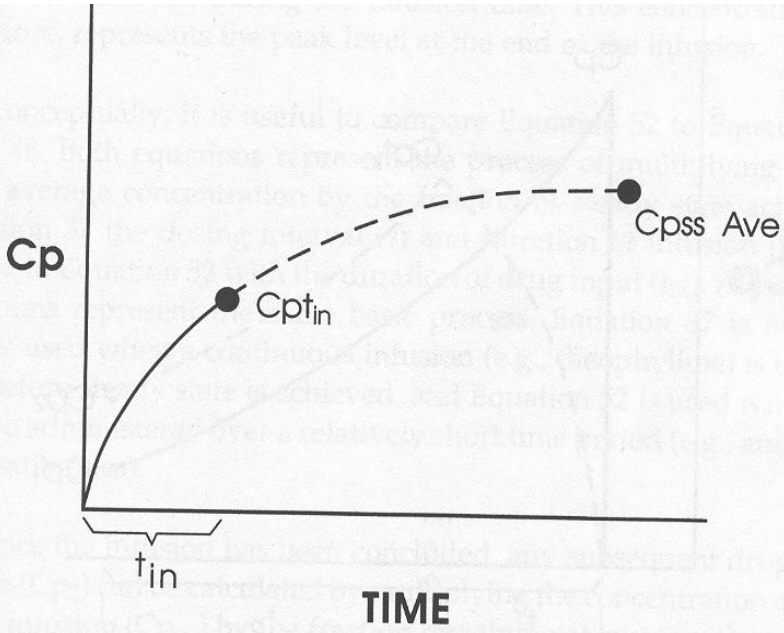
"Fancy" Equations Can be Defined



$$\text{Cpss ave} = \frac{(S)(F)(\text{Dose}/\tau)}{Cl} \qquad \text{(Eq. 35)}$$

$$Cp_2 = \frac{(S)(F)(\text{Dose}/\tau)}{Cl}\,(e^{-Kdt_2}) \qquad \text{(Eq. 51)}$$

Figure 22. Graphic Representation of the Plasma Concentration-Versus-Time Curve that Results When an Infusion Is Continued Until Steady State Is Reached and Then Discontinued. Cpss ave is the steady-state concentration and Cp_2 is the concentration at any interval of time (t_2) after the infusion has been discontinued.

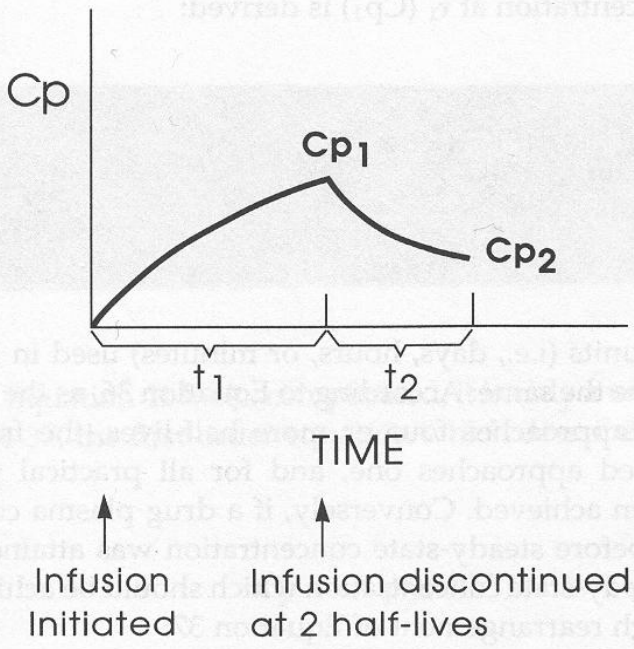


$$\text{Projected Steady-State Concentration} = \frac{(S)(F)(\text{Dose}/t_{in})}{Cl}$$

$$Cp_{t_{in}} = \frac{(S)(F)(\text{Dose}/t_{in})}{Cl}\,(1 - e^{-Kdt_{in}}) \qquad \text{(Eq. 52)}$$

Figure 23. Graphic Representation of a Short Infusion. The plasma concentration at the end of a short infusion ($Cp_{t_{in}}$) can be calculated by multiplying the ''projected steady-state concentration'' (-----) by the fraction of steady state achieved ($1 - e^{-Kdt_{in}}$) during the infusion period (t_{in}).

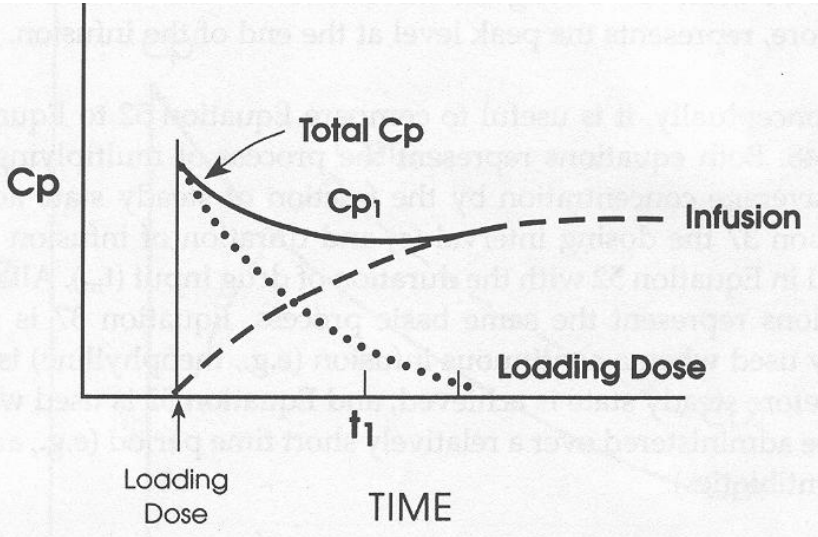
More "Fancy" Equations



$$Cp_1 = \frac{(S)(F)(Dose/\tau)}{Cl}(1 - e^{-Kdt_1}) \qquad \text{(Eq. 37)}$$

$$Cp_2 = \frac{(S)(F)(Dose/\tau)}{Cl}(1 - e^{-Kdt_1})(e^{-Kdt_2}) \qquad \text{(Eq. 41)}$$

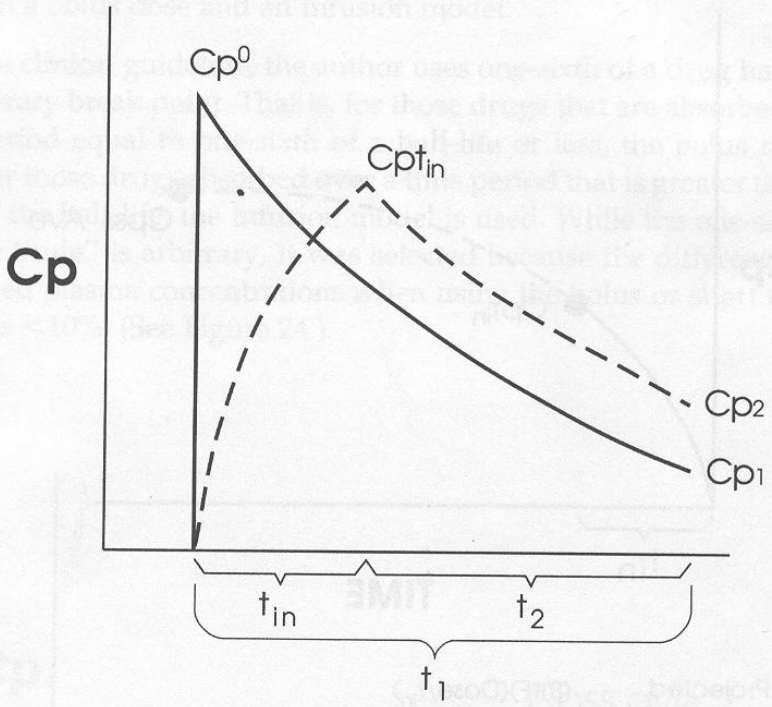
Figure 19. Graphic Representation of an Infusion That Is Discontinued Before Steady State. Cp_1 is a concentration which is achieved any time (t_1) after the infusion is initiated, and Cp_2 is a concentration that results any interval of time (t_2) after the infusion has been discontinued.



$$Cp_1 = \left[\frac{(S)(F)(\text{Loading Dose})}{Vd}(e^{-Kdt_1})\right] + \left[\frac{(S)(F)(Dose/\tau)}{Cl}(1 - e^{-Kdt_1})\right]$$

(Eq. 50) (Eq. 37)

Figure 25. Graphic Representation of the Plasma Level-Time Curve Which Results From a Loading Dose Followed by a Maintenance Infusion. The curve represents a summation of a loading dose curve (····) and an infusion curve (----). Cp_1 is the concentration any time (t_1) after the loading dose has been administered and after the maintenance infusion has been initiated.



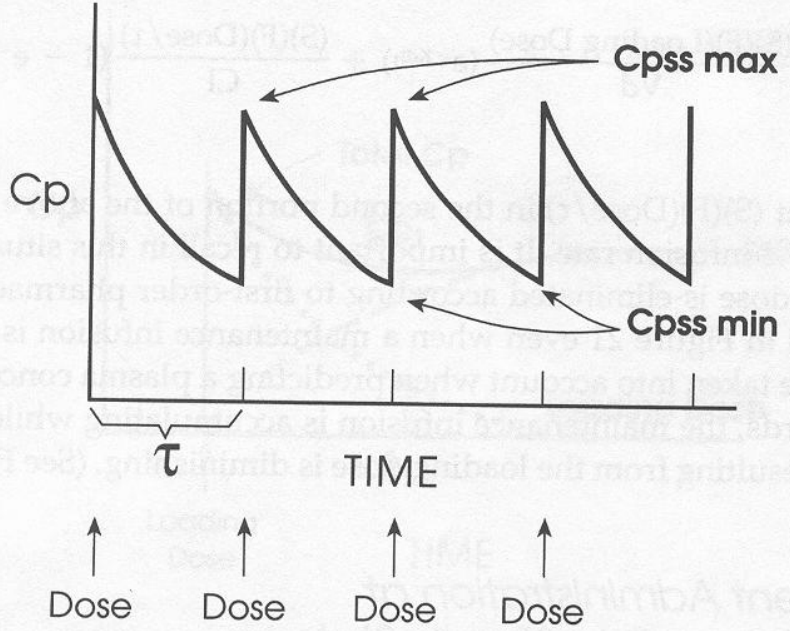
$$Cp^0 = \frac{(S)(F)(\text{Loading Dose})}{Vd} \qquad \text{(Eq. 49)}$$

$$Cp_1 = \frac{(S)(F)(\text{Loading Dose})}{Vd}(e^{-Kdt_1}) \qquad \text{(Eq. 50)}$$

$$Cp_{t_{in}} = \frac{(S)(F)(\text{Dose}/t_{in})}{Cl}(1 - e^{-Kdt_{in}}) \qquad \text{(Eq. 52)}$$

$$Cp_2 = \frac{(S)(F)(\text{Dose}/t_{in})}{Cl}(1 - e^{-Kdt_{in}})(e^{-Kdt_2}) \qquad \text{(Eq. 53)}$$

Figure 24. Graphic Representation of a Drug Administered as a Bolus (—) or as a Short Infusion (---). The bolus dose model assumes that drug input or absorption is instantaneous. The decay interval, t_1 (i.e., $t_{in} + t_2$), is therefore assumed to begin at the start of the infusion. In contrast, the infusion model assumes that the decay interval (t_2) begins at the conclusion of the infusion period (t_{in}).

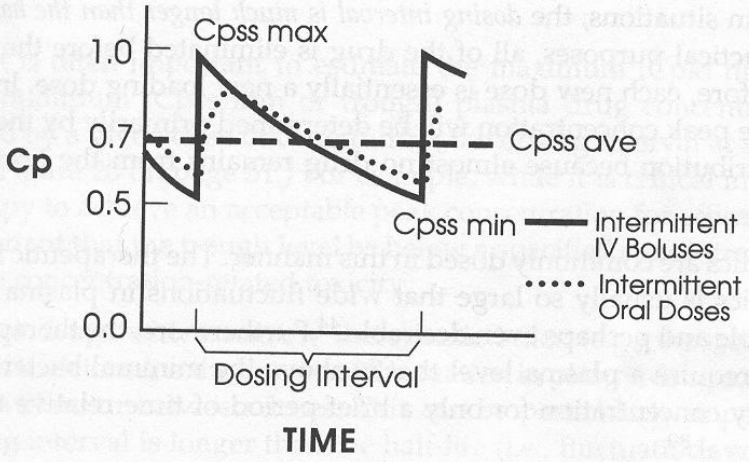


$$\text{Cpss max} = \frac{\dfrac{(S)(F)(\text{Dose})}{Vd}}{(1 - e^{-Kd\tau})} \qquad \text{(Eq. 43)}$$

$$\text{Cpss min} = \frac{\dfrac{(S)(F)(\text{Dose})}{Vd}}{(1 - e^{-Kd\tau})}(e^{-Kdt}) \qquad \text{(Eq. 47)}$$

$$Cpss_1 = \frac{\dfrac{(S)(F)(\text{Dose})}{Vd}}{(1 - e^{-Kd\tau})}(e^{-Kdt_1}) \qquad \text{(Eq. 48)}$$

Figure 26. Graphic Representation of the Steady-State Plasma Concentration Versus Time Curve Which Occurs When Drugs Are Given Intermittently At Regular Dosing Intervals. Any maximum concentration (Cpss max) is interchangeable with any other maximum concentration and any minimum concentration (Cpss min) is interchangeable with any other minimum concentration.



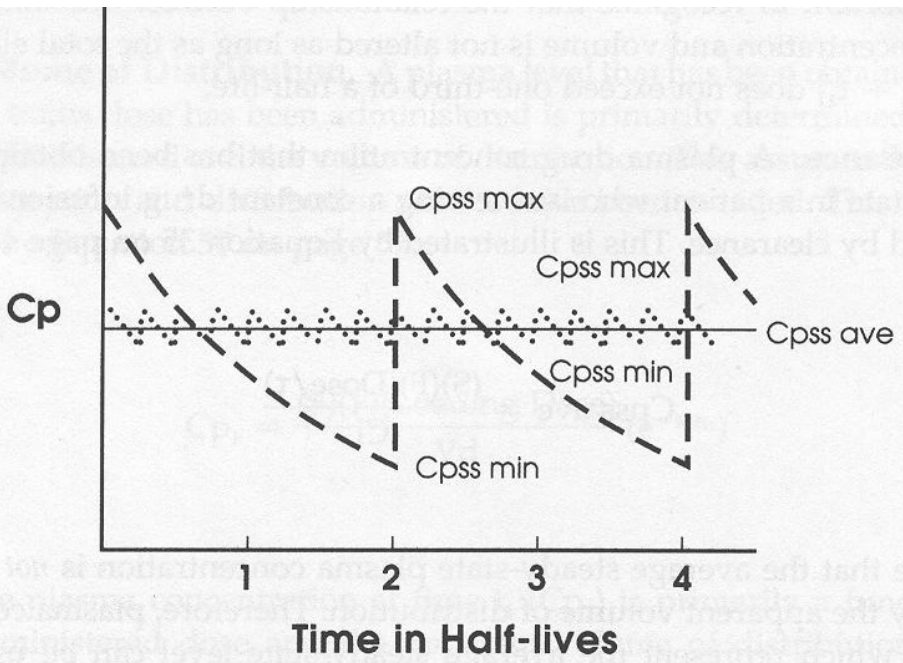
$$\text{Cpss ave} = \frac{(S)(F)(\text{Dose}/\tau)}{Cl} \qquad \text{(Eq. 35)}$$

$$\text{Cpss max} = \frac{\dfrac{(S)(F)(\text{Dose})}{Vd}}{(1 - e^{-K\tau})} \qquad \text{(Eq. 43)}$$

$$\text{Cpss min} = \frac{\dfrac{(S)(F)(\text{Dose})}{Vd}}{(1 - e^{-K\tau})}(e^{-K\tau}) \qquad \text{(Eq. 47)}$$

$$\text{Cpss}_1 = \frac{\dfrac{(S)(F)(\text{Dose})}{Vd}}{(1 - e^{-K\tau})}(e^{-Kt_1}) \qquad \text{(Eq. 48)}$$

Figure 20. Plasma Level-Time Curve for Intermittent Dosing at Steady State. When the dosing interval is equal to the half-life, plasma concentrations are above the average steady-state plasma concentration (Cpss ave) approximately 50% of the time. Oral administration dampens the curve considerably and the maximum concentration at steady state (Cpss max) occurs later and is lower than that produced by IV bolus. The minimum concentration at steady state (Cpss min) is greater than that produced by IV bolus doses because of the effect of absorption. In the equations above, τ is the interval between doses and t_1 is the time from the theoretical peak concentration following a dose to the time of sampling.



$$\text{Cpss ave} = \frac{(S)(F)(\text{Dose}/\tau)}{Cl} \qquad \text{(Eq. 35)}$$

$$\text{Cpss}_1 = \frac{\dfrac{(S)(F)(\text{Dose})}{Vd}}{(1 - e^{-K\tau})}(e^{-Kt_1}) \qquad \text{(Eq. 48)}$$

Figure 31. Plasma Concentrations Relative to Cpss Ave (—) when τ is Much Less Than (····) and Greater Than (----) the Half-Life. When τ is much less than the $t_{1/2}$ (···), all plasma concentrations approximate the average concentration (Cpss ave) and are therefore primarily a function of clearance. When τ is much greater than $t_{1/2}$ (----), the plasma concentrations fluctuate significantly. The degree to which plasma concentrations are determined by clearance and/or volume of distribution is a function of when the plasma level is obtained within the dosing interval.

Example of a Steady State Calculation

- 70 kg patient started on 0.2 mg digoxin PO qd.
- What are the expected approximate peak and trough levels?
  - Digoxin Therapeutic Range: 0.5 – 2.0 ng/ml
  - Digoxin V_d ~ 6 L/kg = 6 * 70 L = 420 L
  - Digoxin $t_{1/2}$ ~ 40 hours
    - Cl = (0.693 * V_d) / $t_{1/2}$ = 7.3 L/hr

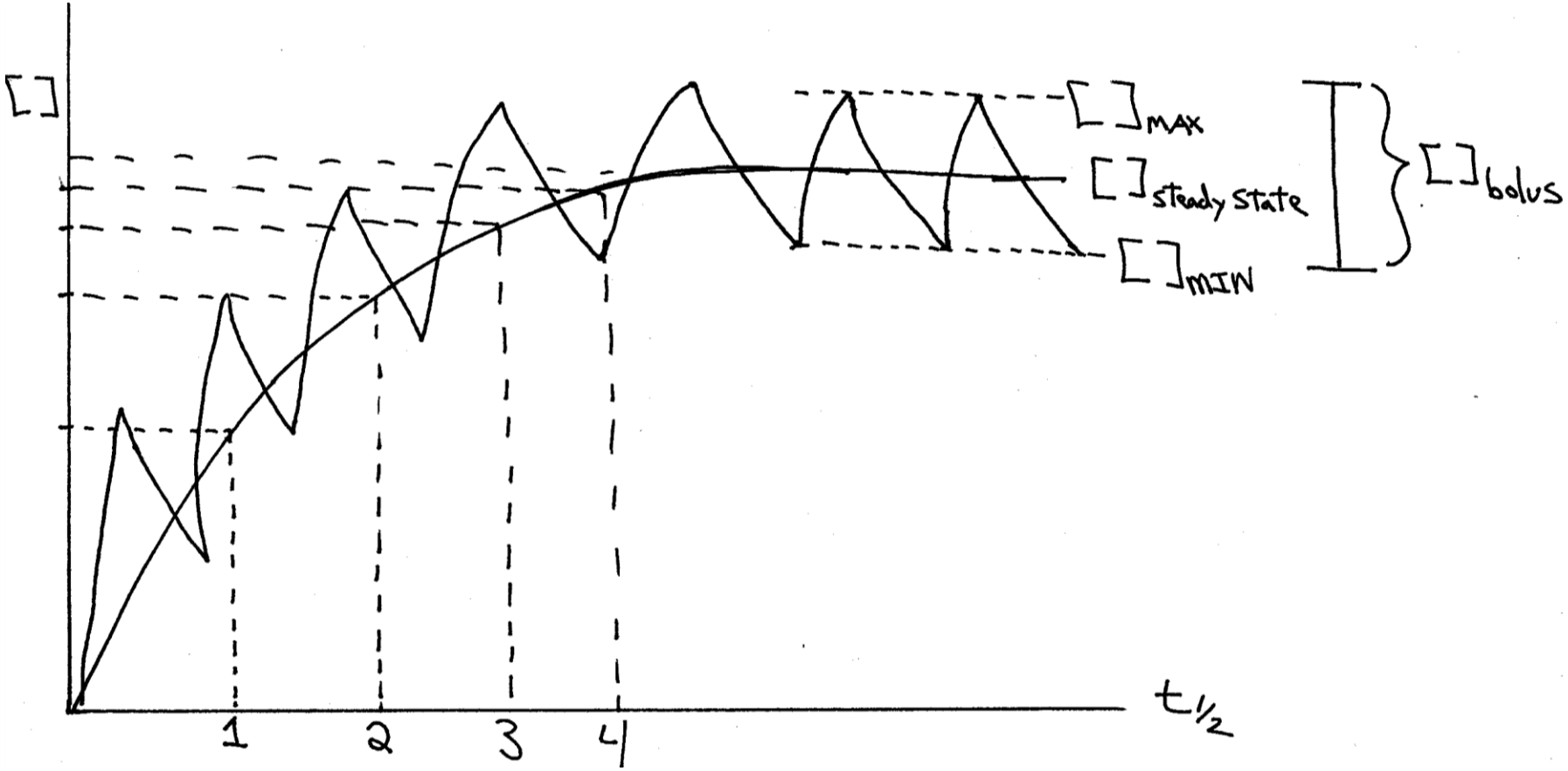
Approximate (easy) Solutions

$[\,]_{bolus}$ = (single dose) / V_d = 0.2 mg/ 420 L = 0.48 ng/ml

$[\,]_{steady\ state}$ = $Rate_{in}$ / Cl = (0.2 mg/24 hrs) / (7.3 L/hr) = 1.1 ng/ml

$[\,]_{max}$ = $[\,]_{steady\ state}$ + ½ * $[\,]_{bolus}$ = 1.1 ng/ml + 0.5 * 0.48 ng/ml = 1.34 ng/ml

$[\,]_{min}$ = $[\,]_{steady\ state}$ - ½ * $[\,]_{bolus}$ = 1.1 ng/ml – 0.5 * 0.48 ng/ml = 0.86 ng/ml



Comparison of Approximate and Exact Calculations for Steady State Min and Max

Approximate (easy) Solutions

$[\ ]_{bolus}$ = (single dose) / V_d = 0.2 mg/ 420 L = 0.48 ng/ml

$[\ ]_{steady\ state}$ = $Rate_{in}$ / Cl = (0.2 mg/24 hrs) / (7.3 L/hr) = 1.1 ng/ml

$[\ ]_{max} = [\ ]_{steady\ state} + ½ * [\ ]_{bolus}$ = 1.1 ng/ml + 0.5 * 0.48 ng/ml = 1.34 ng/ml

$[\ ]_{min} = [\ ]_{steady\ state} - ½ * [\ ]_{bolus}$ = 1.1 ng/ml – 0.5 * 0.48 ng/ml = 0.86 ng/ml

Exact (more complicated) Solutions

$[\ ]_{bolus}$ = (single dose) / V_d = 0.2 mg/ 420 L = 0.48 ng/ml

$[\ ]_{max} = [\ ]_{bolus} / \{1 - \exp(-0.693*\tau/t_{1/2})\}$ = 0.48 ng/ml / (1 - 0.66) = 1.41 ng/ml

$[\ ]_{min} = [\ ]_{max} * \exp(-0.693*\tau/t_{1/2})$ = 1.41 ng/ml * 0.66 = 0.93 ng/ml

If we double the patient's dose from 0.2 mg qd to 0.4 mg qd…

Approximate (easy) Solutions

$[\ ]_{bolus}$ = (single dose) / V_d = 0.4 mg/ 420 L = 0.96 ng/ml

$[\ ]_{steady\ state}$ = $Rate_{in}$ / Cl = (0.4 mg/24 hrs) / (7.3 L/hr) = 2.2 ng/ml

$[\ ]_{max} = [\ ]_{steady\ state} + ½ * [\ ]_{bolus}$ = 2.2 ng/ml + 0.5 * 0.96 ng/ml = 2.68 ng/ml

$[\ ]_{min} = [\ ]_{steady\ state} - ½ * [\ ]_{bolus}$ = 2.2 ng/ml – 0.5 * 0.96 ng/ml = 1.72 ng/ml

Exact (more complicated) Solutions

$[\ ]_{bolus}$ = (single dose) / V_d = 0.2 mg/ 420 L = 0.96 ng/ml

$[\ ]_{max} = [\ ]_{bolus} / \{1 - \exp(-0.693*\tau/t_{1/2})\}$ = 0.96 ng/ml / (1 - 0.66) = 2.82 ng/ml

$[\ ]_{min} = [\ ]_{max} * \exp(-0.693*\tau/t_{1/2})$ = 2.82 ng/ml * 0.66 = 1.86 ng/ml

Another Example of Steady State Calculations

- 70 kg patient with normal renal function started on 2 mg/kg (140 mg) gentamicin PO q8º.
- What are the expected approximate peak and trough levels?
  - Gentamicin Therapeutic Range:
    - Peak: 5 – 10 μg/ml
    - Trough: <2 μg/ml
  - Gentamicin V_d ~ 0.2 L/kg = 0.2 * 70 L = 14 L
  - Gentamicin $t_{1/2}$ ~ 2 hours
    - Cl = (0.693 * V_d) / $t_{1/2}$ = 4.85 L/h
- Notice right away that $t_{1/2} << \tau$

Let's start with the approximate solutions.

Approximate (easy) Solutions

$[\,]_{bolus}$ = (single dose) / V_d = 140 mg/ 14 L = 10 μg/ml

$[\,]_{steady\ state}$ = $Rate_{in}$ / Cl = (140 mg/8 hrs) / (4.85 L/hr) = 3.61 μg/ml

$[\,]_{max} = [\,]_{steady\ state} + ½ * [\,]_{bolus}$ = 3.61 μg/ml + 0.5 * 10 μg/ml = 8.61 μg/ml

$[\,]_{min} = [\,]_{steady\ state} - ½ * [\,]_{bolus}$ = 3.61 μg/ml – 0.5 * 10 μg/ml = –1.4 μg/ml

- The above numbers clearly don't make sense, so we think for a moment…
- What they are telling us is that each gentamicin dose peaks around 8.6 μg/ml and then is nearly completely eliminated before the next dose (~4 half-lives later).

Complication I: 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 (α) followed by the true kinetic profile for drug elimination (β).

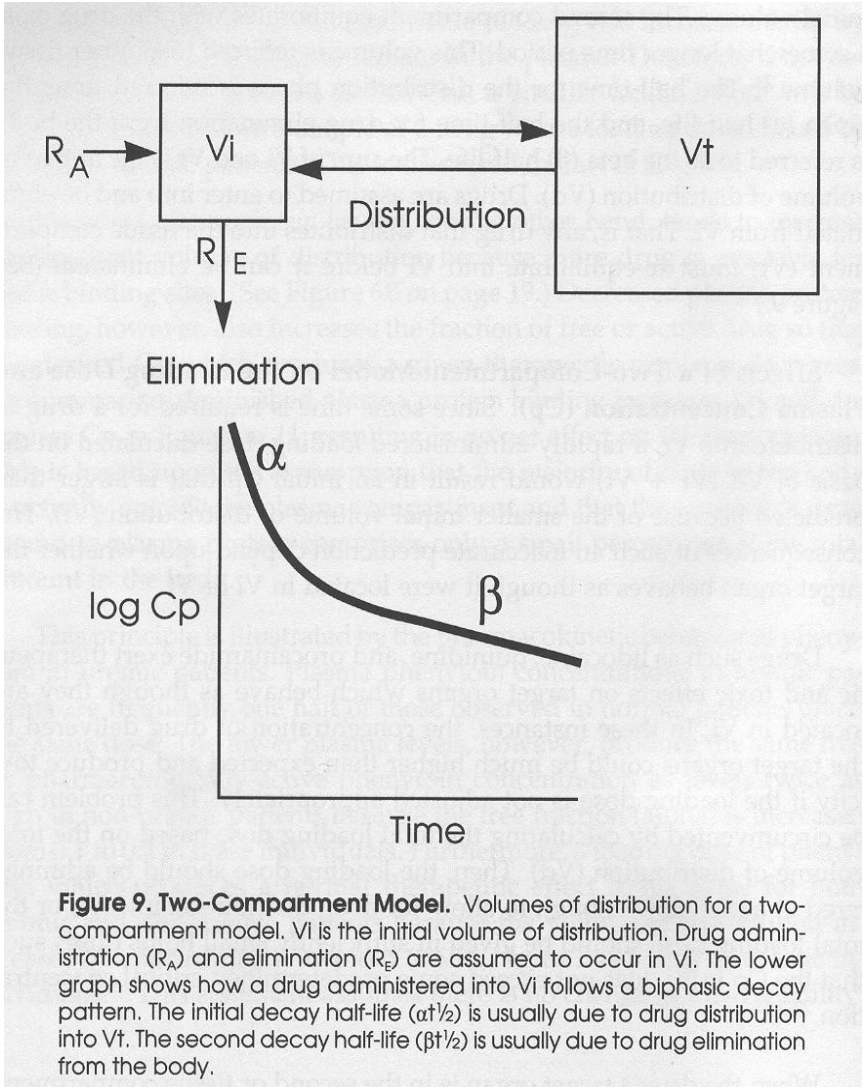


Figure 9. Two-Compartment Model. Volumes of distribution for a two-compartment model. Vi is the initial volume of distribution. Drug administration (R_A) and elimination (R_E) are assumed to occur in Vi. The lower graph shows how a drug administered into Vi follows a biphasic decay pattern. The initial decay half-life ($\alpha t^1/_2$) is usually due to drug distribution into Vt. The second decay half-life ($\beta t^1/_2$) is usually due to drug elimination from the body.

Complication I: Distribution Phase

1. Peak plasma drug levels drawn too early (i.e. before distribution is complete) do not always reflect physiologically relevant drug concentrations.

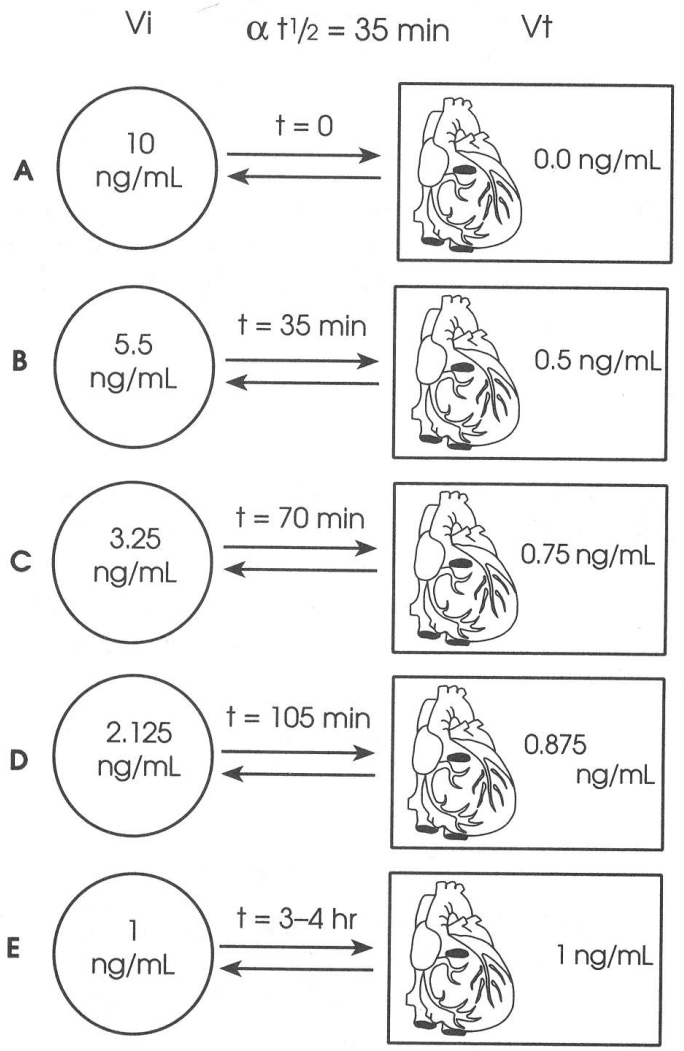
2. Be cautious when looking up V_ds and make sure they reflect the physiologically relevant volume.

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.

Complication I: Distribution Phase

- Best known example of the importance of distribution phase in TDM is for digoxin, which distributes from a smaller volume (~ 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 the site of action is much lower.

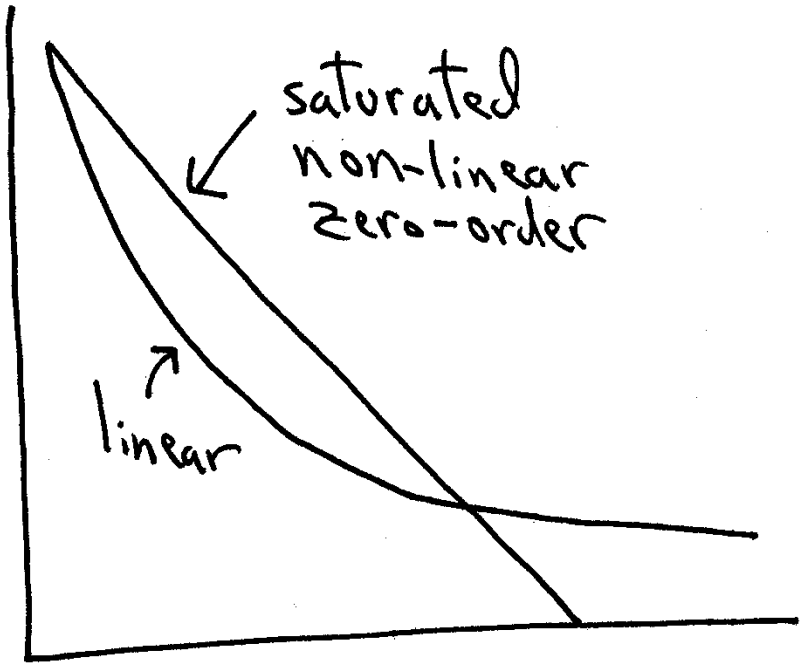


Complication II: Non-linear or Zero-Order Pharmacokinetics

- First-order kinetics, covered above, are often called linear pharmacokinetics because the rate of drug elimination is directly proportional to drug concentration:
  - $Rate_{out} = Cl * [\ ]$ and $Rate_{elimination} = d[\ ]/dt = k * [\ ]$
- However, any drug elimination process (i.e. 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 (saturation), the rate of drug elimination becomes constant and independent of drug concentration resulting in non-linear or zero-order pharmacokinetics:
  - $\mathbf{Rate_{elimination} = d[\ ]/dt = -k \rightarrow [drug]_t = [drug]_{initial} - kt}$
  - $Rate_{out} = V_d * Rate_{elimination} = -k * V_d$

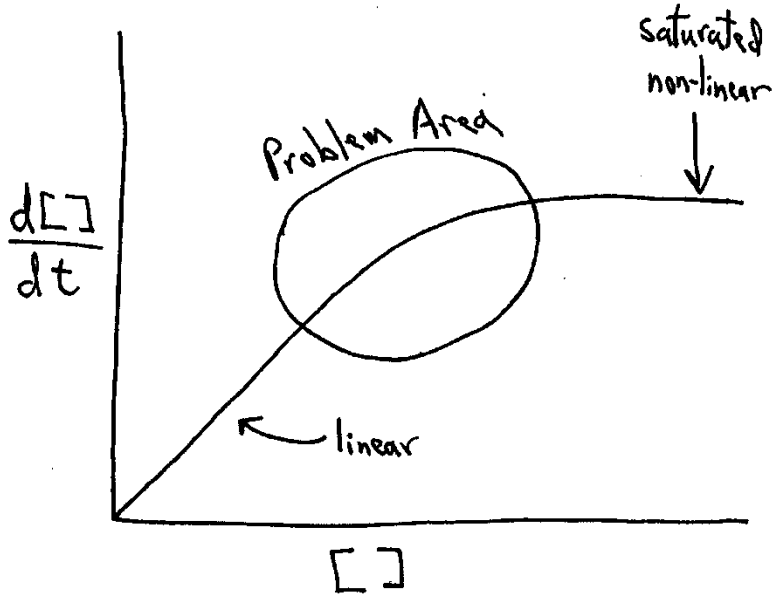
Complication II: Non-linear or Zero-Order Pharmacokinetics

Change in [drug] versus time



- 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.

Complication II: Non-linear or Zero-Order Pharmacokinetics



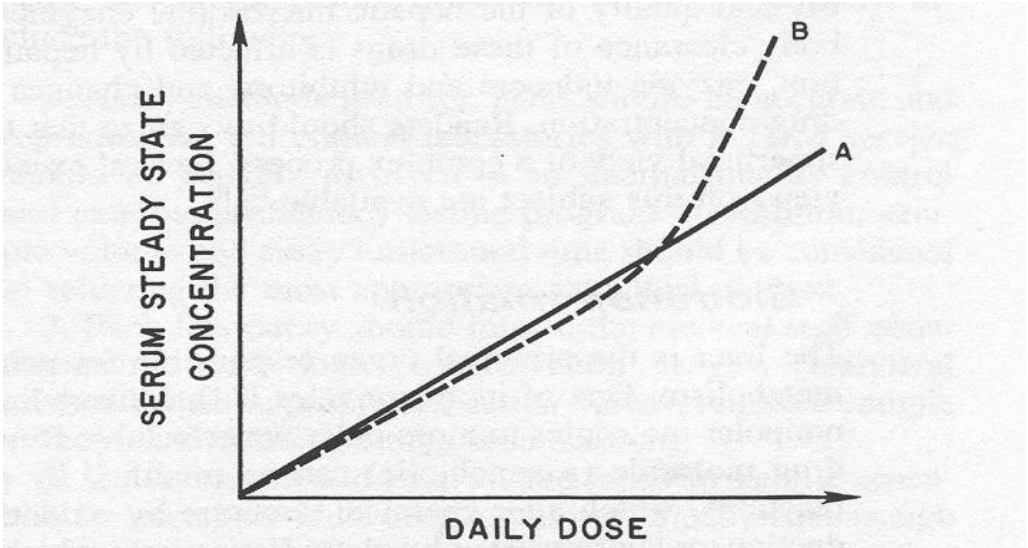


FIGURE **26-10.** Dose–response curves. *Line A* illustrates the linear relationship between serum drug concentration and total daily dose of a drug that displays first-order kinetics. *Line B* illustrates the dose–response relationship for a drug that displays capacity-limited kinetics because of a 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.E.: Practical pharmacokinetic applications. Syva Monitor, January, 1979, pp. 1–4. Syva Co., San Jose, CA.)

Complication III: Free vs. Total Drug Levels

- Many drugs are highly bound (90+%) to serum proteins (primarily albumin).
- In these cases, only the free drug is equilibrated with active sites extravascularly.
- Therefore, the free drug concentration should actually correlate ***best*** with efficacy and toxicity.
- Similarly, the rate of drug elimination is directly controlled by the free drug concentration.
- However, in most cases, we measure the ***total*** (free + bound) drug concentration in blood.

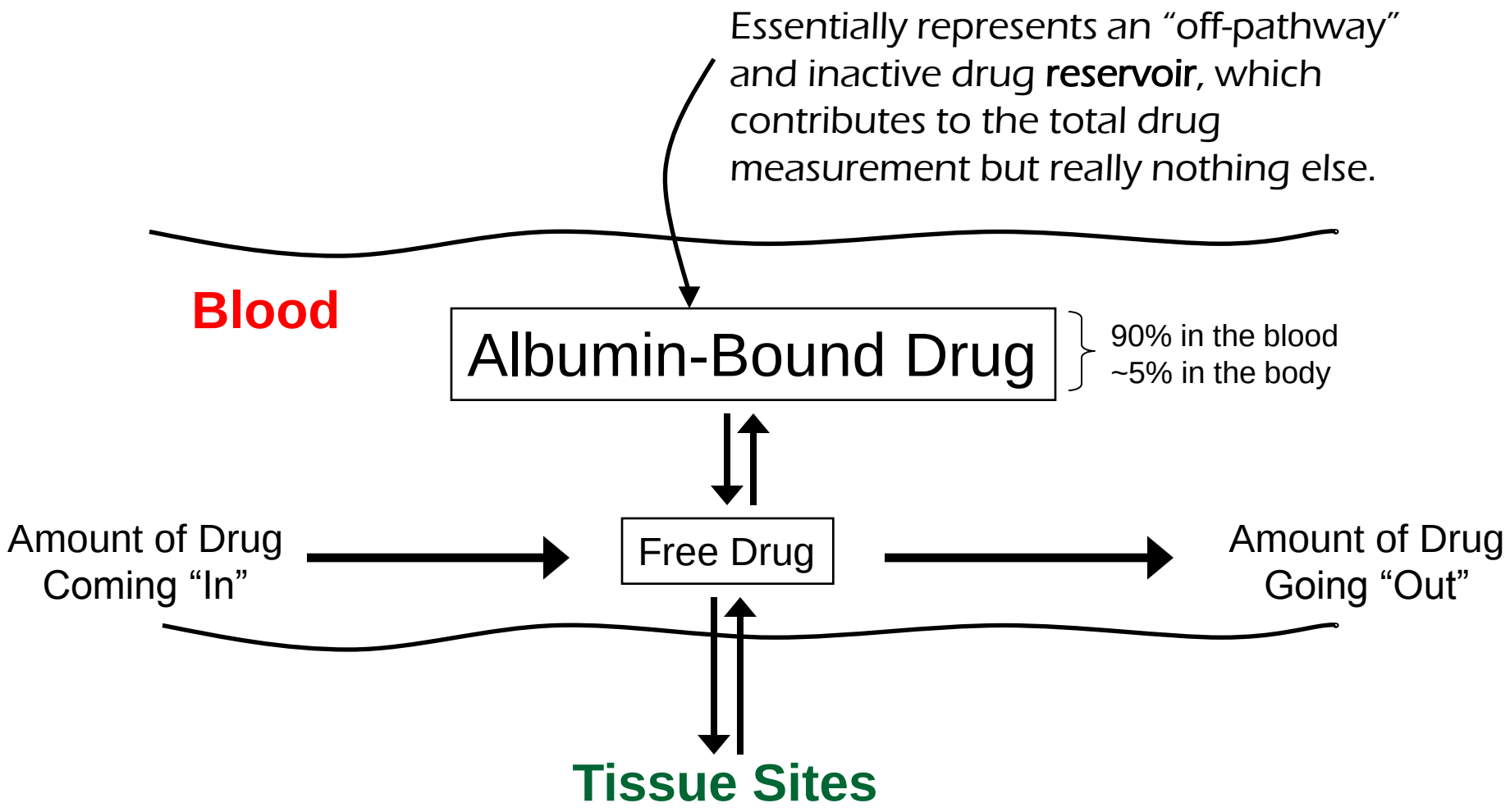
Complication III: Free vs. Total Drug Levels

- Fortunately, most of the time, there is a predictable relationship between free and total drug concentrations (as long as albumin is “normal”).
  - For example, free phenytoin is ~10% of total phenytoin across a relatively wide range of concentrations.
- Pharmacokinetic parameters such as V_d, Cl, $t_{1/2}$ and the reference range are all defined for the total drug concentration (since that is what we measure) based on the assumption that the free is constant fraction of the total.
  - The reference range for total phenytoin is 10 – 20 mg/L, with a corresponding range of 1 – 2 mg/L for free drug.

Complication III: Free vs. Total Drug Levels

- What happens when albumin is much lower than normal (i.e. 2 g/dL instead of 4 g/dL)?
- In terms of phenytoin dosages, free phenytoin levels and elimination rates, not much actually.
  - Note that the amount of phenytoin bound to albumin in the bloodstream is small relative to the overall amount of phenytoin in the body.
    - At 20 mg/L, there is 20 mg/L*0.65L/kg*70kg = 910 mg of phenytoin in the entire body.
    - And 18 mg/L * ~3 L (plasma volume) = 54 mg bound to albumin in the bloodstream.

Complication III: Free vs. Total Drug Levels



Complication III: Free vs. Total Drug Levels

- Imagine a patient on a stable dose of phenytoin with a total drug level of 15 mg/L and a serum albumin of 4 g/dL.
  - free phenytoin = 1.5 mg/L
  - bound phenytoin = 13.5 mg/L
- The patient develops mild nephrosis and their serum albumin slowly declines from 4 to 2 g/dL with no significant change in liver function.
  - What will happen to their free and total phenytoin concentrations?
  - Does their rate of elimination change?
  - Do they need a change in dose?

Complication III: Free vs. Total Drug Levels

- The only thing that happens to this patient is that the amount of drug bound to albumin is cut in half (from ~13.5 to ~6.75 mg/L).
- Note that the amount of drug going in (i.e. the dose), the free phenytoin level and the amount of drug being eliminated are NOT changed.
- The measured free phenytoin will remain at 1.5 mg/L but the total will decline to ~8 mg/L.
  - At this point, the patient's ratio of free:total drug will have increased to ~0.2 (from 0.1 originally).
  - Hence, another way of adjusting the expected ***total*** phenytoin is using the factor "[albumin]/4 g/dL".
- There is no need for a change in dosage!