DOSAGE REGIMEN DESIGN

Subject: Pharmaceutical Care

Submitted To: **Dr. Shazia Akram**

Submitted By: **Shazia Naseem Ch**

Ph.D. Scholar (Pharmaceutics)

(2019-2022)

College of Pharmacy, University of Sargodha

CONTENTS

1. DOSAGE REGIMEN DESIGN

1.1 Dosage Regimen

Dosage regimen is defined as the manner in which a drug is taken. It is the schedule of doses of a medicine including, the dosage form, the time between doses, the duration of treatment and the amount to be taken each time.

1.2 Designing Of Dosage Regimen

For some drugs like analgesics, hypnotics or anti emetics, a single dose may provide effective treatment. However, the duration of most of the illnesses is longer than the therapeutic effect produced by a single dose. In such cases, drugs are required to be taken on a repetitive basis over a period of time depending upon the nature of illness. So for a successful drug therapy, designing of an optimal multiple dosage regimen is required.

2. OBJECTIVE

The primary objective in dosage regimen design is to obtain a safe plasma drug concentration which neither exceeds the maximum safe concentration nor falls below the minimum effective concentration.

3. ASSUMPTIONS

When designing a dosage regimen, it is assumed that all pharmacokinetic parameters are constant. In case any one of these parameter changes, the dosage regimen becomes invalid.

4. CRITERIA FOR OPTIMUM DOSAGE REGIMEN

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

Therapeutic window is a range of doses that produces therapeutic response without causing any significant adverse effect in patients. Generally therapeutic window is a ratio between minimum effective concentrations (MEC) to the minimum toxic concentration (MTC).

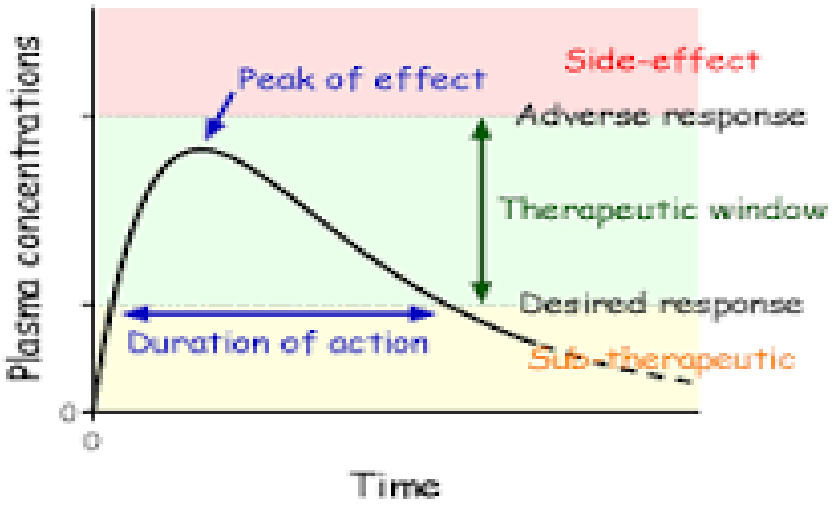

FIG.1 Plasma concentration-Time curve, Therapeutic window

5. APPROACHES FOR DOSAGE REGIMEN DESIGN

Various approaches employed in designing a dosage regimen are;

5.1 Empirical Dosage Regimen

- Designed by the physician
- Based on empirical clinical data, personal experience and clinical observations.
- This approach is, however, not very accurate.

5.2 Individualized Dosage Regimen

- Based on the pharmacokinetics of drug in the individual patient
- Suitable for hospitalized patients but is quite expensive.
- The most accurate approach

5.3 Dosage Regimen on Population Averages

The most often used approach.

The method is based on one of the two models;

5.3.1Fixed Model – here, population average pharmacokinetic parameters are used directly to calculate the dosage regimen.

5.3.2 Adaptive Model – is based on both population average pharmacokinetic parameters of the drug as well as patient variables such as weight, age, sex, body surface area and known patient pathophysiology such as renal disease.

6. IMPORTANT VARIABLES IN DOSAGE REGIMEN DESIGN

- Dose size
- Dosing interval
- Mean steady state blood concentration
- Maximum state blood concentration
- Minimum steady state concentration

7. FACTORS TO BE CONSIDERED IN DOSAGE REGIMEN DESIGN

Numerous factors must be considered in designing a dosage regimen.

7.1 Pharmacokinetic Factors

These include absorption, distribution, metabolism and excretion characteristics of a drug.

7.2 Physiological Factors

Age, Weight, Gender and Nutritional status of a patient under treatment must be considered.

7.3 Pathophysiologic Factors

Existence of diseases like Renal failure, Hepatic diseases, Congestive heart failure, Myocardial infraction etc, must be considered in the patient being treated. This is because co-existence of these diseases will prolong the elimination of drugs. Therefore, the dose in such patients must be carefully adjusted.

7.4 Personal Lifestyle Habits

Lifestyle habits like cigarette smoking, alcohol abuse, voracious eating etc, must also be taken into consideration.

7.5 Exposure of patient to Long Term Medication

Chronic intake of medicines can alert the drug pharmacokinetics.

7.6 Other Factors

These include;

- Desired concentration of drug at site of action
- Alteration in the sensitivity of the receptors to the drug
- Drug dosage form
- Drug interactions
- Tolerance-dependence
- Pharmacogenitics – idiosyncracy

8. MAJOR PARAMETERS TO BE ADJUSTED:

Irrespective of the route of administration and complexity of pharmacokinetic equations, the two major parameters that can be adjusted in developing a dosage regimen are;

1. The dose size — the quantity of drug administered each time

2. The dosing frequency — the time interval between doses

8.1 Dose Size

Dose Size 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 Css,max and Css,min during each dosing interval and greater the chances of toxicity.

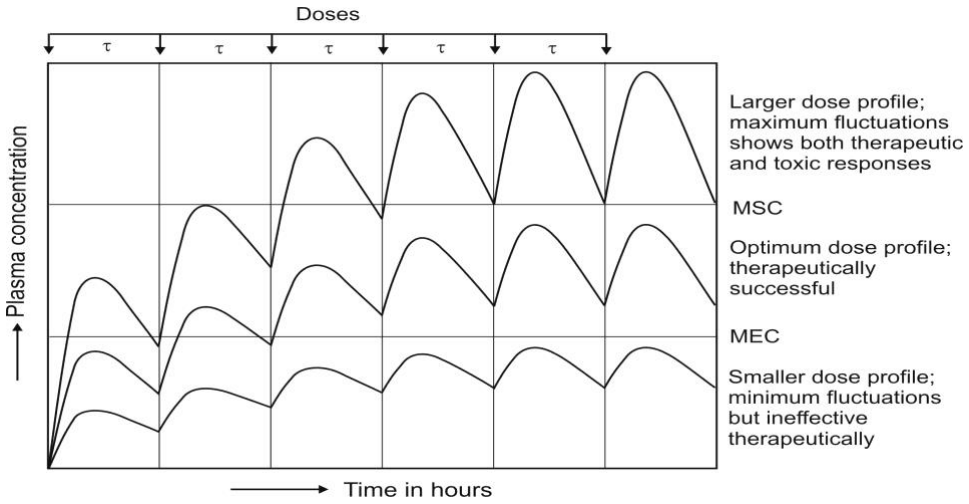

Fig.2 Schematic representation of influence of dose size on plasma concentration-time profile after oral administration of a drug at fixed intervals of time.

8.2 Dosing Frequency

The dosing frequency or time interval between doses is calculated on the basis of half-life of the drug. If the interval is increased and the dose is unchanged, Cmax, Cmin & Cavg decrease but the ratio Cmax/ Cmin 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.

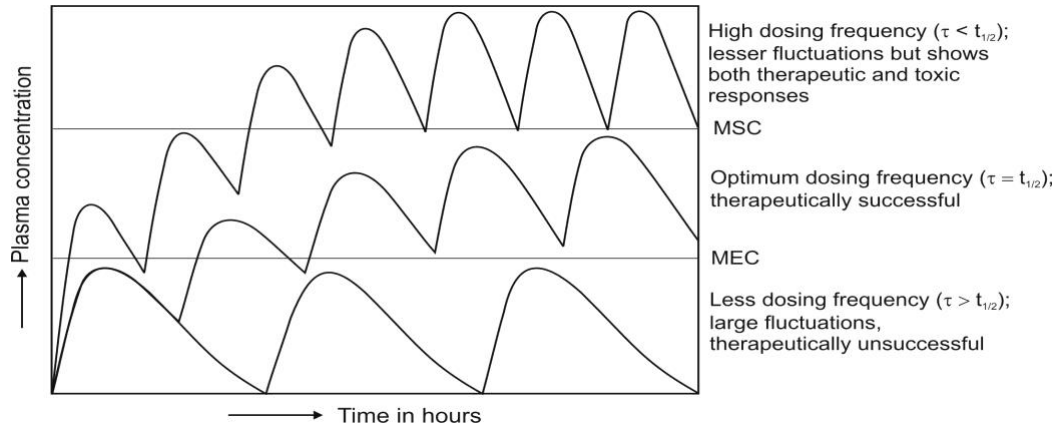

Fig.3 Schematic representation of the influence of dosing frequency on plasma concentration time profile obtained after oral administration of fixed doses of a drug.

8.3 Balance between Dose Size and Frequency

A proper balance between dose size & 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. Every subsequent dose should be administered at an interval equal to half-life of the drug.

A rule of thumb is that ;

1. 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.
2. 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.

9. CALCULATION OF MULTIPLE DOSE REGIMEN

To calculate a multiple-dose regimen, pharmacokinetic parameters are first obtained from the plasma level–time curve generated by single-dose drug studies. With these pharmacokinetic parameters and knowledge of the size of the dose and dosage interval (τ), the complete plasma level–time curve or the plasma level may be predicted at any time after the beginning of the dosage regimen.

9.1 Principal of Superposition

For calculation of multiple-dose regimens, it is necessary to decide whether successive doses of drug will have any effect on the previous dose.

The principle of *superposition* assumes that early doses of drug do not affect the pharmacokinetics of subsequent doses. Therefore, the blood levels after the second, third, or *n*th dose will overlay or superimpose the blood level attained after the (*n*-1)th dose.

The principle of *superposition* allows to project the plasma drug concentration–time curve of a drug after multiple consecutive doses based on the plasma drug concentration–time curve obtained after a single dose.

Basic assumptions are;

(1) The drug is eliminated by first-order kinetics and

(2) The pharmacokinetics of the drug after a single dose (first dose) are not altered after taking multiple doses.

The plasma drug concentrations after multiple doses may be predicted from the plasma drug concentrations obtained after a single dose. The plasma drug concentrations from 0 to 24 hours are measured after a single dose. A constant dose of drug is given every 4 hours and plasma drug concentrations after each dose are generated using the data after the first dose. Thus, the *predicted* plasma drug concentration in the patient is the total drug concentration obtained by adding the residual drug concentration obtained after each previous dose. The superposition principle may be used to predict drug concentrations after multiple doses of many drugs. Because the superposition principle is an overlay method, it may be used to predict drug concentrations after multiple doses given at either *equal* or *unequal* dosage intervals. For example, the plasma drug concentrations may be predicted after a drug dose is given every 8 hours, or 3 times a day before meals at 8 AM, 12 noon, and 6 PM.

Principal of superposition does not apply;

- ☐ When the pharmacokinetics of the drug change after multiple dosing due to various factors including;
  - changing pathophysiology in the patient,
  - saturation of a drug carrier system,
  - enzyme induction, and enzyme inhibition.
- ☐ Drugs that follow nonlinear pharmacokinetics

9.2 Drug Accumulation

When the drug is administered at a fixed dose and a fixed dosage interval, the amount of drug in the body will increase and then plateau to a mean plasma level

higher than the peak *C*p obtained from the initial dose (Figs. 9-1 and 9-2). When the second dose is given after a time interval shorter than the time required to "completely" eliminate the previous dose, *drug accumulation* will occur in the body.

However, if the second dose is given after a time interval longer than the time required to eliminate the previous dose, drug will not accumulate.

As repetitive equal doses are given at a constant frequency, the plasma level–time curve plateaus and a steady state is obtained. At steady state, the plasma drug levels fluctuate between _max *C* and _min *C* . Once steady state is obtained, Cmax and Cmin are constant and remain unchanged from dose to dose.

The Cmax should always remain below the MTC. The _max is also a good indication of drug accumulation.

Accumulation is affected by the elimination half-life of the drug and the dosing interval. The index for measuring drug accumulation *R* is given by;

$$R_{ac} = \frac{1}{1 - e^{-K_E \tau}}$$

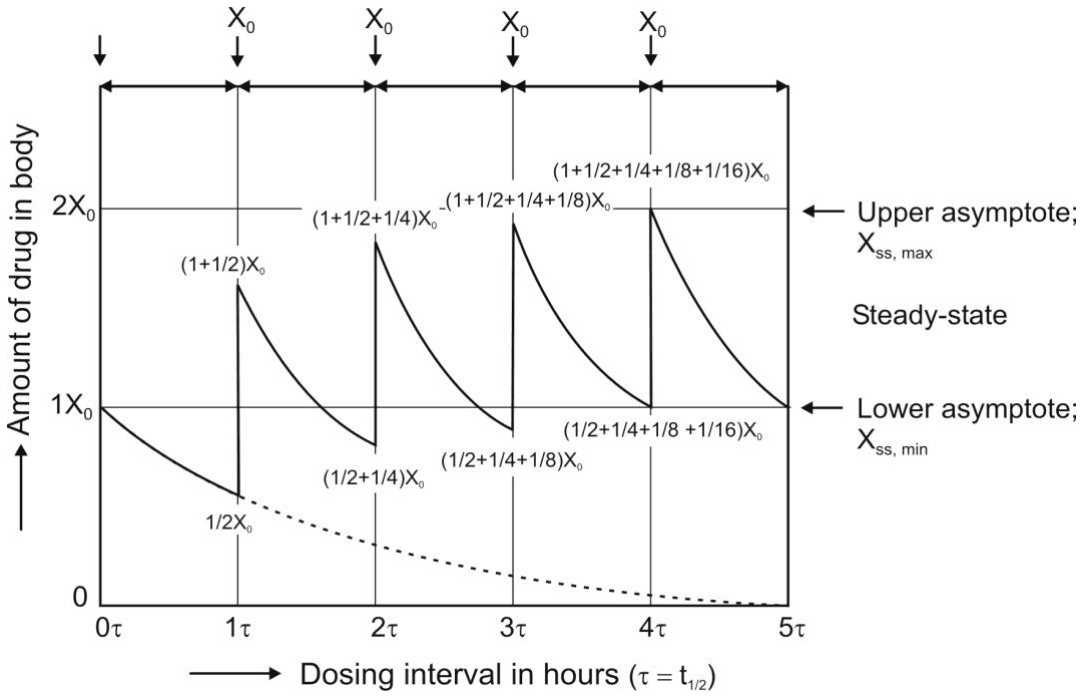

Fig.3 Drug accumulation during multiple dosing.

9.3 Time to reach Steady-State during Multiple Dosing

The time required to reach steady-state depends primarily upon the half-life of the drug. It also means that the rate at which the multiple dose steady-state is reached is determined only by K E. The time taken to reach steady-state is independent of dose size, dosing interval and number of doses.

9.4 Maximum and Minimum Concentration During Multiple Dosing

If n is the number of doses administered, the Cmax and Cmin obtained on multiple dosing after the nth dose is given as:

$$C_{n,\,max} = C_0\left[\frac{1-e^{-nK_E\tau}}{1-e^{-K_E\tau}}\right]$$

The maximum and minimum concentration of drug in plasma at steady-state is found by following equations:

$$C_{ss,\,max} = \frac{C_0}{1-e^{-K_E\tau}}$$

Where Co = concentration that would be attained from instantaneous absorption and distribution (obtained by extrapolation of elimination curve to time zero).

9.5 Fluctuation

Fluctuation is defined as the ratio Cmax/ Cmin . Greater the ratio, greater is the fluctuation.

Like accumulation, it depends upon;

- Dosing frequency
- Half-life of the drug
- Rate of absorption.

The greatest fluctuation is observed when the drug is given as i.v. bolus.

Fluctuations are small when the drug is given extravascularly because of continuous absorption.

10. LOADING AND MAINTENANCE DOSES

A drug does not show therapeutic activity unless it reaches the desired steady-state. It takes about 5 half-lives to attain it and therefore the time taken will be too long if the drug has a long half-life. Plateau can be reached immediately by administering a dose that gives the desired steady-state instantaneously before the commencement of maintenance doses Xo. Such an initial or first dose intended to be therapeutic is called as priming dose or loading dose. A simple equation for calculating loading dose is:

$$X_{0,L} = \frac{C_{ss,av} V_d}{F}$$

After e.v . administration, Cmax is always smaller than that after i.v . administration and hence loading dose is proportionally smaller. For drugs having low therapeutic indices, the loading dose may be divided into smaller doses to be given at various intervals before the first maintenance dose. When V d is not known, loading dose may be calculated by the following equation:

$$\frac{X_{0,L}}{X_0} = \frac{1}{\left(1 - e^{-K_a \tau}\right)\left(1 - e^{-K_E \tau}\right)}$$

The above equation applies when K a >> K E and drug is distributed rapidly. When the drug is given i.v. or when absorption is extremely rapid, the absorption phase is neglected and the above equation reduces to accumulation index :

$$\frac{X_{0,L}}{X_0} = \frac{1}{\left(1 - e^{-K_E \tau}\right)} = R_{ac}$$

10.1 Dose Ratio

The ratio of loading dose to maintenance dose X o,L /X o is called as dose ratio . As a rule, when t = t½, dose ratio should be equal to 2.0 but must be smaller than 2.0 when t > t½ and greater when t < t½. If loading dose is not optimum, either too low or too high, the steady-state is attained within approximately 5 half-lives in a manner similar to when no loading dose is given. Schematic representation of

plasma concentration-time profiles that result when dose ratio is greater than 2.0, equal to 2.0 and smaller than 2.0.

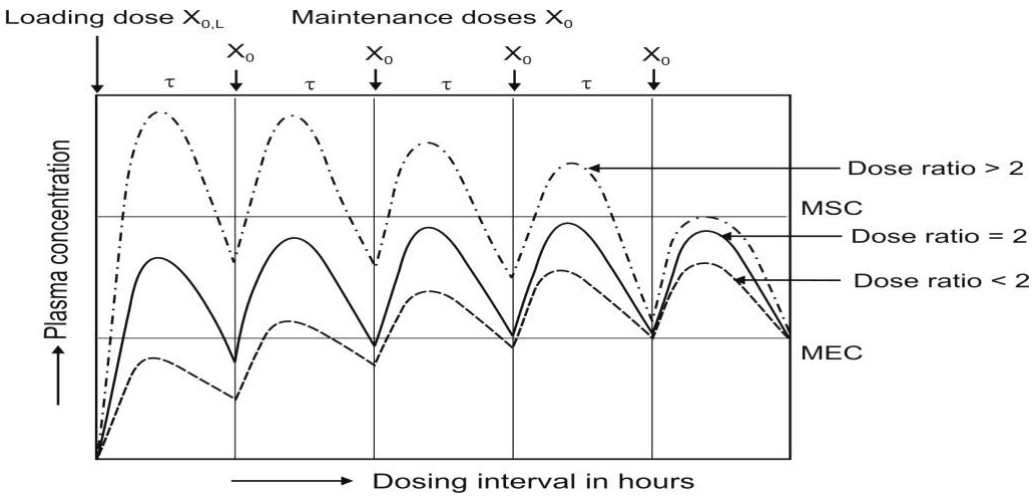

Fig.4 Schematic representation of plasma concentration-time profiles that result when dose ratio is greater than 2.0, equal to 2.0 and smaller than 2.0.

10.2 Maintenance of Drug within the Therapeutic Range

The ease or difficulty in maintaining drug concentration within the therapeutic window depends upon —

1. The therapeutic index of the drug
2. The half-life of the drug
3. Convenience of dosing

12. DESIGN OF DOSAGE REGIMEN FROM PLASMA CONCENTRATIONS

If the therapeutic range, apparent Vd and clearance or half-life of a drug is known, then dosage regimen can be designed to maintain drug concentration within the specified therapeutic range. The latter is defined by lower limit (C lower) and an upper limit (C upper). The maximum dosing interval, which ideally depends upon the therapeutic index (can be defined as a ratio of C upper to C lower) and elimination half-life of the drug, can be expressed by equations

$$\tau_{max} = \frac{2.303 \log \left(C_{upper} / C_{lower} \right)}{K_E}$$

Understandably, the dosing interval selected is always smaller than tmax. The maximum maintenance dose Xo,max that can be given every tmax is expressed as:

$$X_{0,max} = \frac{V_d \left(C_{upper} - C_{lower} \right)}{F}$$

REFERENCES

- Steady State during Multiple Drug Administrations by Mohsen A. Hedaya in Basic Pharmacokinetics (Pg.no: 99-110).
- Multiple-Dosage Regimens by Leon Shargel in Applied Biopharmaceutics & Pharmacokinetics (Chapter no:8).
- Multiple-Dosage Regimens (Repetitive Dosing) by Gilbert S. Banker in Modern Pharmaceutics (Chapter no:3). Gibaldi