Principles of Basic Clinical Pharmacokinetic Parameters

Part II

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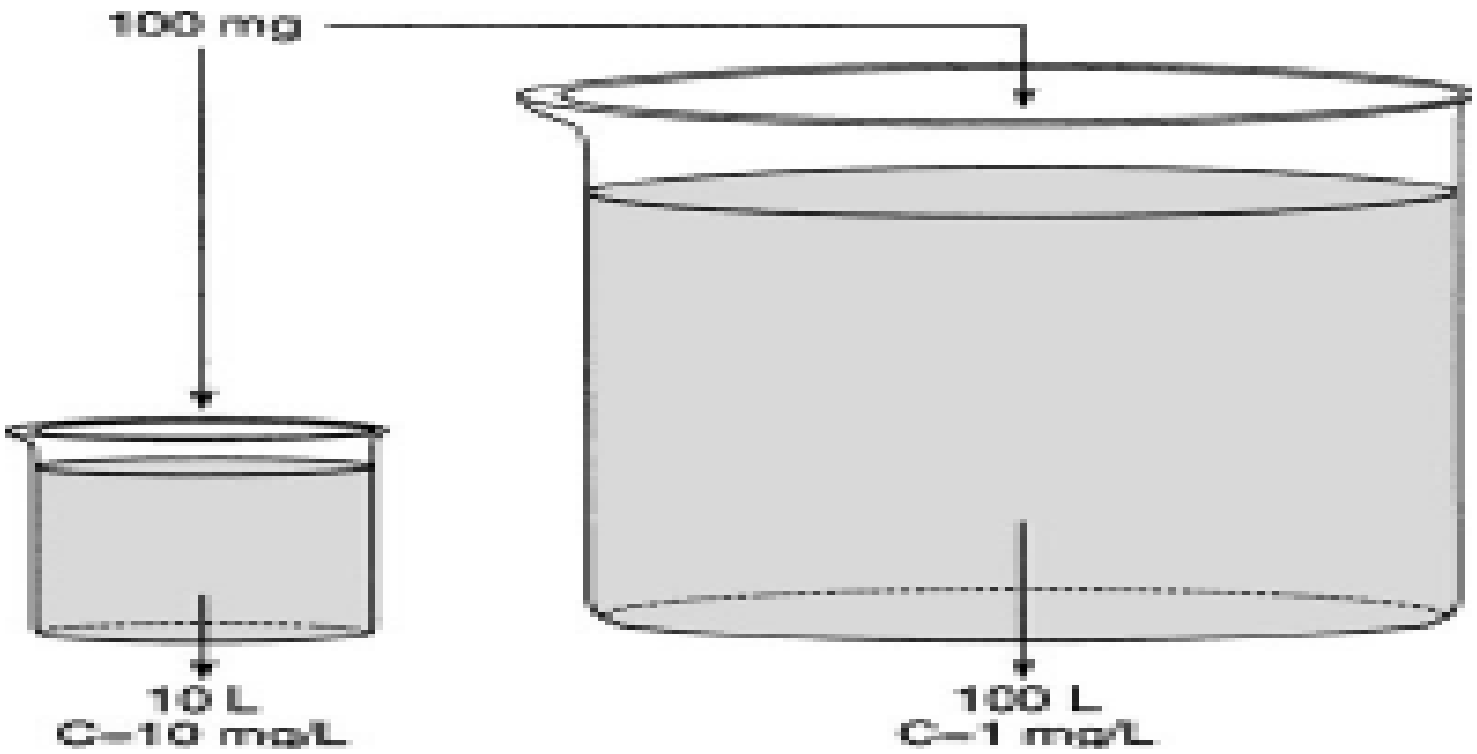
Volume of distribution

- Volume of distribution (V) determines the loading dose (LD) that is required to achieve a particular steady-state drug concentration immediately after the dose is administered:

$$LD = Css \cdot V$$

- The volume of distribution (V) is a *hypothetical volume* that is the proportionality constant which relates the concentration of drug in the blood or serum (C) and the amount of drug in the body (A_B): $A_B = C \cdot V$



It can be thought of as a beaker of fluid representing **the entire space that drug distributes into**. In this case, one beaker, representing a patient with a small volume of distribution, contains 10 L while the other beaker, representing a patient with a large volume of distribution, contains 100 L. If 100 mg of drug is given to each patient, the resulting concentration will be ***10 mg/L*** in the patient with the **smaller volume of distribution**, but ***1 mg/L in*** the patient with the **larger volume of distribution**. If the minimum concentration needed to exert the pharmacological effect of the drug is 5 mg/L, one patient will receive a benefit from the drug while the other will have a subtherapeutic concentration.

Volume of distribution

- Usually an average volume of distribution measured in other patients with similar demographics (age, weight, gender, etc.) and medical conditions (renal failure, liver failure, heart failure, etc.) is used to estimate a loading dose.

- Because of this, most patients will not actually attain steady state after a loading dose, but, hopefully, serum drug concentrations will be high enough so that the patient will experience the pharmacological effect of the drug.

Volume of distribution

- The volume of distribution can be very small if the drug is primarily contained in the blood (warfarin V = 5–7 L), or very large if the drug distributes widely in the body and is mostly bound to bodily tissues (digoxin V = 500 L).

- The physiologic determinates of volume of distribution are:

1. **The actual volume of blood (V_B) and size (measured as a volume) of the various tissues and organs of the body (V_T).**

Volume of distribution

- Therefore, a larger person, such as a 100-kg football player, would be expected to have a larger volume of distribution for a drug than a smaller person, such as a 40-kg grandmother.

2. Drug binding in the blood or serum compared to the binding in tissues.

- For example, the reason warfarin has such a small volume of distribution is that it is highly bound to serum albumin so that the free fraction of drug in the blood (f_B) is very small.

Volume of distribution

- Digoxin has a very large volume of distribution because it is very highly bound to tissues (primarily muscle) so that the free fraction of drug in the tissues (f_T ; f_T = unbound drug concentration in the tissue/total tissue drug concentration) is very small.

- The equation that relates all of these physiologic determinates to the volume of distribution is:

$$V = V_B + (f_B/f_T)\, V_T$$

Volume of distribution

- An example is how the volume of distribution changes when plasma protein binding drug interactions occur;

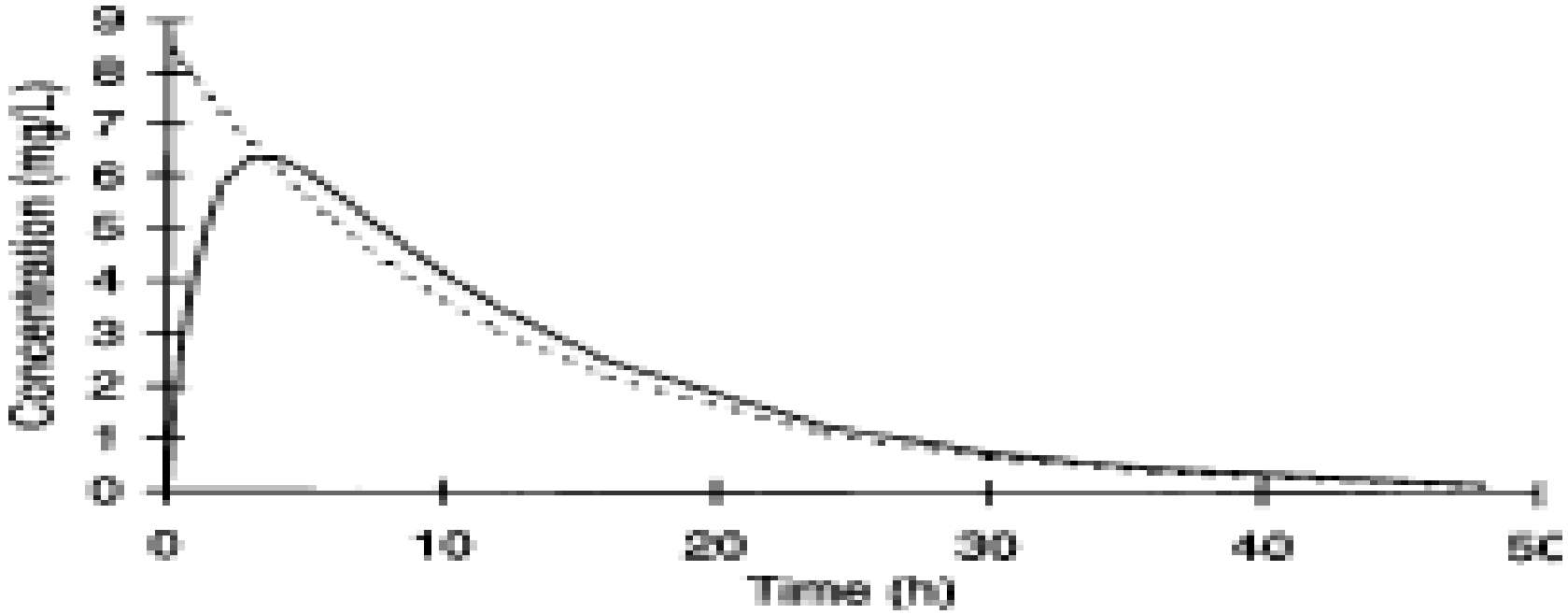
- If a drug that is highly bound to plasma proteins is given to a patient, and then a second drug that is also highly bound to the same plasma protein is given concurrently, the second drug will compete for plasma protein binding sites and displace the first drug from the protein.

- In this case, the free fraction in the serum of the first drug will increase ($\uparrow f_B$), resulting in an increased volume of distribution: $\uparrow V = V_B + (\uparrow f_B / f_T) V_T$.

Half-life and elimination rate constant

- When drugs that follow linear pharmacokinetics are given to humans, serum concentrations decline in a curvilinear fashion after drug absorption and distribution phases are complete.

- This part of the curve is known as the elimination phase.



Serum concentration/time profile for a patient receiving 300 mg of theophylline orally (solid line) and by intravenous bolus (dashed line). Serum concentrations decline in a curvilinear fashion in both cases. When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete.

Half-life and elimination rate constant

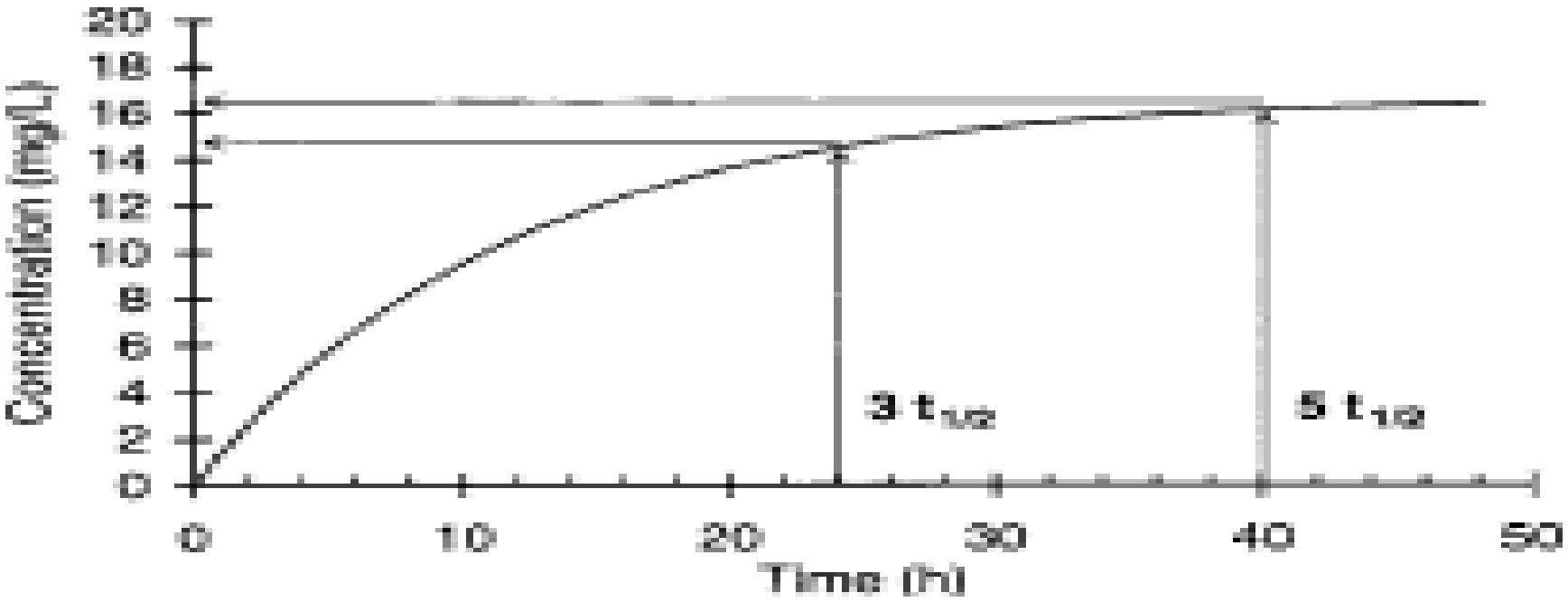
- The time that it takes for serum concentrations to decrease by 1/2 in the elimination phase is a constant and is called the half-life ($t_{1/2}$).

- The half-life describes how quickly drug serum concentrations decrease in a patient after a medication is administered, and the dimension of half-life is time (hour, minute, day, etc.).

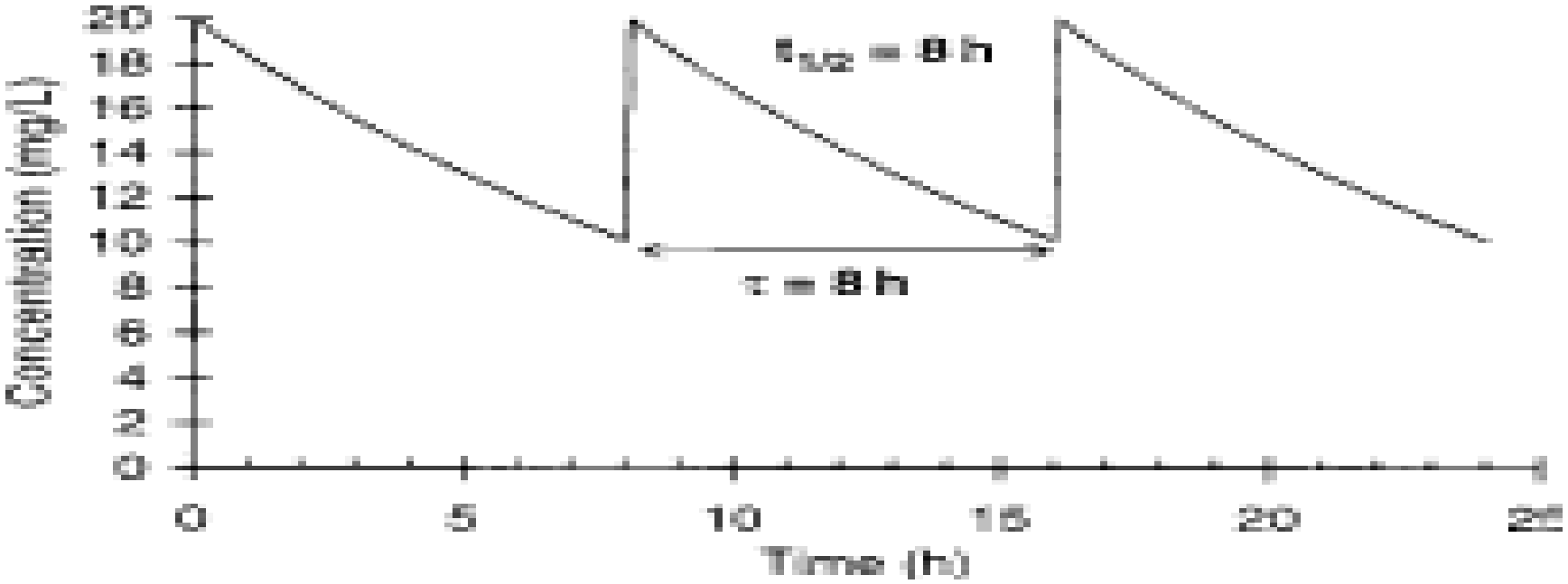
Half-life and elimination rate constant

- Why is half-life important?
  - Time to steady state
  - Dosage interval

- Generally, steady-state drug serum concentrations can be attained after 3–5 estimated half-lives.



The arrows indicate concentrations at 3 half-lives (24 hours, ~90% of Css) and at 5 half-lives (40 hours, ~95% of Css). Since most drug assays have 5–10% measurement error, serum concentrations obtained between 3–5 half-lives after dosing commenced can be considered to be at steady state for clinical purposes and used to adjust drug doses.



The dosage interval for a drug is determined by the half-life of the agent. In this case, the half-life of the drug is 8 hours, and the therapeutic range of the drug is 10–20 mg/L. In order to ensure that maximum serum concentrations never go above and minimum serum concentrations never go below the therapeutic range, it is necessary to give the drug every 8 hours (t = dosage interval).

Half-life and elimination rate constant

- Another common measurement used to denote how quickly drug serum concentrations decline in a patient is the elimination rate constant (k_e).

- The dimension for the elimination rate constant is reciprocal time (hour $^{-1}$, minute $^{-1}$, day $^{-1}$, etc.).

Half-life and elimination rate constant

- The half-life and elimination rate constant are related to each other by the following equation:

$$t_{1/2} = 0.693/ke$$

- The elimination rate constant can also be measured graphically by computing the slope of the log concentration versus time graph during the elimination phase;

$$ke/2.303 = -(\log C_1 - \log C_2)/(t_1 - t_2)$$

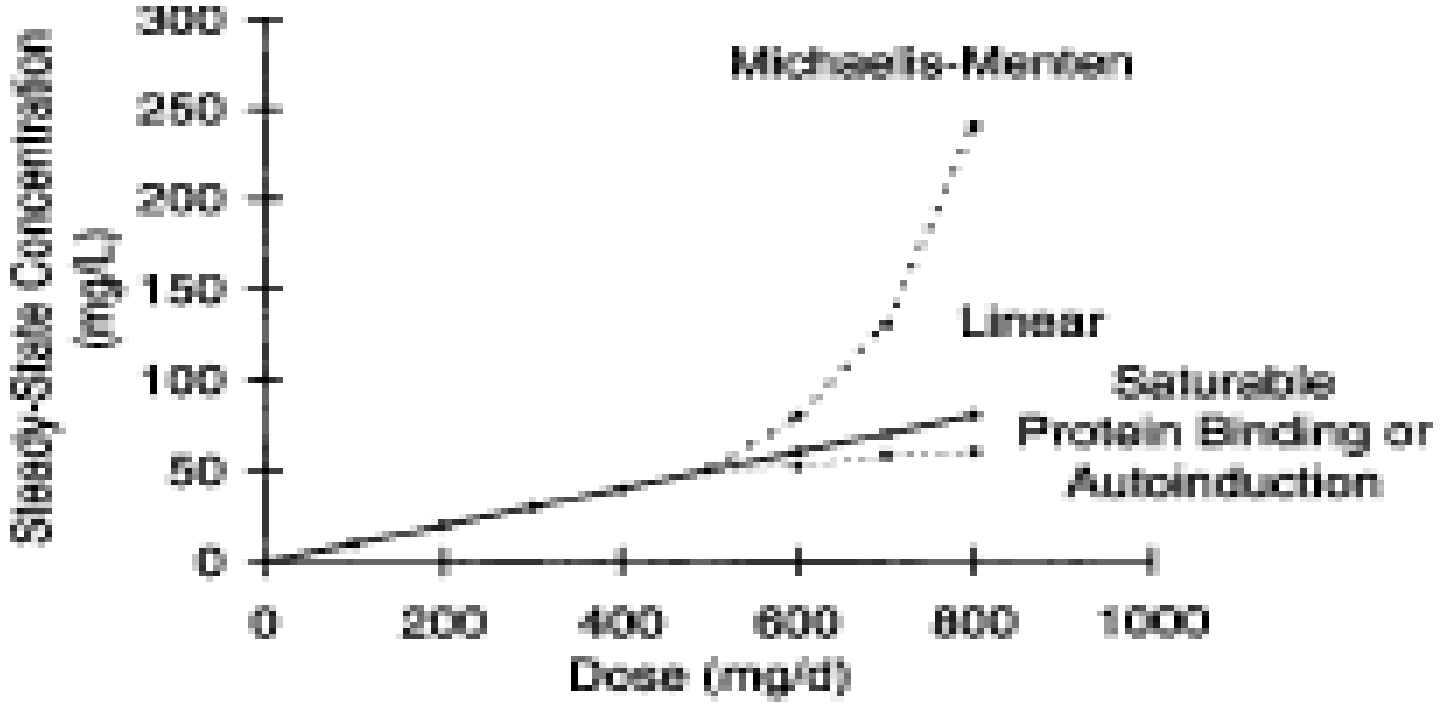
$$ke = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$$

Michaelis-Menten or saturable pharmacokinetics

- Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo *Michaelis-Menten or saturable pharmacokinetics.*

- This is the type of **nonlinear pharmacokinetics** that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug.

- When this occurs, steady-state drug serum concentrations increase in a **disproportionate** manner after a dosage increase.



When doses are increased for most drugs, steady-state concentrations increase in a proportional fashion leading to linear pharmacokinetics (solid line). However, in some cases proportional increases in steady-state concentrations do not occur after a dosage increase. When steady-state concentrations increase more than expected after a dosage increase (upper dashed line), Michaelis-Menten pharmacokinetics may be taking place. If steady-state concentrations increase less than expected after a dosage increase (lower dashed line), saturable plasma protein binding or autoinduction are likely explanations.

Michaelis-Menten or saturable pharmacokinetics

- In this case the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems:

- Rate of metabolism = $(V_{max} \cdot C)/(K_m + C)$,

Vmax: maximum rate of metabolism

C: the substrate concentration

Km: substrate concentration where the rate of metabolism = Vmax /2.

Michaelis-Menten or saturable pharmacokinetics

- The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of a drug is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent.

- As the dose or concentration increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions:

$$Cl = Vmax /(Km + C)$$

Michaelis-Menten or saturable pharmacokinetics

This is why concentrations increase disproportionately after a dosage increase

Michaelis-Menten or saturable pharmacokinetics

- For example, phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants;

Vmax = 500 mg/d

Km = 4 mg/L

The therapeutic range of phenytoin is 10–20 mg/L

- As the steady-state concentration of phenytoin increases from 10 mg/L to 20 mg/L, clearance decreases from 36 L/d to 21 L/d.

Michaelis-Menten or saturable pharmacokinetics

- $Cl = Vmax / (Km + C)$;
- $Cl = (500\ mg/d) / (4\ mg/L + 10\ mg/L) = 36\ L/d$
- $Cl = (500\ mg/d)/(4\ mg/L + 20\ mg/L) = 21\ L/d$

Michaelis-Menten or saturable pharmacokinetics

- Unfortunately, there is so much interpatient variability in Michaelis-Menten pharmacokinetic parameters for a drug that

dosing drugs which follow saturable metabolism is extremely difficult

- For example, phenytoin typically shows Vmax = 100–1000 mg/d and Km = 1–10 mg/L.

Michaelis-Menten or saturable pharmacokinetics

- The volume of distribution (V) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) as well as the unbound concentration of drug in the blood (f_B) and tissues (f_T):

$$V = V_B + (f_B / f_T) V_T$$

Michaelis-Menten or saturable pharmacokinetics

- half-life (t 1/2) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics:

$$t_{1/2} = (0.693 \cdot V)/Cl$$

$$Cl = ke\ V$$

- However, since clearance is dose- or concentration-dependent, half-life also changes with dosage or concentration changes.

Michaelis-Menten or saturable pharmacokinetics

- As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug:

$$\uparrow t_{1/2} = (0.693 \cdot V)/\downarrow Cl$$

- The clinical implication of this finding is that the time to steady state (3–5 $t_{1/2}$) is longer as the dose or concentration is increased for a drug that follows saturable pharmacokinetics.

Michaelis-Menten or saturable pharmacokinetics

- For a drug that is solely removed by metabolism via one enzyme system, the Michaelis-Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css):

$$MD = \frac{Vm \cdot Css}{Km + Css}$$

Michaelis-Menten or saturable pharmacokinetics

- When the therapeutic range for a drug is far below the Km value this equation simplifies to:

$$MD = (Vmax / Km)\ Css$$

or, since Vmax /Km is a constant,

$$MD = Cl \cdot Css$$

- ***Therefore, when Km >> Css, drugs that are metabolized follow linear pharmacokinetics (first order pharmacokinetics).***

Michaelis-Menten or saturable pharmacokinetics

- When the therapeutic range for a drug is far above the Km value, the rate of metabolism becomes a constant equal to Vmax.

- Under these conditions only a fixed amount of drug is metabolized because the enzyme system is completely saturated and cannot increase its metabolic capacity.

- This situation is also known **as zero-order pharmacokinetics**.

Michaelis-Menten or saturable pharmacokinetics

- Based on these facts, it can be seen that any drug that is metabolized by enzymes undergoes Michaelis-Menten pharmacokinetics.

- But, the therapeutic ranges of most drugs are far below the Km for the enzymes that metabolize the agent.

- Because of this, most medications that are metabolized follow linear pharmacokinetics.

- However, even in these cases saturable drug metabolism can occur in drug overdose cases where the drug concentration far exceeds the therapeutic range for the medication.

Any question???