Clinical pharmacokinetics

Volume of distribution

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

$$\mathbf{LD = Css * V}$$

- The volume of distribution is a hypothetical volume that relates drug serum concentrations to the amount of drug in the body. T
- The dimension of volume of distribution is in volume units, such as L or mL.
- 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).
- **Factors affecting volume of distribution**:

1. ***Physiological factors:*** The physiologic determinates of volume of distribution are the actual volume of blood (VB) and size (measured as a volume) of the various tissues and organs of the body (VT). Therefore, a larger person, such as a 160-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. ***How the drug binds in the blood or serum compared to the binding in tissues*** is also an important determinate of the volume of distribution for a drug. 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. 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.

$$V = V_B + \frac{f_B}{f_T} V_T$$

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:

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

Elimination rate constant (k_e)

- Masurement used to denote how quickly drug serum concentrations decline in a patient
- The dimension for the elimination rate constant is reciprocal time ($hour^{-1}$, $minute^{-1}$, day^{-1}, etc.)
- The half-life and elimination rate constant are related to each other by the following equation, so it is easy to compute one once the other is known:

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

- The elimination rate constant can also be measured graphically by computing the slope of the log concentration versus time graph during the elimination phase: using $\log_{10}$

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

or, using natural logarithms:

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

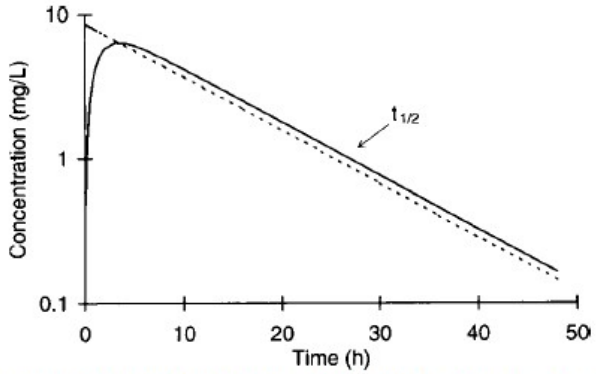

FIGURE 1-8 Serum concentration/time profile for a patient receiving 300 mg of theophylline orally (*solid line*) and by intravenous bolus (*dashed line*). If this data is plotted on semilogarithmic axes, serum concentrations decline in a straight line in both cases. When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete. This same data set is plotted in Figure 1-7 on rectilinear axes.

- The half-life is important because:

1. It determines the time to steady state during the continuous dosing of a drug and the dosage interval.
2. The dosage interval for a drug is also determined by the half-life of the medication. During drug development, it is very common to use the drug half-life as the initial dosage interval for the new drug compound until the pharmacodynamics of the agent can be determined.

Note:

- The ***half-life*** and ***elimination rate constant*** are known as ***dependent parameters*** because their values depend on the clearance (Cl) and volume of distribution (V) of the agent:

$$t_{1/2} = (0.693 \cdot V)/Cl \quad \text{and} \quad k_e = Cl/V$$

The half-life and elimination rate constant for a drug can change either because of a change in clearance or a change in the volume of distribution.

- Because the values for ***clearance*** and ***volume of distribution*** depend solely on physiological parameters and can vary independently of each other, they are known as ***independent parameters***.

Bioavailability (F)

- The fraction of the administered dose that is delivered to the systemic circulation.
- For drugs that follow linear pharmacokinetics, bioavailability is measured by comparing serum concentrations achieved after extravascular and intravenous doses in the same individual.

$$F = AUC_{PO}/AUC_{IV}$$

- If it is not possible to administer the same dose intravenously and extravascularly because poor absorption or presystemic metabolism yields serum concentrations that are too low to measure, the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration:

$$F = (AUC_{PO}/AUC_{IV})(D_{IV}/D_{PO})$$

- When a drug is administered extravascularly, the entire dose may not enter the systemic circulation. For example, an orally administered tablet may not completely dissolve so that part of the dose is eliminated in the stool, or a transdermal patch may not release the entire dose before it is removed from the skin.
- When medications are given orally, intramuscularly, subcutaneously, or by other extravascular routes, the drug must be absorbed across several biologic membranes before entering the vascular system.
- Drug serum concentrations rise while the drug is being absorbed into the bloodstream, reach a ***maximum concentration (Cmax)*** when the ***rate of drug absorption*** equals the ***rate of drug elimination***, and eventually decrease according to the half-life of the drug.
- If a medication is given orally, drug molecules must pass through several organs before entering the systemic circulation.
    a. During absorption from the gastrointestinal tract, the drug molecules will encounter:
        1. enzymes that may metabolize the agent (primarily CYP3A4 substrates since ~90% of cytochrome P-450 contained in the gut wall is CYP3A4) or,

2. pump the drug back into the lumen and prevent absorption from taking place (primarily P-glycoprotein substrates).

b. Once drug molecules are absorbed from the gastrointestinal tract, they enter the portal vein. If the drug is ***hepatically metabolized***, part of the drug may be metabolized by the liver even though the majority of the drug was absorbed from the gastrointestinal tract. Drugs that are substrates for CYP3A4 and CYP2D6 are particularly susceptible to presystemic metabolism by the liver.
c. Blood leaving the liver via the hepatic vein enters the inferior vena cava, and will eventually be pumped through the lung by the right side of the heart before entering the left side of the heart and being pumped into the arterial system.
d. To a lesser extent, some drugs are metabolized by the lung or irreversibly eliminated into expired air.

Note:

- The loss of drug from these combined processes is known as ***presystemic metabolism*** or the ***first-pass effect***.
- For example, the oral bioavailability of both propranolol (a substrate for CYP2D6 and CYP2C19) and verapamil (a substrate for CYP3A4 and P-glycoprotein) is about ~10% even though the oral dosage forms for each agent release 100% of the drug into the gastrointestinal tract.

Bioequivalence

- A desirable attribute of a generic drug dosage form is that it produce the same serum concentration/time profile as its brand name counterpart. When generic drugs meet this requirement, then generic drug product is said to be bioequivalent to the brand name drug.
- In theory, it should be possible to substitute a bioequivalent generic drug dosage form for a brand name product without a change in steady-state drug serum concentrations or therapeutic efficacy.
- This is because the drug company manufacturing the generic drug ***does not have to prove that the drug is safe and effective*** since those studies were done by the pharmaceutical company producing the brand name drug.
- Bioequivalence is achieved when the serum ***concentration/time curve*** for the generic and brand name drug dosage forms are deemed indistinguishable from each other using statistical tests.

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- Concentration/time curves are superimposable when the area under the total serum concentration/time curve ***(AUC)***, maximum concentration ***(Cmax)***, and time that the maximum concentration occurs ***(Tmax)*** are identical within statistical limits.
- In order to achieve the Food and Drug Administration's (FDA) definition of oral bioequivalence and be awarded an "AB" rating in the FDA publication ***Approved Drug Products with Therapeutic Equivalence Evaluations*** (also known as The ***Orange Book***),

$$F_{relative} = AUC_{generic}/AUC_{brand}$$