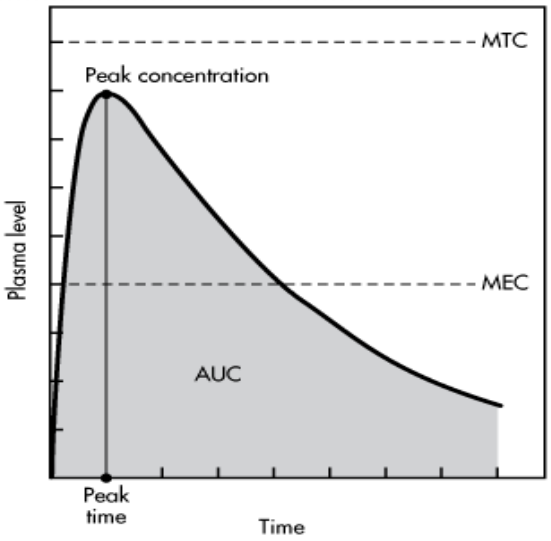
Multiple-Dosage Regimens

After single-dose drug administration, the plasma drug level rises above and then falls below the minimum effective concentration (MEC), resulting in a decline in therapeutic effect.

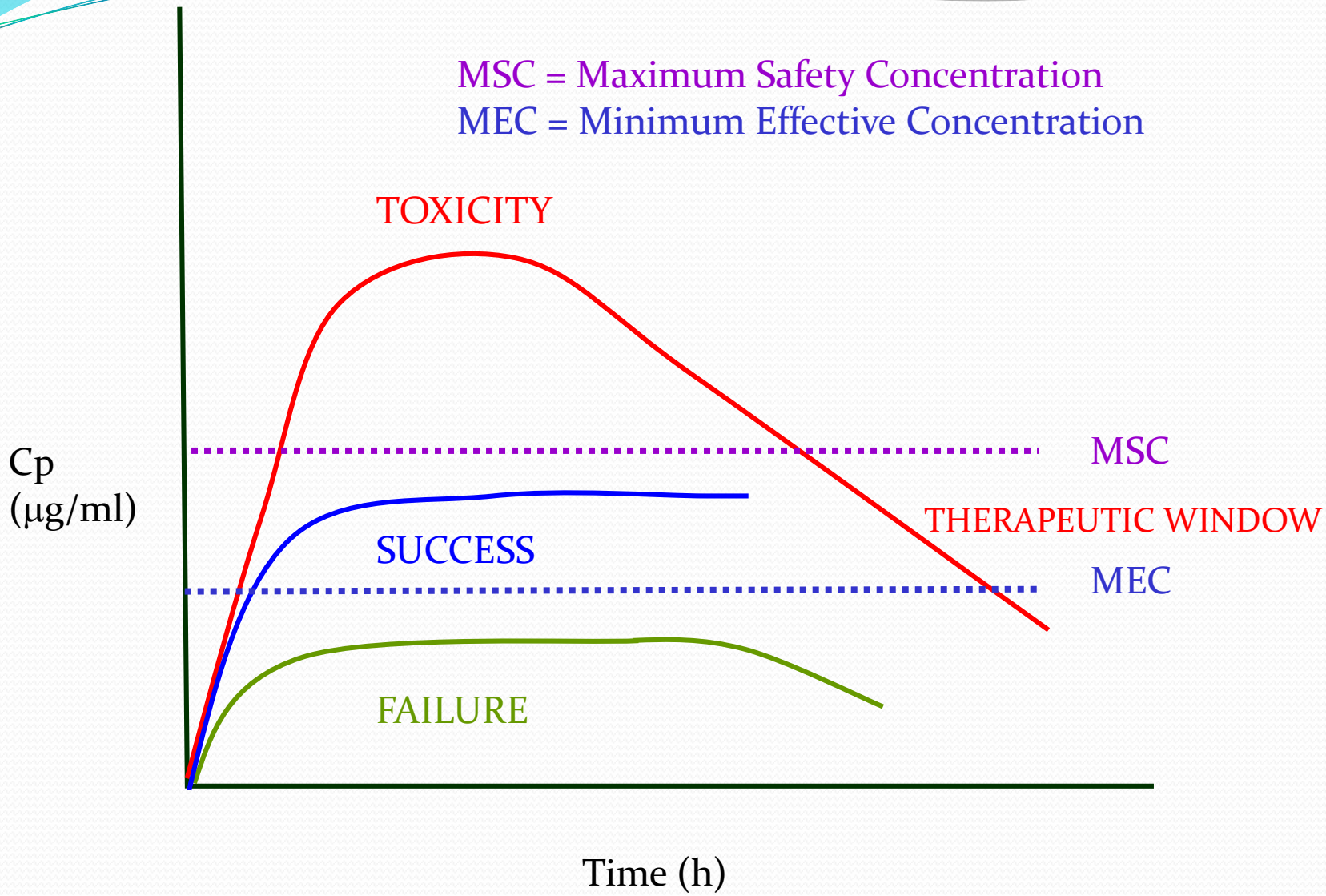


- To maintain prolonged therapeutic activity, many drugs are given in a multiple-dosage regimen.

Multiple-Dosage Regimens

- The plasma levels of drugs given in multiple doses must be maintained within the narrow limits of the therapeutic window (C_P above the MEC and below the MTC) to achieve optimal clinical effectiveness.

- Dosage regimen is established for drug to provide the correct plasma level without excessive fluctuation and drug accumulation outside the therapeutic window.



Multiple-Dosage Regimens

Criteria for optimum dosage regimen:

I. The plasma levels of drug given must be maintained within the therapeutic window.
   - Ex. The therapeutic range of theophylline is 10-20µg/L.
     So, the best is to maintain the C_p around 15µg/L.

II. Should be convenient to the patient
   - It is difficult to take I.V. injection every ½ hour or one tablet every 2 hour, this lead to poor compliance.

Multiple-Dosage Regimens

Factors affecting the design of dosage regimen:

(1) The size of the drug dose.

(2) The frequency of drug administration (τ) (i.e., the time interval between doses).

Superposition Principle

- The superposition principle can be used when all the PK processes are linear.
- That is when distribution, metabolism, and excretion (DME) processes are linear or first order.
- Thus, concentrations after multiple doses can be calculated by adding together the concentrations from each dose. Also, doubling the dose will result in the concentrations at each time doubling.

- principle of *superposition*
- The basic assumptions are
- (1) that the drug is eliminated by first-order kinetics and
- (2) that the pharmacokinetics of the drug after a single dose (first dose) are not altered after taking multiple doses.

Drug Accumulation

- When a drug is administered at regular intervals over a prolonged period, the rise and fall of drug concentration in blood will be determined by the relationship between the half-life of elimination and the time interval between doses.

- If the drug amount administered in each dose has been eliminated before the next dose is applied, repeated intake at constant intervals will result in similar plasma levels.

Drug Accumulation

- If intake occurs before the preceding dose has been eliminated completely, the next dose will add on to the residual amount still present in the body, i.e., **the drug accumulates.**

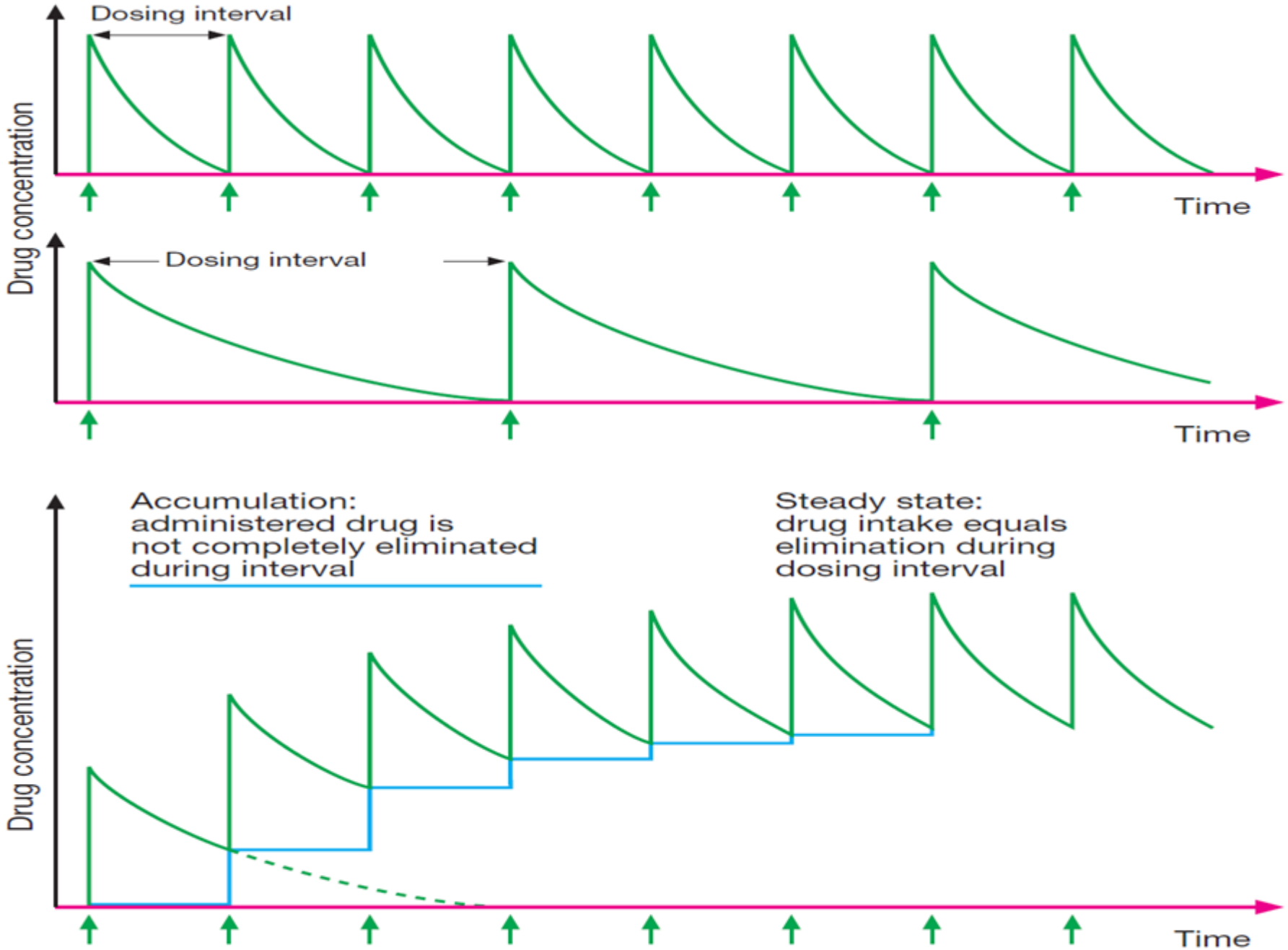
- The shorter the dosing interval relative to the elimination half-life, the larger will be the residual amount of drug to which the next dose is added and the more extensively will the drug accumulate in the body.

Drug Accumulation

- At a given dosing frequency, the drug does not accumulate infinitely and a **steady state (Css) or accumulation equilibrium is eventually reached**.

- This is so because the activity of elimination processes is concentration dependent.

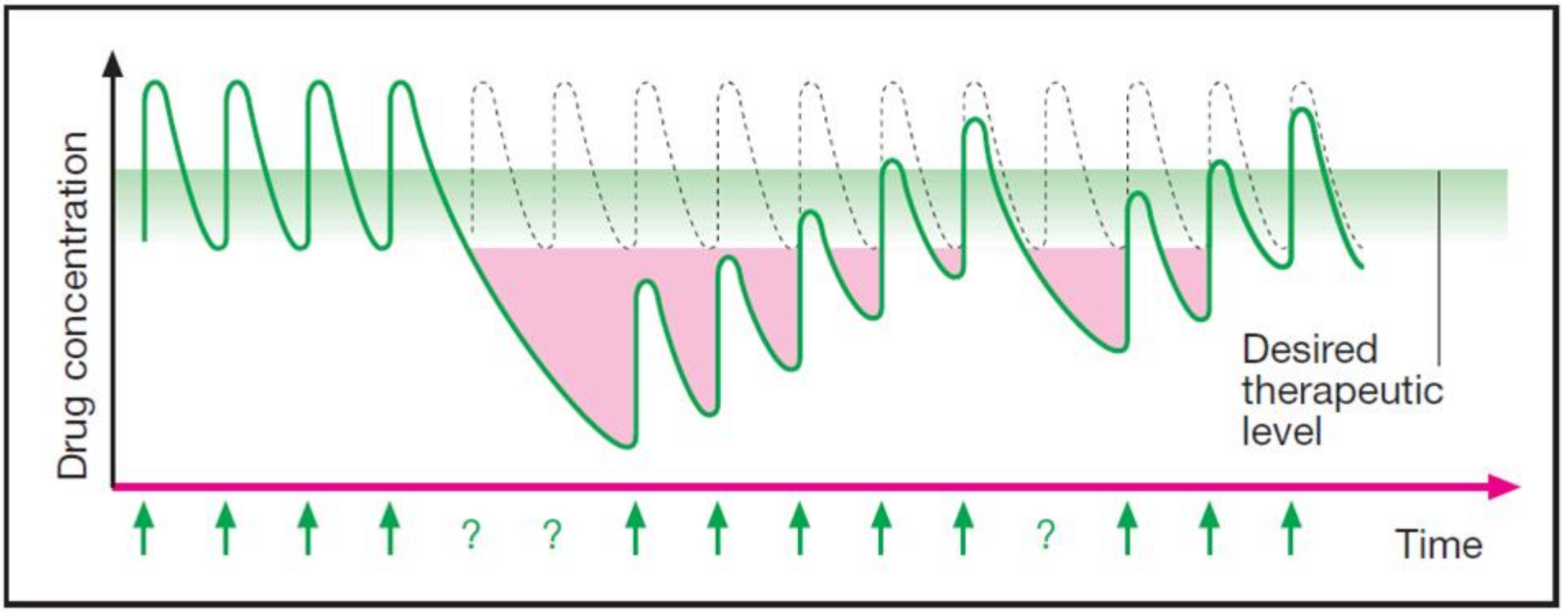
- The higher the drug concentration rises, the greater is the amount eliminated per unit of time.



Time course of drug concentration in blood during regular intake

Drug Accumulation

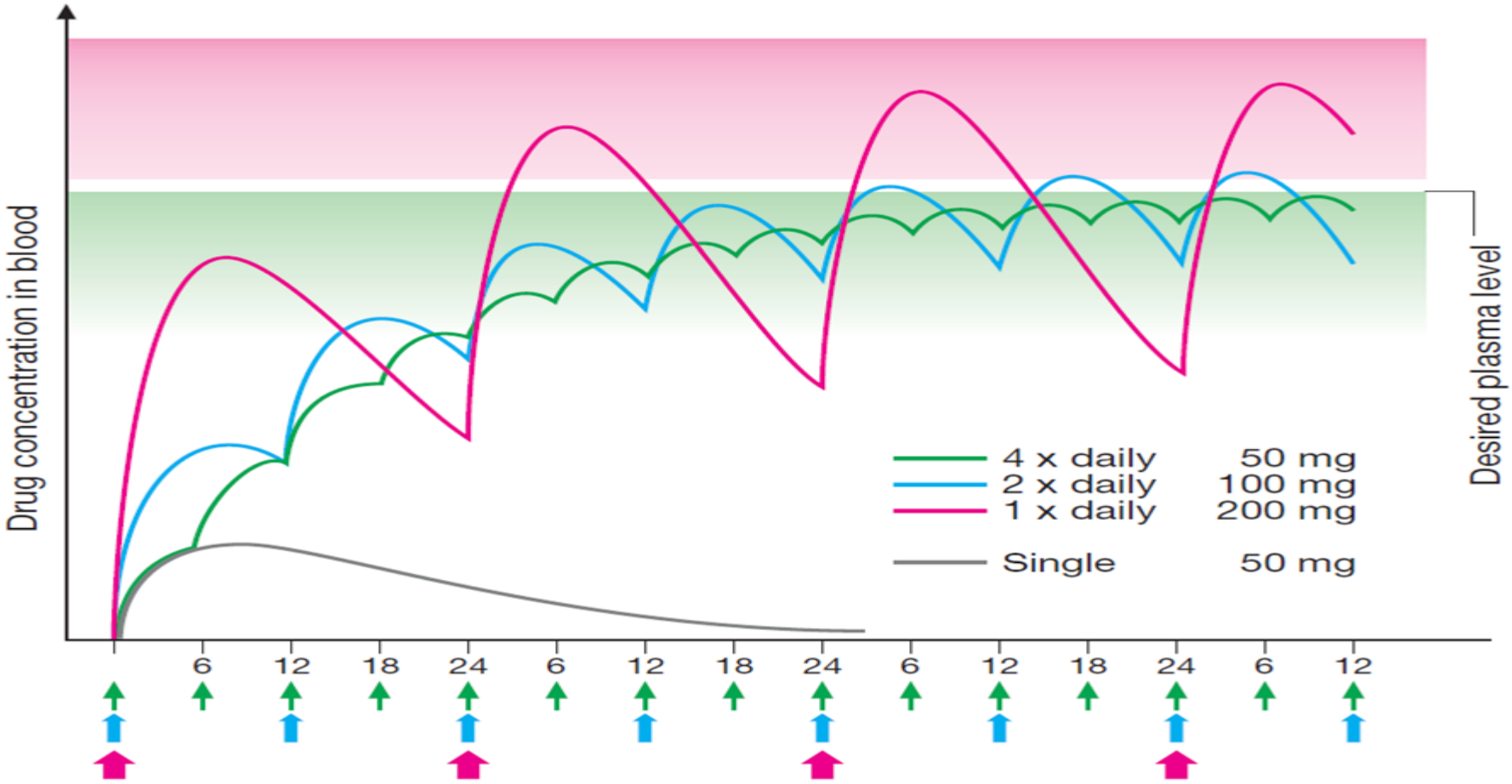
if two successive doses are omitted, the plasma level will drop below the therapeutic range and a longer period will be required to regain the desired plasma level.



Time course of drug concentration with irregular intake

Drug Accumulation

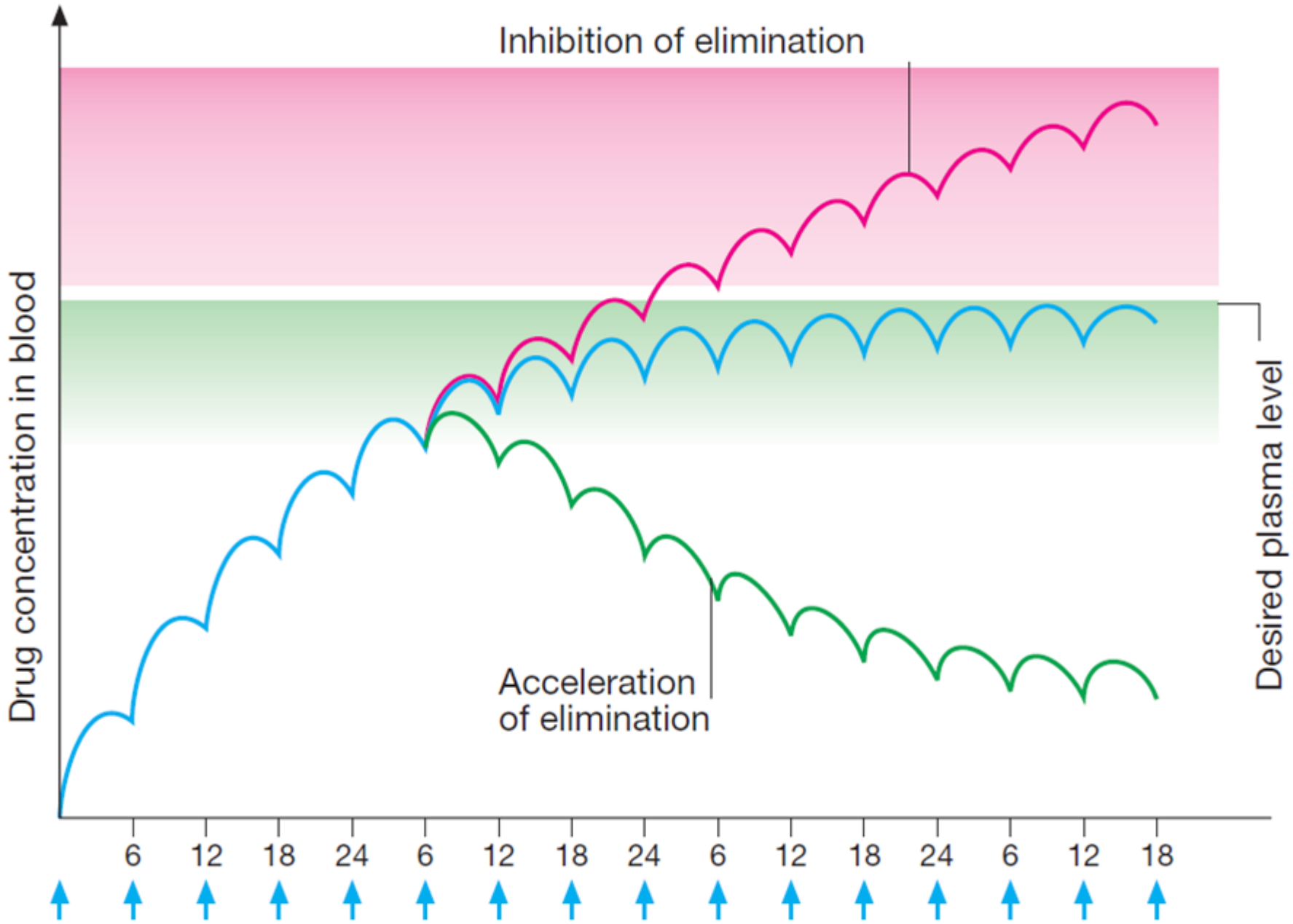
- When the daily dose is given in several divided doses, the mean plasma level shows little fluctuation.



Accumulation: dose, dose interval, and fluctuation of plasma level

Drug Accumulation

- The time required to reach steady state accumulation during multiple constant dosing depends on **the rate of elimination**.
- The steady-state plasma level declines to a new value corresponding to the new rate of elimination.
- When elimination is impaired (e.g., in progressive renal insufficiency), the mean plasma level of renally eliminated drugs rises and may enter a toxic concentration range.

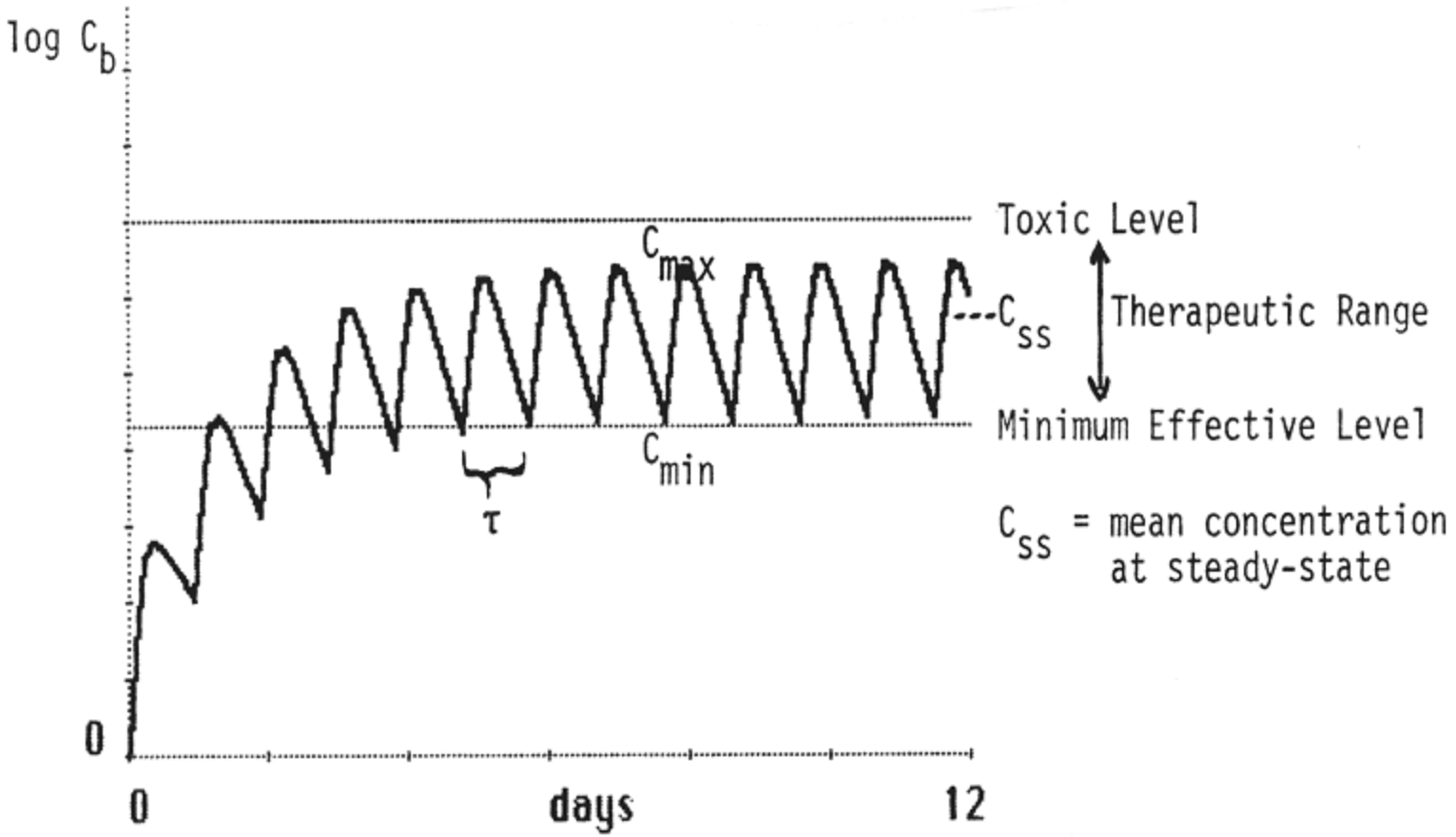


Changes in elimination kinetics in the course of drug therapy

Drug Accumulation

- The 2nd dose is taken before the 1st dose is eliminated.
- Subsequent doses are then taken following the identical interval (τ).
- Accumulation of the drug up to a steady-state is seen where drug intake = drug elimination.
- If dose (D) and τ are properly selected, blood levels will rise and fall between peak (C_{max}) and (C_{min}) within the therapeutic range (TR):

Drug Accumulation



Dose: 100 mg every $t_{1/2}$

Repetitive Intravenous Injections

- The maximum amount of drug in the body following a single rapid IV injection is equal to the dose of the drug.

- For a one-compartment open model, the drug will be eliminated according to first-order kinetics.

$$D_B = D_0 e^{-kt}$$

- If τ is equal to the dosage interval, then the amount of drug remaining in the body after several hours can be determined with:

$$D_B = D_0 e^{-k\tau}$$

Repetitive Intravenous Injections

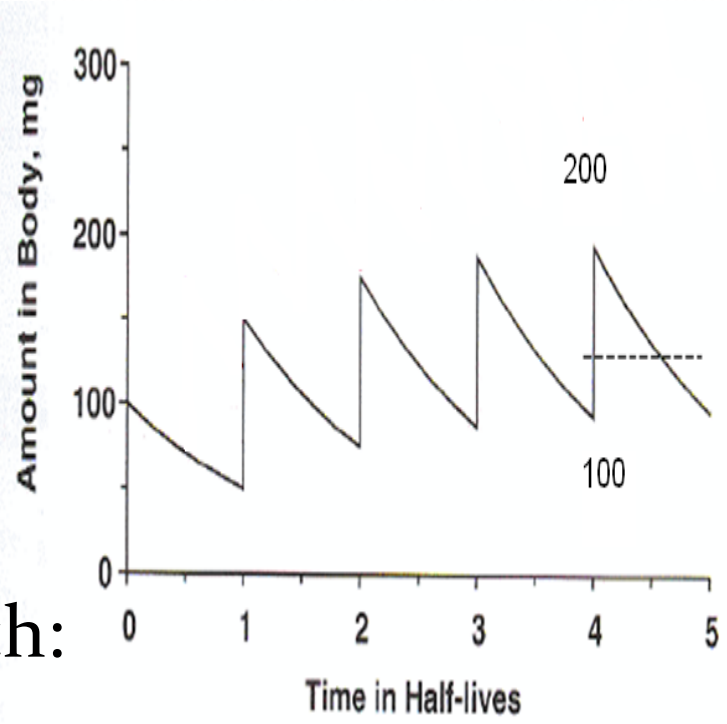
- The fraction (f) of the dose remaining in the body is related to the elimination constant (k) and the dosage interval (τ) as follows:

$$f = \frac{D_B}{D_0} = e^{-k\tau}$$

- If τ is large, f will be smaller because D_B (the amount of drug remaining in the body) is smaller.

Repetitive Intravenous Injections

- If the dose D_o= 100mg is given by rapid injection every $t_{1/2}$, then $\tau = t_{1/2}$.
  - After the 1st $t_{1/2}$ the D_B= 50mg.
  - After the 2nd dose the D_B= 150mg.
  - After the 2nd $t_{1/2}$ the D_B= 75mg.
  - After the 3rd $t_{1/2}$ the D_B= 175mg, and so on.



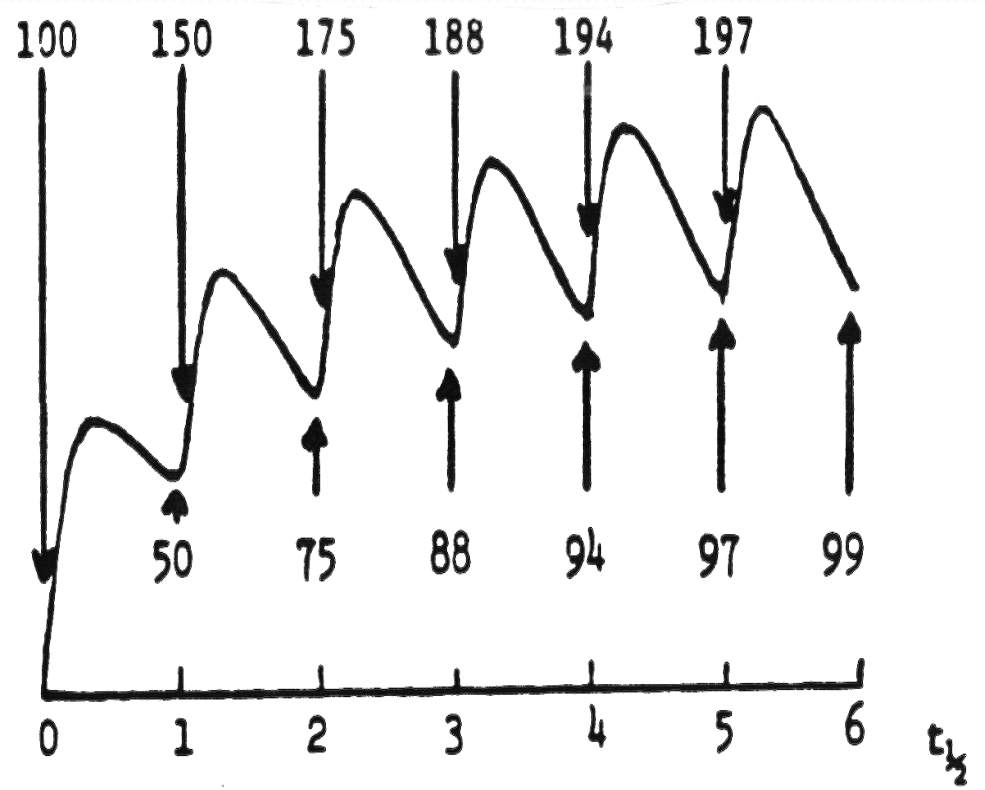
you will reach equilibrium at which:

D_{max} =200mg and D_{min} =100mg

Note that: $D^{ss}_{max} - D^{ss}_{min} = D_0$

mg Drug in Body after Each Dose

mg Drug in Body after each $t_{1/2}$ as well as Mg Drug Eliminated per $t_{1/2}$



Thus, the absolute amount of drug eliminated per unit time increases with increasing body load, which is exactly what characterizes a 1st order process. This is the sole reason why a steady-state is reached, i.e. Drug Going Out = Drug Coming In.

Example

- A patient receives **1000 mg every 6 hours** by repetitive IV injection of an antibiotic with **an elimination half-life of 3 hours**. Assume the drug is distributed according to a one-compartment model and **the volume of distribution is 20 L**.

a. Find the maximum and minimum amount of drug in the body.
b. Determine the maximum and minimum plasma concentration of the drug.

solution

- We must first find the value of *k* from the $t_{½}$.

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{3} = 0.231 hr^{-1}$$

- The time interval(τ) is equal to 6 hours:

$$f = e^{-(0.231)(6)} = 0.25$$

- In this example, 1000 mg of drug is given intravenously, so the amount of drug in the body is immediately increased by 1000 mg.

- At the end of the dosage interval (ie, before the next dose), the amount of drug remaining in the body is 25% of the amount of drug present just after the previous dose, because *f* = 0.25.

solution

- if the value of f is known, a table can be constructed relating the fraction of the dose in the body before and after rapid IV injection.

Table Fraction of the Dose in the Body before and after Intravenous Injections of a 1000-mg Dose		
	Amount of Drug in Body	
Number of Doses	Before Dose	After Dose
1	0	1000
2	250	1250
3	312	1312
4	328	1328
5	332	1332
6	333	1333
7	333	1333
∞	333	1333

Repetitive Intravenous Injections

- The maximum amount of drug in the body is 1333 mg.
- The minimum amount of drug in the body is 333 mg.
- The difference between the maximum and minimum values, D_o, will always equal the injected dose.

$$D_{max} - D_{min} = D_0$$
$$1333 - 333 = 1000mg$$

- D_{max}^{∞} can also be calculated directly by:

$$D_{max}^{\infty} = \frac{D_0}{1 - f}$$
$$D_{max}^{\infty} = \frac{1000}{1 - 0.25} = 1333mg$$
$$D_{min}^{\infty} = 1333 - 1000 = 333mg$$

Repetitive Intravenous Injections

- The average amount of drug in the body at steady state:

$$D_{av}^{\infty} = \frac{FD_0}{k\tau}$$

$$D_{av}^{\infty} = \frac{FD_0 1.44 t_{1/2}}{\tau}$$

- Any equations can be used for repetitive dosing at constant time intervals and for any route of administration as long as elimination occurs from the central compartment

$$D_{av}^{\infty} = \frac{(1)(1000)(1.44)(3)}{6} = 720mg$$

- Since the drug in the body declines exponentially (ie, first-order drug elimination), the value D^{∞}_{av} is not the arithmetic mean of D^{∞}_{max} and D^{∞}_{min}.

Repetitive Intravenous Injections

- To determine the concentration of drug in the body after multiple doses:

$$C^{\infty}_{\max} = \frac{D^{\infty}_{\max}}{V_D} \quad \text{0r} \quad C^{\infty}_{\max} = \frac{C^{o}_{P}}{1-e^{-k\tau}}$$

$$C^{\infty}_{\min} = \frac{D^{\infty}_{\min}}{V_D} \quad \text{0r} \quad C^{\infty}_{\min} = \frac{C^{o}_{P}e^{-kt}}{1-e^{-k\tau}}$$

$$C^{\infty}_{av} = \frac{D^{\infty}_{av}}{V_D} \quad \text{0r} \quad C^{\infty}_{av} = \frac{FD_0}{V_D k\tau}$$

- For this example, the values for $C^{\infty}_{\max}$, $C^{\infty}_{\min}$, and C^{∞}_{av} are 66.7, 16.7, and 36.1 μg/mL, respectively.

Repetitive Intravenous Injections

- The C^{∞}_{av} is equal to the AUC for a dosage interval at steady state divided by the dosage interval .

$$C^{\infty}_{av} = \frac{[AUC]^{t_2}_{t_1}}{\tau}$$

$$[AUC]^{t_2}_{t_1} = \frac{FD_0}{Cl_T} = \frac{FD_0}{kV_D}$$

Repetitive Intravenous Injections

- To know the plasma drug concentration at any time after the administration of *n* doses of drug:

$$C_P = \frac{D_0}{V_D}\left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kt}$$

Where: n is the number of doses given.
t is the time after the nth dose.

- At steady state, e^{-nk} approaches zero and equation reduces to:

$$C_P^{\infty} = \frac{D_0}{V_D}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt}$$

where C_P^{∞} is the steady-state drug concentration at time t after the dose.

Example

- The patient in the previous example received 1000 mg of an antibiotic every 6 hours by repetitive IV injection. The drug has an apparent volume of distribution of 20 L and elimination half-life of 3 hours. Calculate:

a) The plasma drug concentration C_p at 3 hours after the second dose.
b) The steady-state plasma drug concentration C^{∞}_p at 3 hours after the last dose
c) C^{∞}_{max}
d) C^{∞}_{min}
e) C_{SS}.

Solution

a. The C_p at 3 hours after the second dose ($n = 2$, $t = 3$ hrs)

$$C_P = \frac{1000}{20}\left(\frac{1-e^{-(2)(0.231)(6)}}{1-e^{-(0.231)(6)}}\right)e^{-(0.231)(3)} = 31.3mg/l$$

b. The C^{∞}_p at 3 hours after the last dose. Because steady state is reached:

$$C_P^{\infty} = \frac{1000}{20}\left(\frac{1}{1-e^{-(0.231)(6)}}\right)e^{-(0.231)(3)} = 33.3mg/l$$

c. The C^{∞}_{max} is:

$$C_{\max}^{\infty} = \frac{1000/20}{1-e^{-(0.231)(6)}} = 66.7mg/l$$

Solution

d. The C^{∞}_{min} may be estimated as the drug concentration after the dosage interval , or just before the next dose.

$$C^{\infty}_{min} = C^{\infty}_{max} e^{-kt} = 66.7 e^{-(0.231)(6)} = 16.7 mg/l$$

e. The C_{SS} is estimated by:

$$C_{SS} = \frac{1000}{(0.231)(20)(6)} = 36.1 mg/l$$

Because the drug is given by IV bolus injections, $F = 1$

C^{∞}_{av} is represented as C_{SS} in some references.

Multiple Oral Dose Administration

- To start the plasma concentration achieved following a single oral dose can be given by:

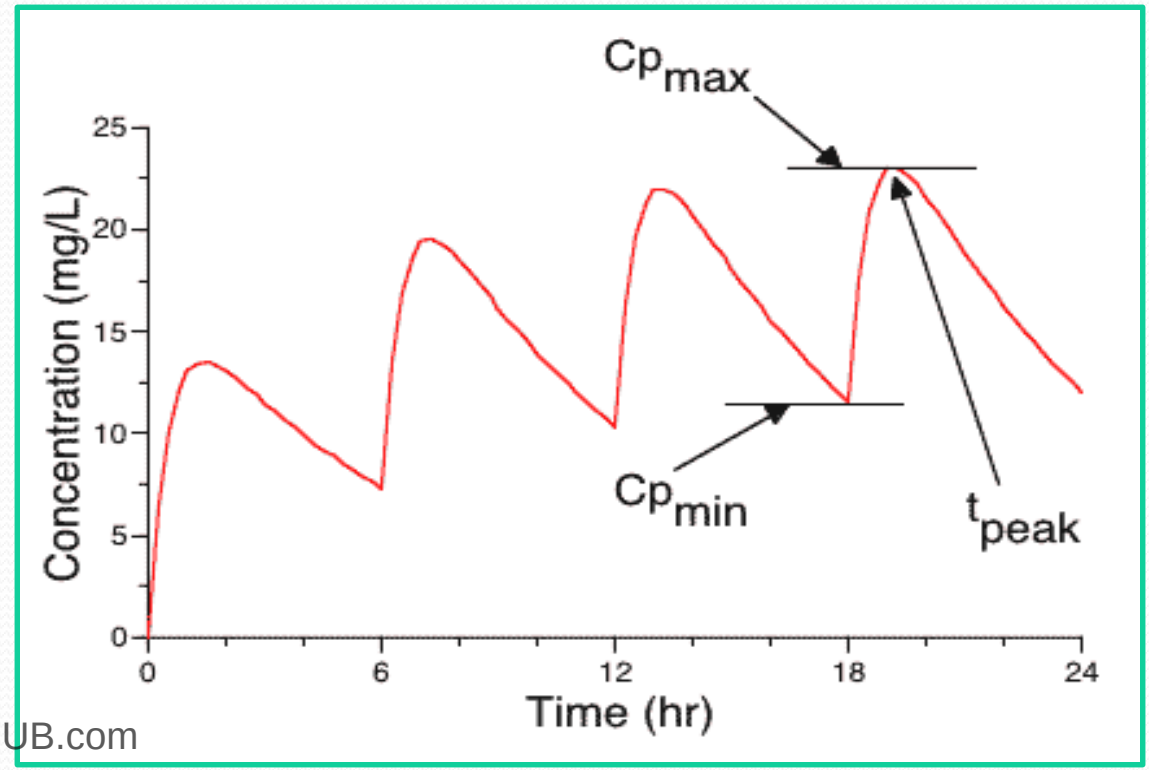
$$C_P = \frac{Fk_aD_0}{V_D(k_a - k)}\left(e^{-kt} - e^{-k_at}\right)$$

- This can be converted to an equation describing plasma concentration at any time following:

$$C_P = \frac{Fk_aD_0}{V_D(k_a - k)}\left(\left[\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right]e^{-kt} - \left[\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right]e^{-k_at}\right)$$

Multiple Oral Dose Administration

- The plasma concentration versus time curve described by this equation is similar to the IV curve in that there is accumulation of the drug in the body to some plateau level and the plasma concentrations fluctuate between a minimum and a maximum value.



Plot of Cp Versus Time for Multiple Oral Doses

Multiple Oral Dose Administration

- The Cp_{max} value could be calculated at the time t = t_{peak} after many doses, but it is complicated by the need to determine the value for t_{peak}.

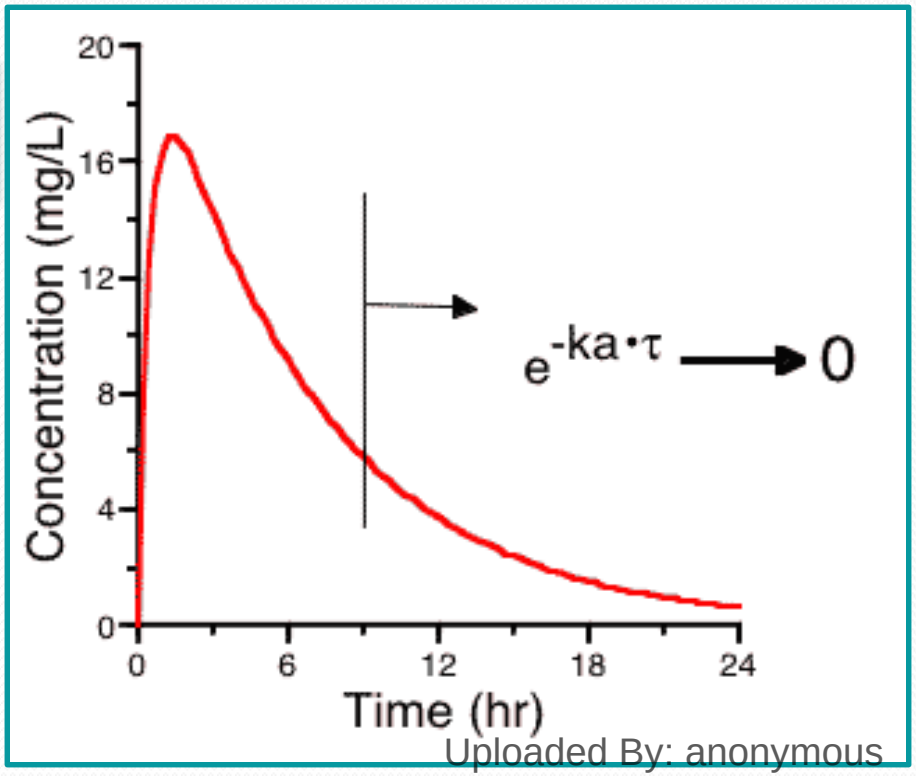
- However Cp_{min} can be more easily determined:

$$C_{\min}^{\infty} = \frac{k_a F D_0}{V_D (k_a - k)} \left(\frac{1}{1 - e^{-k\tau}} \right) e^{-k\tau}$$

Multiple Oral Dose Administration

- if we assume that the subsequent doses are given after the plasma concentration has peaked and $e^{ka \cdot \tau}$ is close to zero. That is the next dose is given after the absorption phase is complete.

Plot Cp Versus Time after a Single Dose showing Possible Time of Second Dose



- Cp_{min} then becomes:

$$C_{P\min} = \frac{Fk_aD_0}{V_D(k_a - k)}\left[\frac{e^{-k\tau}}{1-e^{-k\tau}}\right]$$

Multiple Oral Dose Administration

- if we assume that ka >> k then (ka - k) is approximately equal to ka and ka/(ka - k) is approximately equal to one.

$$C_{P\min} = \frac{FD_0}{V_D}\left[\frac{e^{-k\tau}}{1-e^{-k\tau}}\right]$$

- Equation above is an even more extreme simplification.
- It can be very useful if we don't know the ka value but we can assume that absorption is reasonably fast.
- It will tend to give concentrations that are lower than those obtained with the full equation (previous eq.). Thus any estimated fluctuation between Cp_{min} and Cp_{max} will be overestimated using the simplified equation.

Multiple Oral Dose Administration

$$C_{\max}^{\infty} = \frac{FD_0}{V_D}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt_P}$$

$$C_{\min}^{\infty} = \frac{k_a FD_0}{V_D(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}$$

$$t_{\max} = \frac{2.3}{k_a-k}\log\frac{k_a}{k}$$

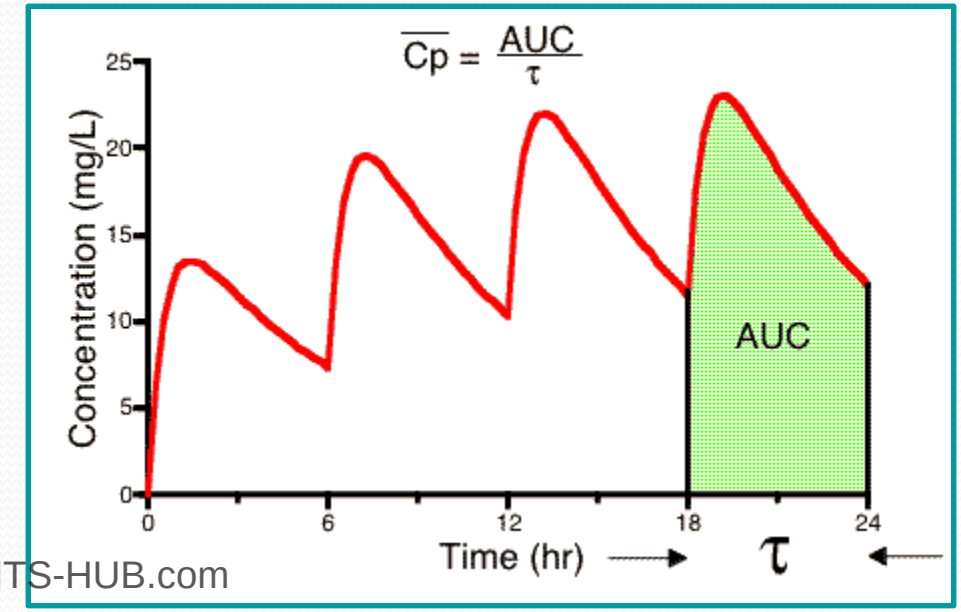
$$t_p = \frac{1}{k_a-k}\ln\frac{k_a\left(1-e^{-k\tau}\right)}{k\left(1-e^{-k_a\tau}\right)}$$

$$C_{av}^{\infty} = \frac{D_{av}^{\infty}}{V_D} \quad \text{0r} \quad C_{av}^{\infty} = \frac{FD_0}{V_D k\tau}$$

Multiple Oral Dose Administration

- C^{∞}_{av} ($\overline{Cp}$) is the average plasma concentration during the dosing interval at steady state.

- This term is defined as the area under the plasma concentration versus time curve during the dosing interval at steady state divided by the dosing interval.



Plot of Cp versus Time after Multiple Oral Administration showing AUC at Steady State

Multiple Oral Dose Administration

$$C_{av}^{\infty} = \frac{[AUC]_{t_1}^{t_2}}{\tau}$$

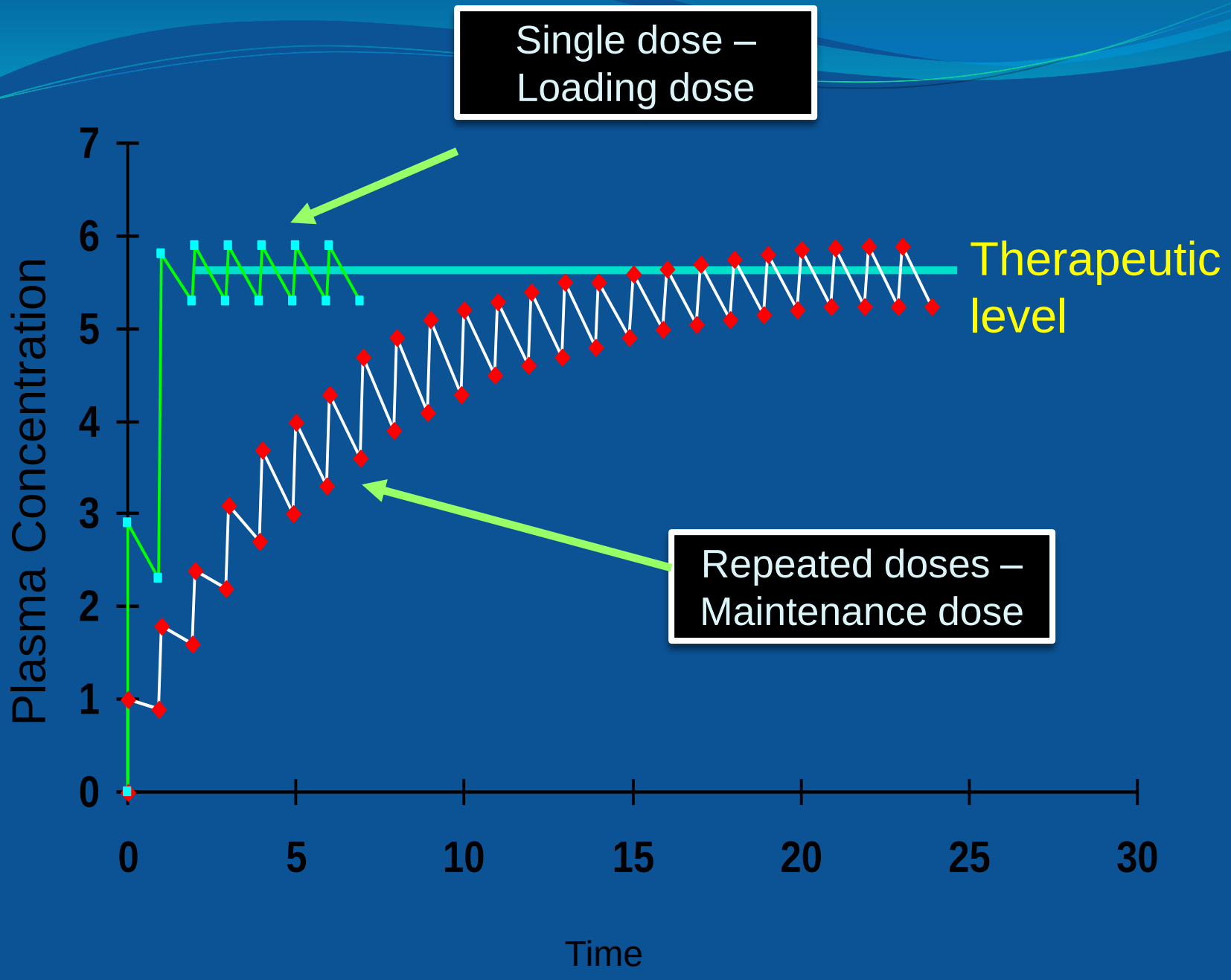
$$[AUC]_{t_1}^{t_2} = \frac{FD_0}{Cl_T} = \frac{FD_0}{kV_D}$$

$$C_{av}^{\infty} = \frac{FD_0}{kV_D\tau}$$

- Note that the AUC during one dosing interval at steady state is the same as the AUC from zero to infinity after one single dose.

Loading Dose

- Since extravascular doses require time for absorption into the plasma to occur, therapeutic effects are delayed until sufficient plasma concentrations are achieved.
- To reduce the onset time of the drug a loading or initial dose of drug is given.
- The main objective of the loading dose is to achieve desired plasma concentrations, C^{∞}_{av}, as quickly as possible.
- A maintenance dose is given to maintain C^{∞}_{av} and steady state so that the therapeutic effect is also maintained.



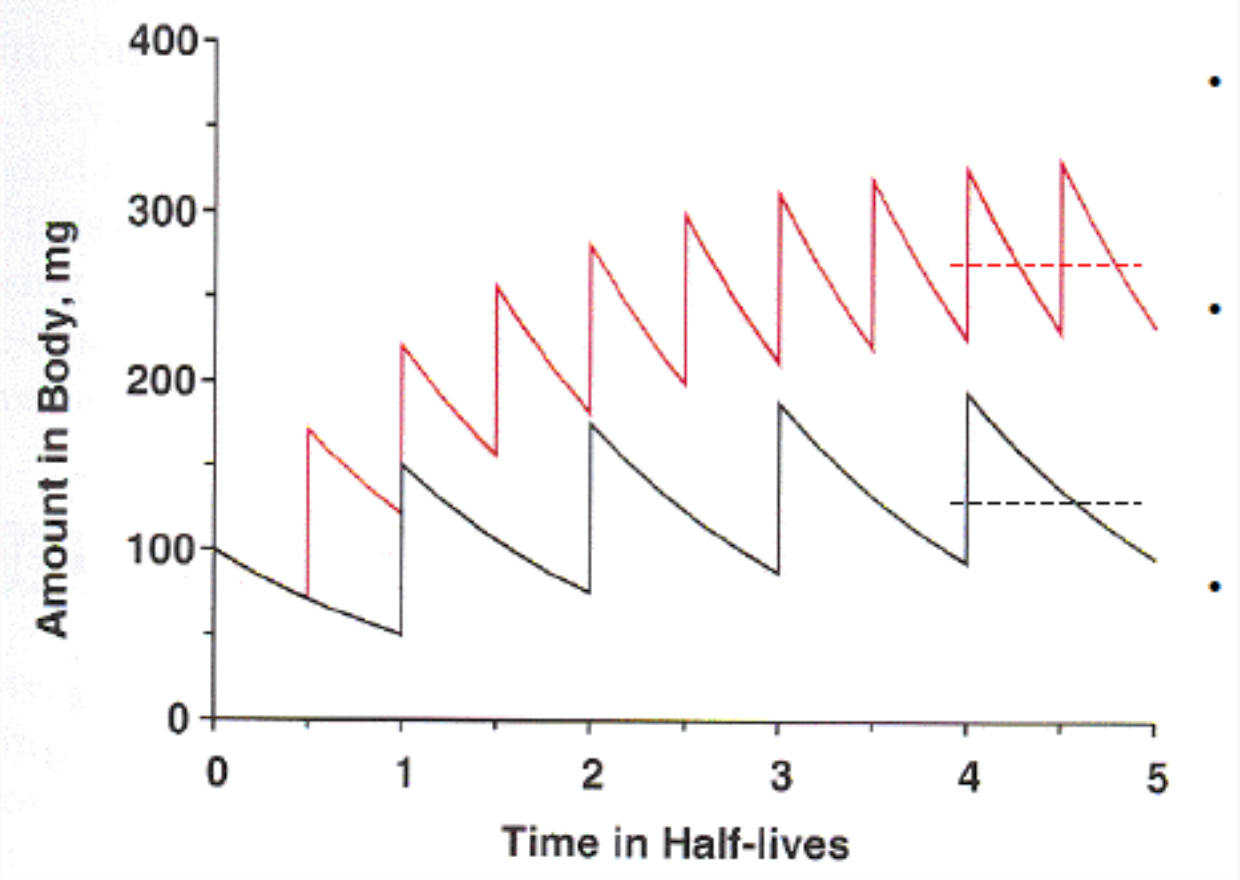
Loading Dose

- The time required for the drug to accumulate to a steady-state plasma level is dependent mainly on its elimination half-life.

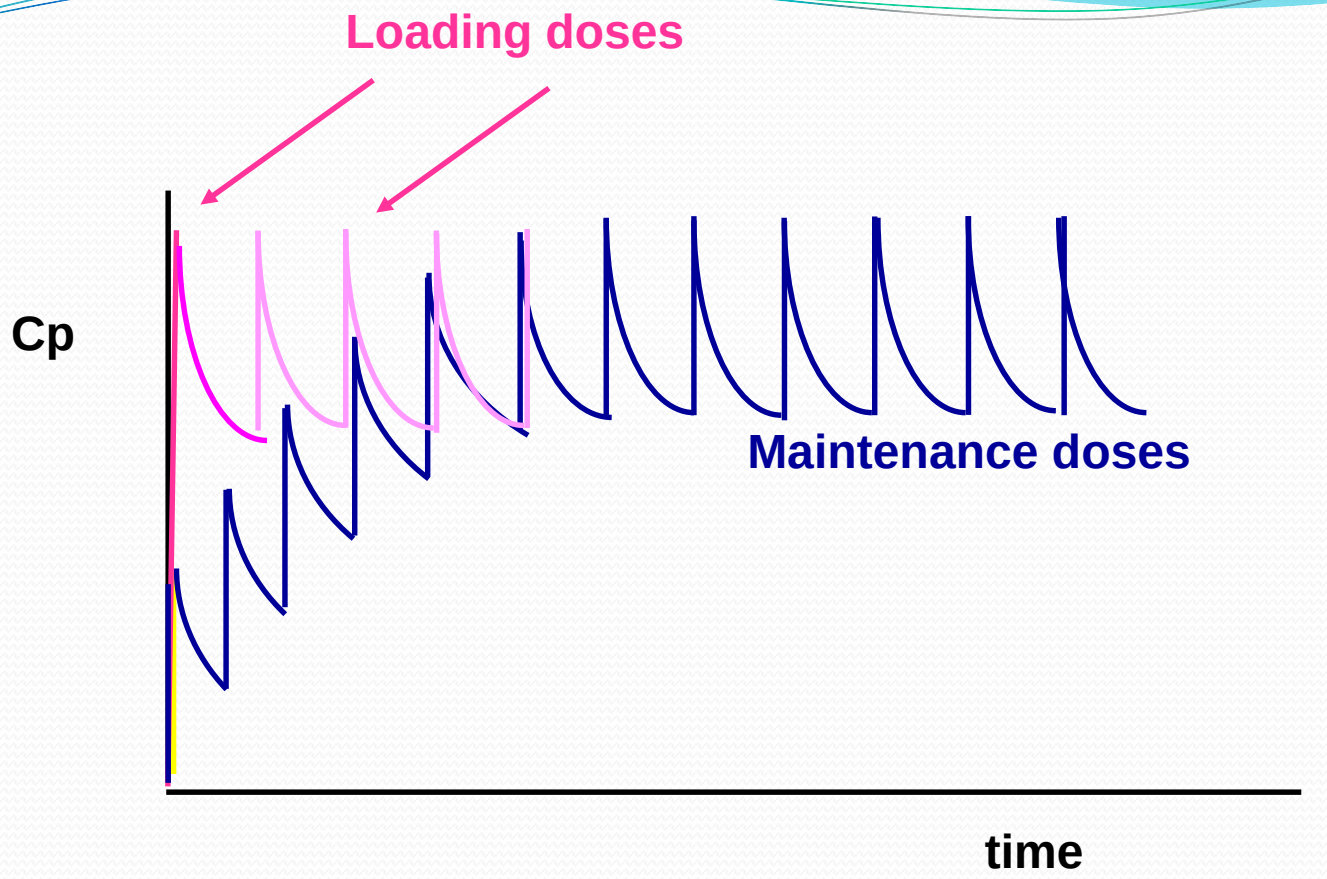
- The time needed to reach 90% of C^{∞}_{av} is approximately 3.3 half-lives, and the time required to reach 99% of C^{∞}_{av} is equal to approximately 6.6 half-lives.

- For a drug with a half-life of 4 hours, it will take approximately 13 and 26 hours to reach 90% and 99% of C^{∞}_{av}, respectively.

Elimination $T_{1/2}$ determines accumulation and fluctuation in blood concentration at steady-state



- Greater accumulation when drug is dosed more frequently relative to half-life (1 $T_{1/2}$ vs. 0.5 $T_{1/2}$)
- Repeating amount or conc.-time profiles reached at steady-state; average level (---, ---) proportional to dosing rate
- Longer dosing interval leads to greater fluctuation during steady-state



e.g. Tetracycline $t_{1/2}$ = 8 hours

500mg loading dose followed by 250mg every 8 hours

How long does it take to reach steady-state?

This depends entirely on the $t_{1/2}$ of the drug:

Half-lives of the drug	% of steady-state	
1	50	
2	75	
3	88	
4	93	PRACTICAL STEADY-STATE
7	99	

Thus, it takes 4 $t_{1/2}$s for all drugs!!

Ex.	$t_{1/2}$(hr)	time to steady-state (hr)
antibiotics	1	4
acetaminophen	2	8
propranolol	4	16
carbamazepine	15	60 or - 3 days
digoxin, diazepam	40	160 or - 1 week
phenobarbital	100	400 or - 2 weeks
chloroquine	9 days	36 days or - 1 month

Multiple Oral Dose Administration

- The relationship between **loading dose** and **maintenance dose** and thus **drug accumulation** during multiple dose administration can be studied by looking at the ratio between the minimum concentration at steady state and the concentration one dosing interval, τ, after the first dose. [Assuming $e^{-ka \cdot \tau}$ is close to zero].

$$\frac{C_{P\min}}{C_{P1}^{\tau}} = \frac{\frac{Fk_aD_0}{V_D(k_a-k)}\left[\frac{e^{-k\tau}}{1-e^{-k\tau}}\right]}{\frac{Fk_aD_0}{V_D(k_a-k)}e^{-k\tau}} = \frac{1}{1-e^{-k\tau}} = \frac{1}{1-f}$$

Multiple Oral Dose Administration

- This turns out to be the same equation as for the IV bolus. Therefore we can calculate a loading dose just as we did for an IV multiple dose regimen.

$$\text{Loading Dose} = \frac{\text{Maintenance Dose}}{1 - f}$$

- **This equation holds if each dose is given after the absorption phase of the previous dose is complete.**

Example

- With F = 1.0; V = 30 liter; $t_{1/2}$ = 6 hours or k_{el} = 0.693/6 = 0.116 hr^{-1}, calculate the dose given every 12 hours that will achieve an average plasma concentration of 15 mg/L.

Solution

$$C_{av}^{\infty} = \frac{FD_0}{kV_D\tau}$$

$$D_0 = \frac{C_{av}^{\infty} kV_D\tau}{F} = \frac{15 \times 0.116 \times 30 \times 12}{1.0} = 624mg$$

Multiple Oral Dose Administration

- We could now calculate the loading dose

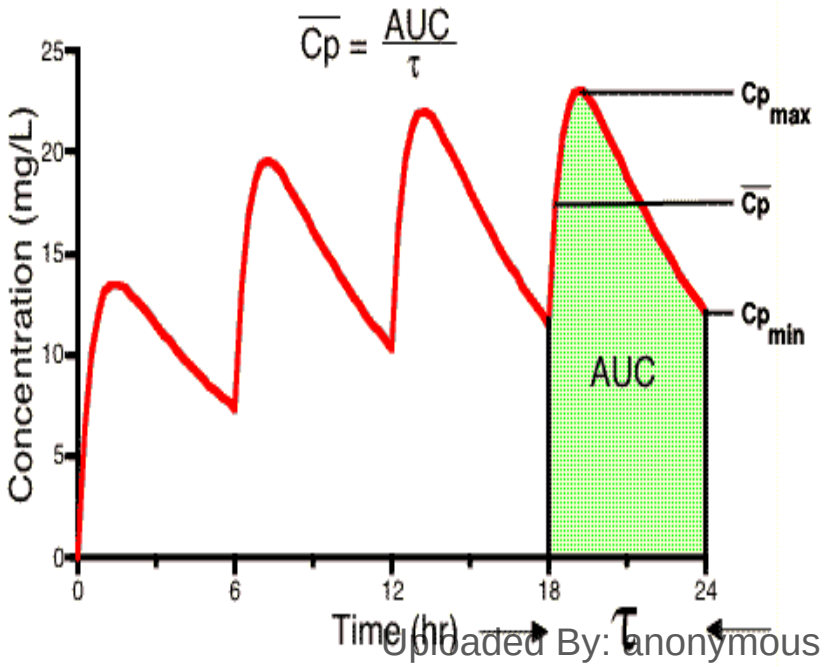
$$f = e^{-k\tau} = e^{-(0.166)(12)} = 0.25$$

$$\text{Loading Dose} = \frac{\text{Maintenance Dose}}{1 - f} = \frac{624}{1 - 0.25} = 832mg$$

- To get some idea of the fluctuations in plasma concentration we could calculate the C_{pmin} value.
- Assuming that ka >> k and that $e^{-ka\tau}$ --> 0, using Equation:

$$C_{P\min} = \frac{FD_0}{V_D}\left[\frac{e^{-k\tau}}{1-e^{-k\tau}}\right] = \frac{1.0\times 624}{30}\times\left[\frac{0.25}{1-0.25}\right] = 6.93 mg/L$$

Therefore the plasma concentration would probably fluctuate between 7 and 23 mg/L (very approximate) with an average concentration of about 15 mg/L.



Multiple Oral Dose Administration

- As an alternative we could give half the dose, 312 mg, every 6 hours to achieve:

$$C_{P\min} = \frac{FD_0}{V_D}\left[\frac{e^{-k\tau}}{1-e^{-k\tau}}\right] = \frac{1.0\times 312}{30}\times\left[\frac{0.5}{1-0.5}\right] = 10.4 mg/L$$

- The C^{∞}_{av} would be the same

$$C^{\infty}_{av} = \frac{FD_0}{kV_D\tau} = \frac{1\times 312}{0.116\times 30\times 6} = 15 mg/L$$

- Thus the plasma concentration would fluctuate between about 10.4 to 20 with an average of 15 mg/L.

Example: Superposition Principle

- Calculate drug concentration at 24 hours after the first dose of 200 mg. The second dose of 300 mg was given at 6 hours and the third dose of 100 mg at 18 hours. The apparent volume of distribution is 15 L and the elimination rate constant is 0.15 hr^{-1}.

Superposition Principle

$$Cp^1 = \frac{200}{15} \bullet e^{-0.15 \times t} = 0.364\ mg/L \text{ at } 24\ \text{hr}$$

$$Cp^2 = \frac{300}{15} \bullet e^{-0.15 \times (t-6)} = 1.344\ mg/L$$

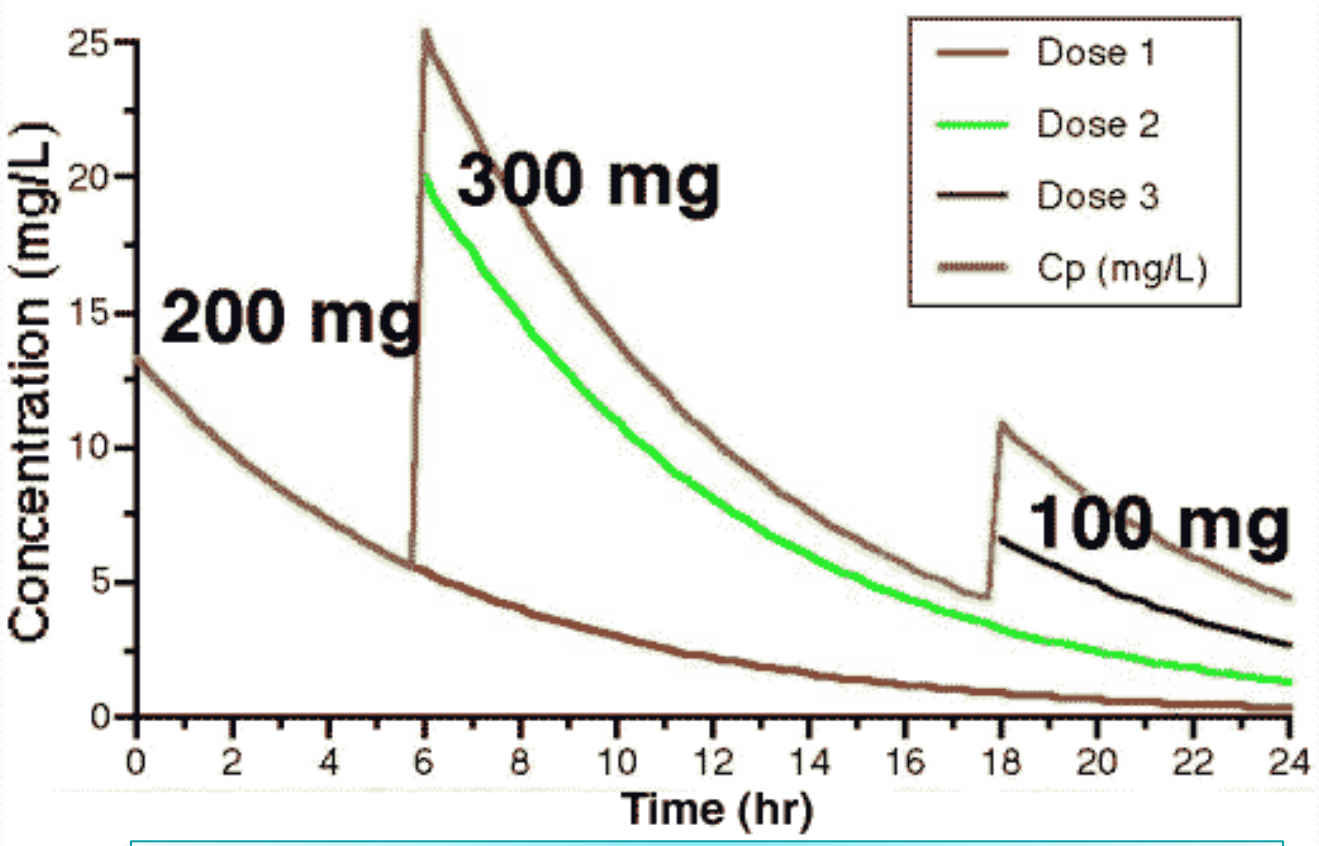
$$Cp^3 = \frac{100}{15} \bullet e^{-0.15 \times (t-18)} = 2.710\ mg/L$$

$$Cp = Cp^1 + Cp^2 + Cp^3 = 4.42\ mg/L$$

- This method involved calculating the contribution from each dose at 24 hours after the first dose.

Superposition Principle

- This result is shown graphically in in the following figure:

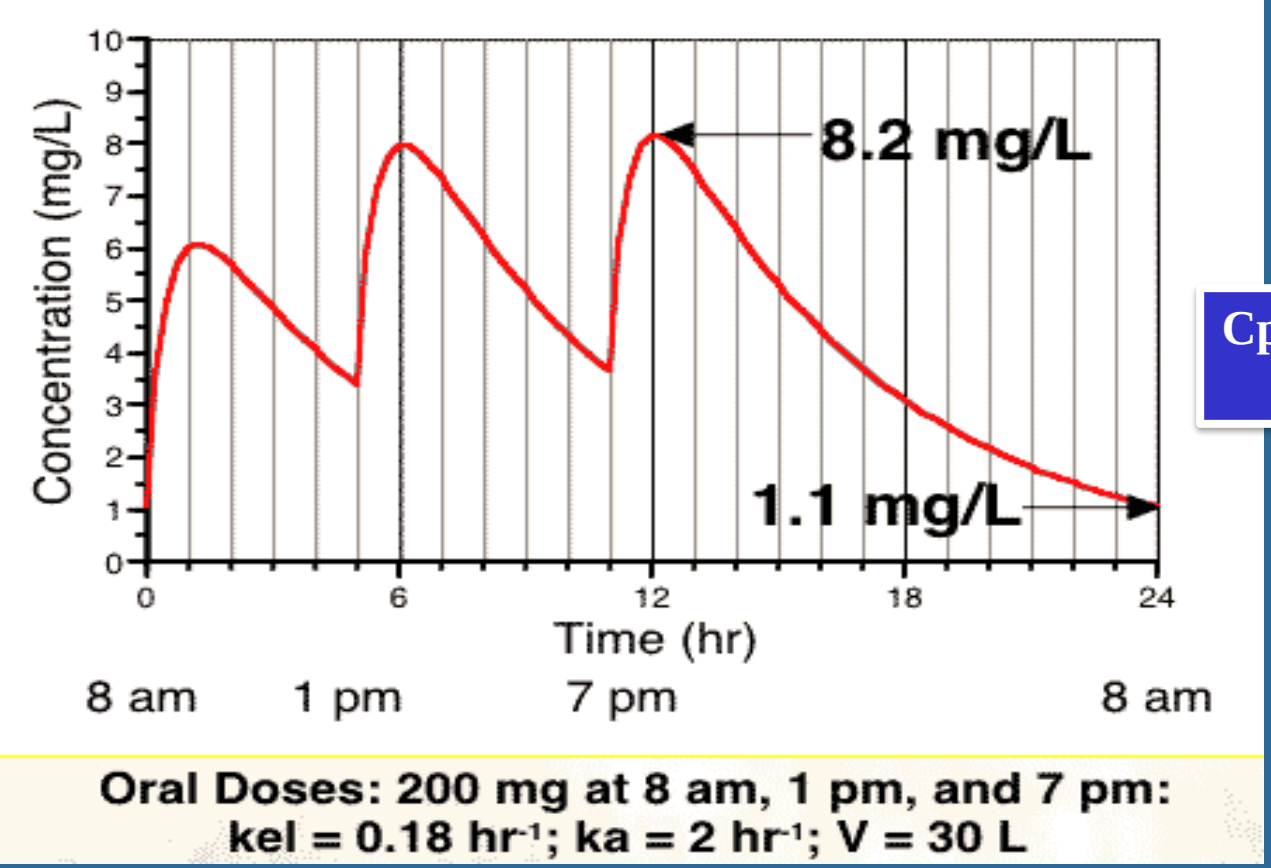


Drug Concentration after Three IV Bolus Doses

Non-uniform dosing intervals

- The calculations we have looked at consider that the dosing intervals are quite uniform, however, commonly this ideal situation is not adhered to completely.

- Dosing three times a day may be interpreted as with meals, the plasma concentration may then look like the plot in Figure:



Cp versus Time during Dosing at 8 am, 1 pm, and 7 pm

- The ratio between Cp_{max} and Cp_{min} is seven fold (8.2/1.1 = 7.45) in this example.

- This regimen may be acceptable if :
  1) The drug has a wide therapeutic index
  2) There is no therapeutic disadvantage to low overnight plasma concentrations, e.g., analgesic of patient stays asleep.

Homework # 5

- An adult male patient (46 years old, 81 kg) was given orally 250 mg of tetracycline hydrochloride every 8 hours for 2 weeks. From the literature, tetracycline hydrochloride is about 75% bioavailable and has an apparent volume of distribution of 1.5 L/kg. The elimination half-life is about 10 hours. The absorption rate constant is 0.9 hr^{-1}. From this information, calculate:

a) C_{max} after the first dose.

b) C_{min} after the first dose.

c) Plasma drug concentration C_p at 4 hours after the 7th dose.

d) Maximum plasma drug concentration at steady-state $C^{\infty}_{max.}$

e) Minimum plasma drug concentration at steady-state $C^{\infty}_{min.}$

f) Average plasma drug concentration at steady-state C^{∞}_{av}.