Multiple-Dosage Regimens III

❶ Plasma Concentration-Time Curve
❷ Comparison with IV Infusion
❸ Time to Steady State
❹ Initial Rate of Accumulation
❺ Loading Dose

Plasma Concentration-Time Curve I

- for $f = e^{-k_e \times T}$, $f^N = (e^{-k_e \times T})^N = e^{-N \times k_e \times T}$
- the drug amount immediately after the Nth dose, at the time $t = (N\text{-}1) \times T$ (from Eq. 10)

$$n_{max}^{N} = D_0 \times \frac{1-f^N}{1\text{-}f} = D_0 \times \frac{1-e^{-N \times k_e \times T}}{1-e^{-k_e \times T}} \quad (14)$$

- and the plasma concentration

$$c_{max}^{N} = \frac{D_0}{V_D} \times \frac{1-e^{-N \times k_e \times T}}{1-e^{-k_e \times T}} \quad (15)$$

Plasma Concentration-Time Curve II

- for the time interval following the Nth dose

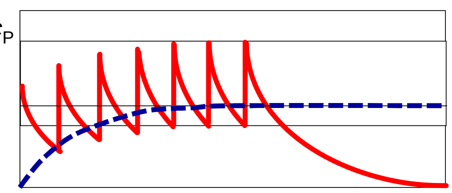
$$c^N(t) = \frac{D_0}{V_D} \times \frac{1-e^{-N \times k_e \times T}}{1-e^{-k_e \times T}} \times e^{-k_e \times t}; \quad 0 \le t \le T \quad (16)$$

- if the time measurement starts with the first dose, the Nth dose is given at the time $t = (N\text{-}1) \times T$, then

$$c^N(t) = \frac{D_0}{V_D} \times \frac{1-e^{-N \times k_e \times T}}{1-e^{-k_e \times T}} \times e^{-k_e \times [t-(N\text{-}1) \times T]} \quad (17)$$

Multiple-Dosage Regimens and IV Infusion I

- IV infusion - continuous input at the rate R
- multiple-dosage regimen - discontinuous, repeated input at the rate D_0/T



Multiple-Dosage Regimens and IV Infusion II

- the equation for the plasma concentration/ time profile for IV infusion can be adapted for multiple-dosage regimen

$$c_P(t) = \frac{R}{k_e \times V_D} \times (1-e^{-k_e \times t})$$

$$c_{av}(t) = \frac{D_0}{k_e \times T \times V_D} \times (1-e^{-k_e \times t}) \quad (18)$$

- Eq. 18 can be used to estimate the 'average' drug amount characteristics
  - time to the steady state
  - initial rate

Time to Steady State I

- time course of plasma drug concentration (Eq. 18)

$$c_{av}(t) = \frac{D_0}{k_e \times T \times V_D} \times (1-e^{-k_e \times t})$$

time-dependent

$$c_{av}^{\infty} = \frac{D_0}{k_e \times T \times V_D} \quad (19)$$

- time to reach the steady-state concentration is
  - not influenced by D_0, V_D, or T
  - determined solely by the rate constant of elimination k_e or by the half-life $t_{1/2}$

Time to Steady State II

The fraction of the steady-state concentration X(t) that has been achieved at the time t depends on k_e as can be seen from rearrangement of Eqs. 18 and 19:

$$X(t) = \frac{c_{av}(t)}{c_{av}^{\infty}} = 1 - e^{-k_e \times t} \quad (20)$$

For one-compartment model, the elimination rate constant can be expressed using the half-life $t_{1/2}$:

$$k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{t_{1/2}} \quad (21)$$

Time to Steady State III

Combination of Eqs. 20 and 21

$$X(t) = \frac{c_{av}(t)}{c_{av}^{\infty}} = 1 - e^{-\frac{\ln 2}{t_{1/2}} \times t} = 1\text{-}e^{-0.693 \times N} \quad (22)$$

shows the relation between the duration of infusion expressed via the number N = $t / t_{1/2}$ of half-lives of the drug and the fraction X of the steady-state concentration. N can be separated:

$$N = \frac{1}{\ln 2} \times \ln \frac{1}{1\text{-}X(t)} = 1.443 \times \ln \frac{1}{1\text{-}X(t)} \quad (23)$$

Time to Steady State IV

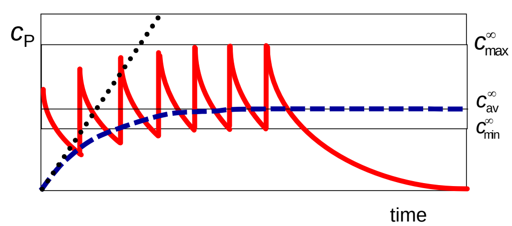
The relations between the duration of multiple-dosage regimen in the number of half-lives N and the fraction X(t) of the average steady-state concentration:

N	X(t)
1	0.5
2	0.75
3	0.87
4	0.94

X(t)	N
0.50	1
0.80	2.3
0.90	3.3
0.99	6.6

Initial Rate of Accumulation I

- Eq. 18 can be used to determine the rate of the initial build-up of the drug in the body $c_{av}(t) = \frac{D_0}{k_e \times T \times V_D} \times (1 - e^{-k_e \times t})$ (18)



Initial Rate of Accumulation II

- for x → 0, the function $e^{-x} \approx 1 - x$ (Taylor expansion)
- applying the Taylor expansion to Eq. 18 (x = k_e)

$$c_{av}(t) = \frac{D_0}{k_e \times T \times V_D} \times (1 - e^{-k_e \times t}) \cong \frac{D_0}{k_e \times T \times V_D} \times [1 - (1 - k_e \times t)] = \frac{D_0 \times k_e \times t}{k_e \times T \times V_D}$$

- for short times

$$c_{av}(t) = \frac{D_0}{T \times V_D} \times t \quad (24)$$

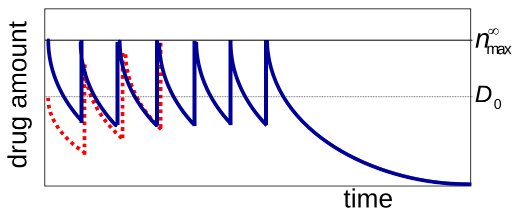
Initial Rate of Accumulation III

- Eq. 24 passes through the origin

$$c_{av}(t) = \frac{D_0}{T \times V_D} \times t \quad (24)$$

- the initial rate (slope) is
  --- proportional to the dose D_0
  --- inversely proportional to
  - the dosing interval T
  - the volume of distribution V_D

Loading Dose



- if the 1st dose is equal to $n^{\infty}_{max} = \frac{D_0}{1\text{-}f} = \frac{D_0}{1-e^{-k_e \times T}}$, the steady-state level is achieved immediately
- the second and next doses are D_0

Scheduling of Dosage Regimens

- the steady-state plasma level requires a constant dosage interval (4, 6, 8, 12, 24… hrs)
- if the drug is given only during the waking hours - significant drop in the plasma level during the night
- solutions
  --- the use of other drugs with long elimination half-lives
  --- controlled-release formulation of the same drug

Practice Problem 28.1

- an antibiotic with fast absorption and fast plasma/tissue distribution has $t_{1/2}$=3 h and V_D = 40 L/kg
- a patient receives 1000 mg every 6 hrs

- determine
  - body drug amount at t = 15 hr

Eq. 16 or 17

Practice Problem 28.2

- a drug with fast absorption and fast plasma/tissue distribution has $t_{1/2}$=4 h and V_D = 1 L/kg
- a patient (70 kg) receives 1000 mg every 6 hrs

- determine the time when the steady-state (99%) will be achieved

(Eq. 21)

Practice Problem 28.3

A drug (200 mg) is given to a patient every 8 hours. For the given conditions, the volume of distribution is V_D = 120 L. The average steady-state concentration is 4 mg/L. Calculate the optimal loading dose that will lead to immediate achievement of the steady state. State explicitly the drug amount in the first (loading) dose and in subsequent doses.

Eqs. 4 and 26