Lecture-8
Biopharmaceutics

Apparent volume of distribution and clearance

Significance of the apparent volume of distribution

- The apparent volume of distribution is not a true physiologic volume
- Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass.
- For some drugs, the volume of distribution may be several times the body mass.
- Equation 3.9 (V_D = Dose /C_p^0)shows that the apparent V_D is dependent on C_p^0. For a given dose, a very small C_p^0 may occur in the body due to concentration of the drug in peripheral tissues and organs.
- For this dose, the small C_p^0 will result in a large V_D

- Drugs with a large apparent V_D are more concentrated in ---------- and less concentrated -------- .
- If a drug is highly bound to plasma proteins or remains in the vascular region, then C_p^0 will be higher, resulting in a ---------- apparent V_D .
- Consequently, binding of a drug to peripheral tissues or to plasma proteins will significantly affect V_D
- The apparent V_D is a volume term that can be expressed as a simple volume or in terms of percent of body weight.

- In expressing the apparent V_D in terms of percent body weight, a 1-L volume is assumed to be equal to the weight of 1 kg.
- For example, if the V_D is 3500 mL for a subject weighing 70 kg, the V_D expressed as percent of body weight is equal to ----------

- If V_D is a very large number-i.e., > 100% of body weight-then it may be assumed that the drug is concentrated in certain ---------- compartments.
- Thus, the apparent V_D is a useful parameter in considering the relative a mounts of drug in the vascular and in the extravascular tissues.

Table 3.1 Fluid in the body

Water compartment	Percent of body weight	Percent of total body water
plasma	4.5	7.5
Total extracellular water	27.0	45.0
Total intracellular water	33.0	55.0
Total body water	60.0	100.0

- For each drug, the apparent V_D is constant. In certain pathologic cases, the apparent V_D for the drug may be altered if the distribution of the drug is changed.
- For example, in edematous condition, the total body water and total extracellular water increases; this reflected in a -------- apparent V_D value for a drug that is highly water soluble.
- Similarly, change in total body weight and lean body mass (which normally occur with age) may also affect the apparent V_D .

Clearance

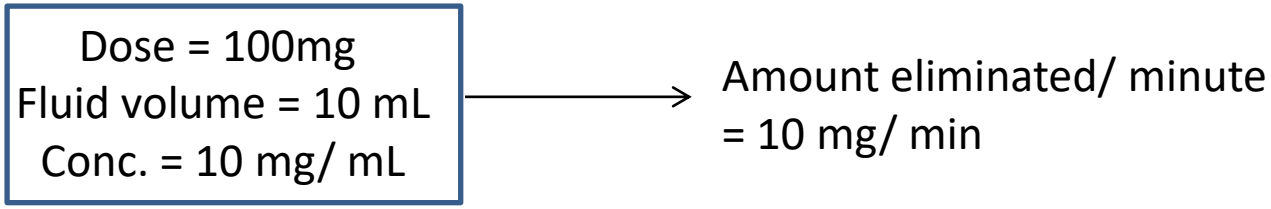
- Clearance is a measure of drug elimination from the body without identifying the mechanism or process.

➢ **Drug clearance in the one-compartment model**

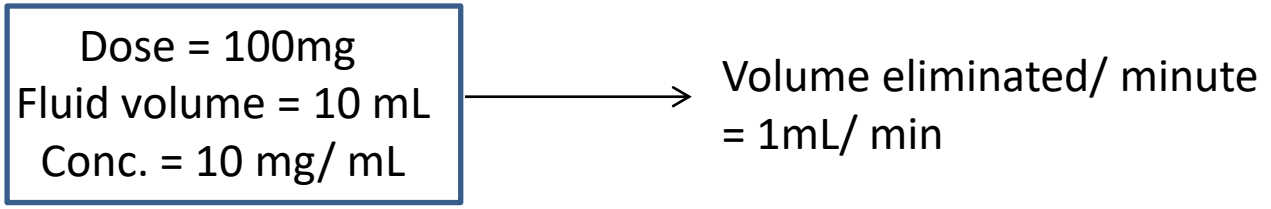
- Drug clearance refers to the volume of plasma fluid that is cleared of drug per unit time.
- Clearance may also be considered as the fraction of drug removed per unit time multiplied by the V_D .

Approaches describe clearance

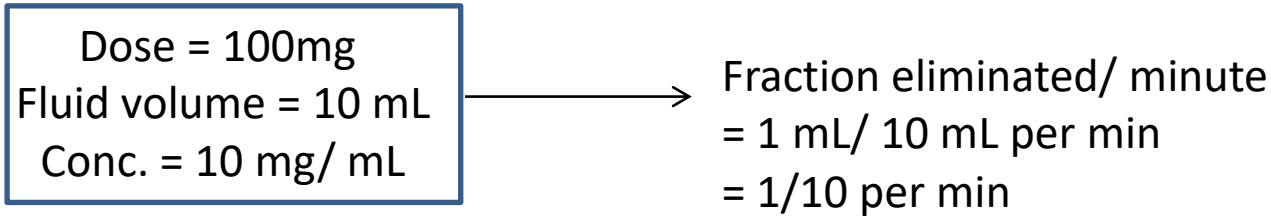
a. Mass approach



b. Clearance (volume) approach



c. Fractional approach



One-compartment model equation in terms of Cl and V_D

- Equation 3.20 may be rewritten in terms of clearance and volume of distribution by substituting Cl/V_D for k. The clearance concept may also be applied a biologic system in physiologic modeling without the need of a theoretical compartment.
- $C_p = C_p^0 e^{-kt}$ (3.20)
- $C_p = D_0/V_D e^{-(Cl/V_D)t}$ (3.21)
- Equation 3.21 is applied directly in clinical pharmacy to determine clearance and volume of distribution in patients. When only one sample is available, i.e., C_p is known at one sample time point, t after a given dose, the equation cannot be determined unambiguously because two unknown parameters must be solved, i.e., Cl and V_D.
- In practice, the mean values for Cl and V_D of a drug are obtained from the population values in the literature.

Practical focus

- The IV single dose Equation 3.22 may be modified to calculate the elimination rate constant or half-life of a drug in a patient when two plasma samples and their time of collection are known:
- $ln\ Cp = ln\ C_p^0 - kt$ (3.22)
- Or
- $\log Cp = \log C_p^0 - kt/2.3$

If the first plasma sample is taken at t_1 instead of zero and corresponds to plasma drug concentration, then C_2 is the concentration at time t_2 and t is set to (t_2-t_1).

$C_2 = C_1\ e^{-k\ (t_2-t_1)}$

$ln\ C_2 = ln\ C_1 - k\ (t_2-t_1)$ (3.23)

- Rearranging:

$$\ln C_2 - \ln C_1 = -k\,(t_2 - t_1)$$

$$K = (\ln C_1 - \ln C_2) / (t_2 - t_1) \quad (3.24)$$

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

$$t_{1/2} = 0.693\,(t_2 - t_1) / \ln C_1 - \ln C_2 \quad (3.25)$$

Where

t_1 = time of first sample collection

C_1 = plasma drug concentration at t_1

t_2 = time of second sample collection

C_2 = plasma drug concentration at t_2

Clearance from drug-eliminating tissues

- Clearance may be applied to any organ that is involved in drug elimination from the body. As long as first-order elimination process are involved, clearance represents the sum of the clearances for each drug-eliminating organ as shown in Equation 3.26.
- $Cl_T = Cl_R + Cl_{NR}$ (3.26)
- Where Cl_R is renal clearance or drug clearance through the kidney, and Cl_{NR} is nonrenal clearance through other organs.
- Cl_{NR} is assumed to be due primarily to hepatic clearance (Cl_H) in the absence of other significant drug clearances, such as elimination through the lung or the bile, as shown in Equation 3.27:
- $Cl_T = Cl_R + Cl_H$ (3.27)

- Drug clearance considers that the drug in the body is uniformly dissolved in a volume of fluid (apparent volume of distribution, V_D)from which drug concentrations can be measured easily.
- Typically, plasma fluid concentration is measured and drug clearance is then calculated as the fixed volume of plasma fluid (containing the drug) cleared of drug per unit of time.
- The units for clearance are volume/time (e.g., mL/min, L/hr).

- For some drugs, the elimination rate process is more complex and a noncompartment method may be used to calculate certain pharmacokinetic parameters such as clearance. In this case, clearance can be determined directly from the plasma drug concentration-versus-time curve by
- $$Cl_T = \frac{D_0}{[AUC]_0^\infty} \quad (3.33)$$
- Where D_0 is the dose and $[AUC]_0^\infty = \int_0^\infty C_p \, dt$