Multiple – Dosage Regimens

Introduction to Multiple Dosage Regimens

- Before diving into the specific models, it's important to understand **why multiple dosage regimens are needed**.
- When a drug is administered, it is absorbed (if not injected intravenously), distributed in the body, metabolized (often in the liver), and then eliminated (often through the kidneys). This is called **ADME**.
- If a drug is given just once, its concentration in the blood (plasma) rises and then falls over time.
- However, in clinical therapy, maintaining the drug concentration within a **therapeutic window** (between minimum effective concentration and minimum toxic concentration) is crucial.
- A **single dose** might not maintain therapeutic concentration for a sufficient duration, so the drug must be given **repetitively**.
- Hence, **multiple dose regimens** are employed to keep drug concentrations within the therapeutic range for an extended period.
- Pharmacokinetic modeling helps us understand and predict the concentration-time profile of the drug with multiple dosing.
- There are two broad models used:
    - **One-compartment open model**
    - **Two-compartment open model**
- The word **open** signifies that the drug can leave the system (i.e., it can be eliminated), as opposed to a closed system where there is no elimination.

Repetitive Intravenous Injections – One Compartment Open Model

Overview of the Model

- In this case, the drug is administered directly into systemic circulation (IV route).
- The **one-compartment open model** assumes the entire body acts as a single, uniform compartment.
- This model simplifies the drug distribution and assumes **instantaneous mixing** of the drug in blood/plasma.
- **Elimination** is assumed to follow **first-order kinetics** (i.e., the rate of elimination is proportional to the concentration).

Key Assumptions

- Drug distributes instantaneously and uniformly throughout the compartment.

- Elimination starts immediately after administration.
- First-order elimination kinetics.
- Drug is administered at regular intervals (τ).
- The same dose is given each time (fixed-dose regimen).

Mathematical Framework

Single IV Bolus Dose

- For a single IV bolus dose (amount = **D**), plasma concentration at any time **t** is:

$$C(t) = \frac{D}{V_d} \cdot e^{-k \cdot t}$$

  - $C(t)$: concentration at time t
  - D: dose
  - V_d: volume of distribution
  - k: elimination rate constant

Multiple Dosing at Regular Intervals

- When doses are repeated every **τ** hours, the total concentration at any time is the **sum of residual concentrations** from each prior dose:

$$C_n(t) = \sum_{i=0}^{n-1} \left(\frac{D}{V_d} \cdot e^{-k \cdot (t + i\tau)}\right)$$

- This series forms a **geometric progression**, enabling the derivation of **maximum and minimum concentrations** at steady state:
  - **Peak (just after a dose):**

$$C_{\text{max,ss}} = \frac{D}{V_d} \cdot \frac{1}{1 - e^{-k \cdot \tau}}$$

  - **Trough (just before the next dose):**

$$C_{\text{min,ss}} = C_{\text{max,ss}} \cdot e^{-k \cdot \tau}$$

Key Concepts

Accumulation

- When the dosing interval $\tau < 4 \cdot t_{1/2}$, drug accumulation occurs.
- Accumulation Ratio:

$$R = \frac{1}{1 - e^{-k \cdot \tau}}$$

Steady State

- Achieved when the rate of drug input equals the rate of drug elimination.
- Reached typically after **4–5 half-lives** of the drug.

Fluctuation

- The difference between peak and trough concentration:

$$\text{Fluctuation} = C_{max,ss} - C_{min,ss}$$

A wider dosing interval increases fluctuation.

Clinical Significance

- Understanding IV bolus kinetics is critical for drugs with narrow therapeutic ranges.
- Helps in designing optimal dosing regimens.
- Ensures therapeutic effect without toxicity.

Repetitive Extravascular Dosing – One Compartment Open Model

Overview of the Model

- Here, the drug is administered by extravascular routes: **oral, subcutaneous, intramuscular, rectal, etc.**
- The drug has to be **absorbed into systemic circulation** before it can distribute and be eliminated.
- This adds an extra step (absorption), compared to IV dosing.
- Still considered a **one-compartment model** where the body behaves like a single, uniform compartment.

Key Parameters

- **ka** = absorption rate constant
- **k** = elimination rate constant
- **F** = bioavailability (fraction of dose that reaches systemic circulation)
- **D** = administered dose
- **Vd** = volume of distribution
- **τ** = dosing interval

Mathematical Framework

Single Extravascular Dose

$$C(t) = \frac{F \cdot D \cdot k_a}{V_d(k_a - k)}[e^{-k \cdot t} - e^{-k_a \cdot t}]$$

- Where:
  - F: bioavailability (fraction absorbed)
  - D: dose
  - k_a: absorption rate constant
  - k: elimination rate constant

Multiple Doses at Interval τ

- The total concentration at time **t** after n doses is:

$$C(t) = \sum_{i=0}^{n-1} \frac{F \cdot D \cdot k_a}{V_d(k_a - k)}[e^{-k \cdot (t - i\tau)} - e^{-k_a \cdot (t - i\tau)}]$$

- At steady state, this becomes a geometric series again.

Key Concepts

Lag in Onset

- Due to the absorption process.
- The **time to peak concentration (Tmax)** is delayed compared to IV.
- Affected by k_a: faster absorption gives quicker Tmax.

Accumulation and Steady State

- Still governed by elimination half-life.
- Steady-state occurs after ~4–5 half-lives.

Fluctuations

- More pronounced if k_a is low (slow absorption).
- Absorption rate can impact bioavailability and Tmax.

Clinical Considerations

- Bioavailability becomes a critical factor here.
- Drugs with poor absorption or first-pass metabolism may require higher or more frequent doses.
- Time to reach steady state is again approximately 4–5 half-lives.

Multiple Dose Regimen – Two Compartment Open Model

Overview of the Model

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