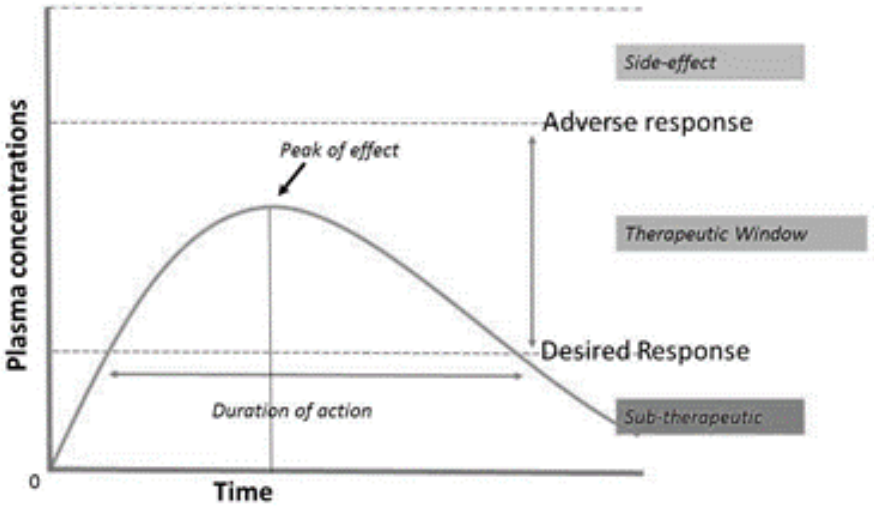
Multiple-Dosage Regimens

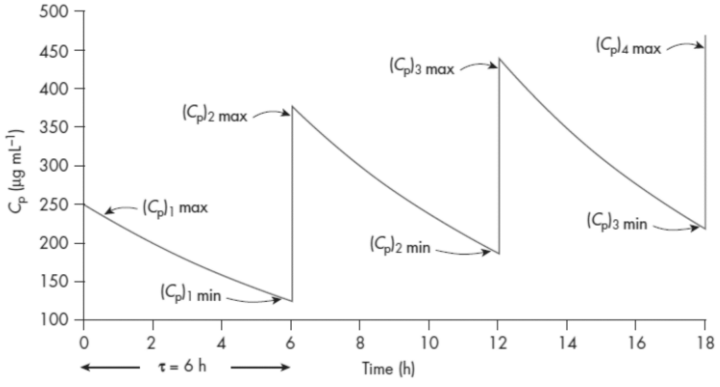
Some drugs, such as analgesics, hypnotics and antiemetics, may be used effectively when administered as a single dose. However, single dose is not convenient for the treatment of chronic diseases. After single-dose drug administration, the plasma drug level rises above and then falls below the ***minimum effective concentration*** **(MEC)**, resulting in a decline in therapeutic effect.



To treat chronic disease, multiple-dosage or IV infusion regimens are used to maintain the plasma drug levels within the narrow limits of the therapeutic window (eg, plasma drug concentrations above the MEC but below the *minimum toxic concentration* or MTC) to achieve optimal clinical effectiveness.

Important definitions in multiple dosing

- **Dosage regimen.** The systematized dosage schedule for a drug therapy, or the optimized dose (D_0) and dosing interval (τ, tau) for a specific drug.
- **Drug accumulation (R)**. The buildup of drug in the blood/body through sequential dosing.
  - **Drug *superposition*:** early doses of drug do not affect the pharmacokinetics of subsequent doses. Blood levels after the second, third, or *n*th dose will overlay or superimpose the blood level attained after the previous dose.



- **Steady-state condition.** Steady state is achieved at a time when, under a given dosage regimen, the mass (amount) of drug administered (for intravenous) or absorbed (for extravascular route), is equal to the mass (amount) of drug eliminated over a dosing interval.
- **Loading dose (D_L).** A single dose administered in order to reach steady-state condition instantly.
- **Maintenance dose (D_m).** The dose administered every dosing interval to maintain the steady-state condition.

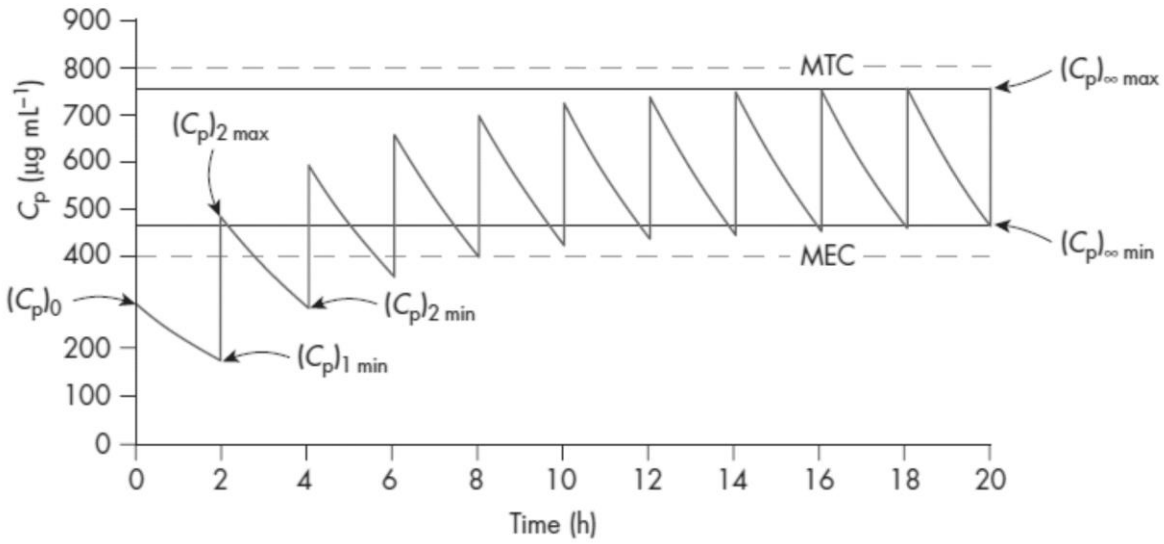
There are two main parameters that can be adjusted in developing a dosage regimen:
(1) the size of the drug dose.
(2) τ, the frequency of drug administration (ie, the time interval between doses).

DRUG ACCUMULATION (R)
Accumulation is affected by the elimination half-life of the drug and the dosing interval. The index for measuring drug accumulation *R* is

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

The value of *R* simply indicates how high the plasma concentration will be at steady state compared with the first dose of the drug at a comparable time within the dosage regimen.

Steady-state plasma concentration – Multiple IV Bolus Inj



$$\boldsymbol{C_t^{\infty} = \frac{C_p^0 \cdot e^{-kt}}{1 - e^{-k\tau}}}$$

Where (C_t^{∞}) is plasma concentration at any time after the drug reaches steady-state concentration; C_p^0 is initial plasma concentration which is equal to is equal to D_0/V_D.

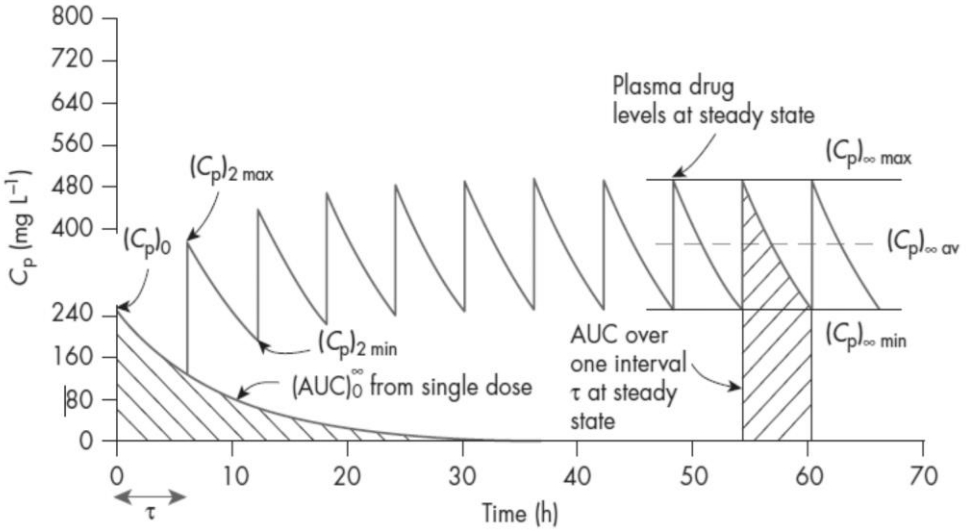
$$\boldsymbol{C_{min}^{\infty}\ (\text{trough}) = \frac{C_p^0 \cdot e^{-k\tau}}{1 - e^{-k\tau}}} \qquad \boldsymbol{C_{min}^{\infty} = C_{max}^{\infty} \cdot e^{-k\tau}}$$

$$\boldsymbol{C_{max}^{\infty}\ (\text{peak}) = \frac{C_p^0}{1 - e^{-k\tau}}}$$

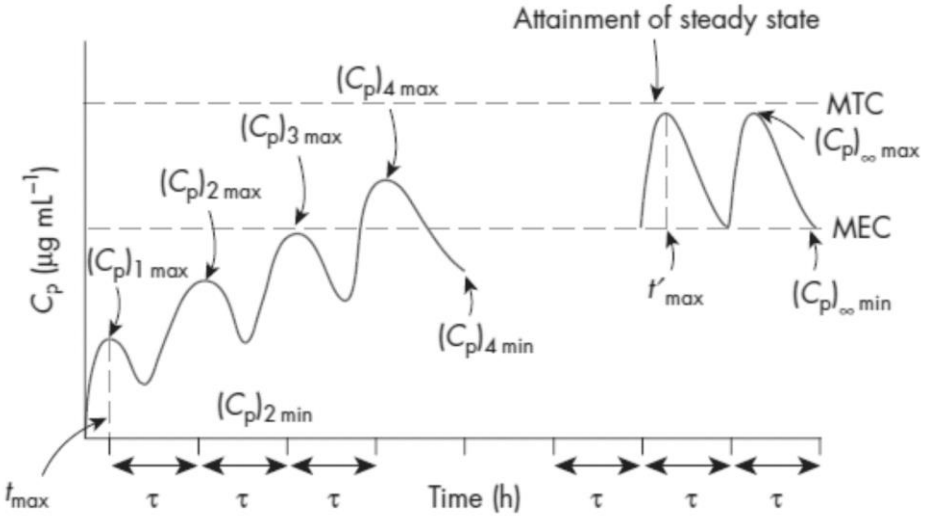
$$C_{av}^{\infty} = \frac{C_p^0}{k\tau} = \frac{D_0}{V_D k\tau}$$

Average plasma concentration at steady state (C_{av}^{∞}) can also be calculated from AUC by the following equation:

$C_{av}^{\infty} = \frac{[AUC]_{t1}^{t2}}{\tau}$ or by $C_{av}^{\infty} = \frac{[AUC]_0^{\infty}}{\tau}$



Steady-state plasma concentration – Multiple Oral Administrations



- **$C_P = \frac{F\ k_a D_0}{V_D(k_a - k)}\ (e^{-kt} - e^{-k_a t})$ ……. Plasma concentration at any time after single dose administration.**
- **$C_p^{\infty} = \frac{F\ k_a D_0}{V_D(k_a - k)}\ [(\frac{1}{1 - e^{-k\tau}})e^{-kt} - (\frac{1}{1 - e^{-k_a\tau}})e^{-k_a t}]$**
- Where (C_p^{∞}) is plasma concentration at any time after the drug reaches steady-state concentration.

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

$$C_{max}^{\infty}\,(\text{peak}) = \frac{F\,D_0}{V_D}\;\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt_p}$$

t_p is the time of peak plasma concentration following multiple doses.

$t_{max} = \frac{2.3\,log\,(k_a/k)}{(k_a - k)}$ …. t_{max} following single dose administration

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

$C_{av}^{\infty} = \frac{F\,D_0}{V_D k\tau}$

The ''average'' steady-state plasma concentration is influenced by the following parameters:

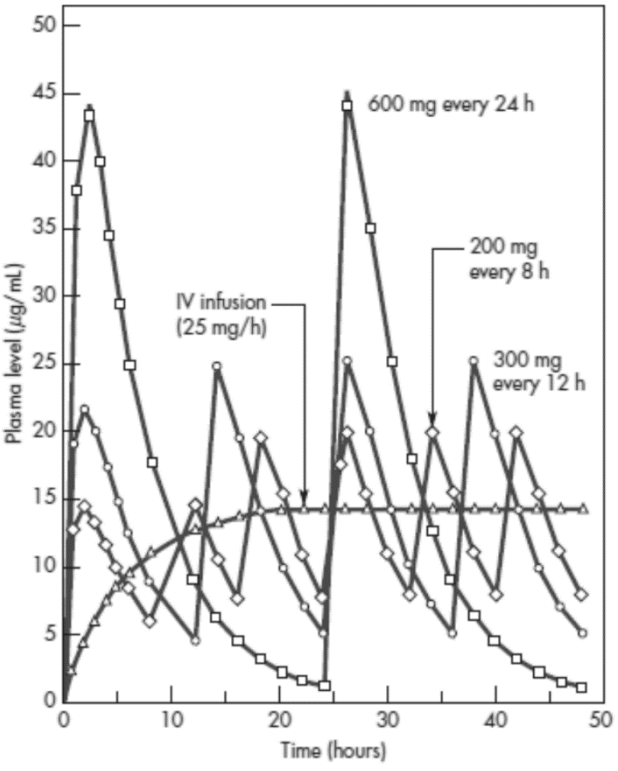
1. The dose administered.
2. The chosen dosing interval.
3. The absolute bioavailability (F), when applicable.
4. The systemic clearance of the drug.

Since systemic clearance for a drug is constant, at normal conditions, the three first parameters are the most important.

The larger the dosing interval, the lower will be the ''average'' steady-state plasma concentration. However, if the ratio of dose over dosing interval is maintained constant, the ''average''steady-state concentration will remain unchanged.

For example, administration of a 400 mg dose of a drug at every 8 h or the administration of 200 mg dose at every 4 h will provide identical ''average'' steady-state plasma concentrations.

In renally impaired subjects, there will be a decrease in the systemic clearance of a drug eliminated by the kidneys; and, therefore, the normal dosage regimen of that drug will provide higher ''average'' steady-state concentration



- The dosage adjustment in case of decreased clearance can be accomplished by three approaches.

1. Administration of a smaller dose at a normal dosing interval.
2. Administration of a normal dose at a longer dosing interval (i.e. decreasing the frequency of drug administration).
3. A combination of both (i.e. administration of a smaller dose less frequently).

Designing or establishing the dosage regimen for a drug

1. Know the therapeutic range and/or the effective concentration range for the drug.
2. Select the desired or targeted ''average'' steady state plasma concentration. For example, if the therapeutic range is 10– 30mg/L, choose 20mg/L as the targeted ''average'' steady-state concentration.
3. Use $C_{av}^{\infty} = \frac{D_0}{V_D k \tau}$ (for an intravenous bolus administration):
4. Select the dosing interval (it is a safe and good practice to start with a dosing interval equal to the drug's elimination half-life).
5. Using this dosing interval, and rearranging the equation in Step 3, calculate the dose (D_0) needed to attain the desired ''average'' steady-state concentration. $D_0 = C_{av}^{\infty}\, V_D\, K\, \tau$
6. Using the calculated dose and dosing interval (numbers may be rounded off to the nearest whole no. like 109.15 mg to 100 or 125 mg), calculate the ''average'' steady-state concentration, peak steady-state concentration and trough steady-state concentration.
8. Make sure that the calculated peak steady-state concentration is below the minimum toxic concentration and calculated trough steady-state concentration is above the minimum effective concentration.
9. If necessary, make small adjustments (fine tuning) in the dose and dosing interval.

Calculation of loading and maintenance doses

The steady state plasma concentration is usually attained after 6.6 $t_{1/2}$ (if the drug is administered at time interval $\tau = t_{1/2}$). This is a long time before the desired ''average'' steady-state drug concentration is attained. Therefore, an intravenous bolus loading dose (D_L) may be administered to obtain an instant steady-state condition.
Maintenance dose (D_M): is the dose required to maintain plasma concentration level at steady state.

$$\textbf{Dose ratio} = \frac{D_L}{D_M} = \frac{1}{1 - e^{-k\tau}}$$

If the calculated dose ration equals to 2, the loading dose will be equal to double the initial drug dose.