o [redacted]

The magnitude of both therapeutic and toxic responses depends upon dose size.

Dose size calculation also requires the knowledge of amount of drug absorbed after administration of each dose.

Greater the dose size, greater the fluctuations between $C_{ss,max}$ and $C_{ss,min}$ during each dosing interval and greater the chances of toxicity.

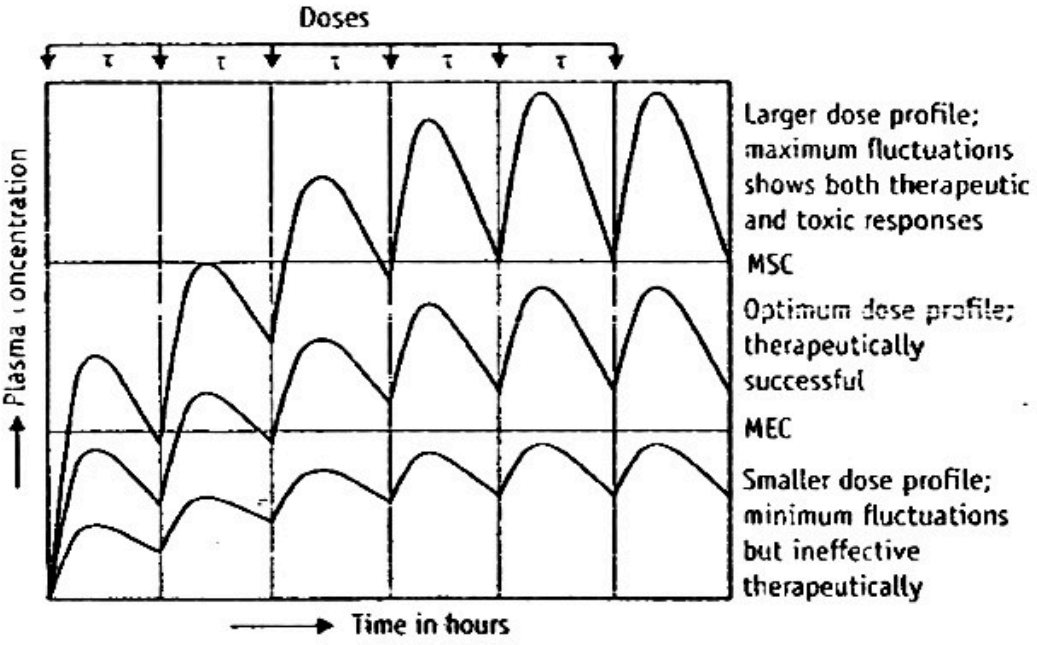

Fig. Schematic representation of influence of dose size on plasma concentration-time profile after oral administration of a drug at fixed intervals of time.

• For a drug that is given in multiple doses for an extended period of time, the dosage regimen is usually calculated so that the avaraje steady-state blood level is within the therapeutic range.

• The Dose can be calculated with equation:

$$C_{av} = \frac{1.44\, D_0\, t_{1/2}\, F}{V_D\, \tau}$$

F = fraction of drug absorbed and is equal to 1 for drug administered intravenously

τ = Dosing interval

Practice problem:

Pharmacokinetic data for clindamycin were reported by DeHaan et al (1972) as follows:

$K = 0.247\ hr^{-1}$

$t_{1/2} = 2.81\ hr$

$V_D = 43.9\ L/1.73\ m^2$

What is the Steady state concentration of the drug after 150mg of the drug given orally every 6 hours for a week? (Assume the drug is 100% absorbed)

Solution:

$$C_{av} = \frac{1.44 D_o t_{1/2} F}{V_D \tau}$$

$$= \frac{1.44 \times 150000 \times 2.81 \times 1}{43900 \times 6} = 2.3\ mcg/mL$$

□ [redacted]

• The dose interval (inverse of dosing frequency) is calculated on the basis of half-life of the drug.

If the interval is increased and the dose is unchanged, C_{max}, C_{min} and C_{av} decrease but the ratio C_{max}/C_{min} increases.

• Opposite is observed when dosing interval

is reduced or dosing frequency increased. It also results in greater drug accumulation in the body and toxicity.

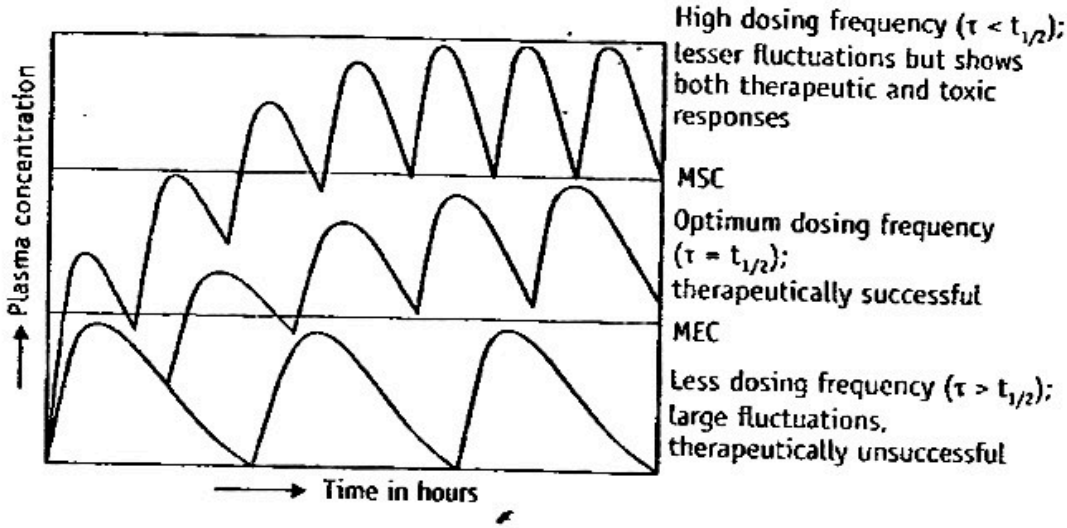

Fig. Schematic representation of the influence of dosing frequency on plasma concentration-time profile obtained after oral administration of fixed doses of a drug.

-A proper balance between both dose size and dosing frequency is often desired to attain steady-state concentration with minimum fluctuations and to ensure therapeutic efficacy and safety. The same cannot be obtained by giving larger doses less frequently. However, administering smaller doses more frequently results in smaller fluctuations.

• Generally speaking, every subsequent dose should be administered at an interval equal to half-life of the drug. A rule of thumb is that:

• For drugs with wide therapeutic index such as penicillin, larger doses may be administered at relatively longer intervals (more) than the half-life of drug) without any toxicity problem.

• For drugs with narrow therapeutic index such as digoxin, small doses at frequent intervals (usually less than the half-life of the drug) is better to obtain a profile with least fluctuations which is similar to that observed with constant rate infusion or controlled-release system.

• Determination of Both Dose and Dosage interval:

Both the dose and the dosage interval should

be considered in the dosage regimen calculation.

- Ideally, the calculated dosage regimen should maintain the serum drug concentrations between (C_{max}) and (C_{min}).
- For intravenous multiple-dosage regimens the ratio of C_{max}/C_{min} may be expressed by:

$$\frac{C_{max}}{C_{min}} = \frac{1}{e^{-XT}}$$

- A maximum dosage interval (τ) may be calculated that will maintain the serum concentration b/w C_{min} and C_{max}.
- After the dosage interval is calculated, then a dose may be calculated.