INTRODUCTION TO DOSING PATTERN AND DRUG THERAPY

- **Dosage Regimen** - Dosage regimen is defined as the manner in which the drug is taken.
- For some drugs like analgesics single dose is efficient for optimal therapeutic effect however the duration of most illnesses are 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.

- An optimal multiple dosage regimen is the one in which the drug is administered in suitable doses with sufficient frequency that ensures maintenance of plasma conc. within the therapeutic window for entire duration of therapy.

INTRODUCTION TO DOSING PATTERN AND DRUG THERAPY

- For successful therapy, design of an optimal multiple dosage regimen is necessary.
- Multiple dosage regimen:- is defined as the manner in which the drug is administered in suitable doses by suitable route, with sufficient frequency that insures maintenance of plasma conc. within therapeutic window for entire period of therapy
- In Designing dosage regimen the two major parameters that can be adjusted in developing a dosage regimen are...

1) The Dose size – The quantity of drug administered.
2) The Dosing frequency – The time interval between Doses.

INDIVIDUALIZATION OF DOSING PATTERN OR DOSING REGIMEN

- It is the most accurate approach and is based on the pharmacokinetics of drug in the individual patient.
- The approach is suitable for hospitalized patients but is quite expensive.
- Same dose of drug may produce large differences in pharmacologic response in different individuals, this is called as **Intersubject variability**.

- In other words it means that the dose required to produ certain response varies from individual to individual.

INDIVIDUALIZATION OF DOSING PATTERN OR DOSING REGIMEN

- The main objective of at optimizing the individualization is aimed dosage regimen.
- An inadequate therapeutic response calls for a higher dosage whereas drug related toxicity calls for a reduction in dosage.
- Thus in order to aid individualization, a drug must be made available in dosage forms of different dose strengths. The number of dose strengths in which a drug should be made available depends upon two major factors:
  - The therapeutic index of the drug
  - The degree of inter subject variability.

- Smaller the therapeutic index and greater the variability, more the number of dose strengths required.

ADVANTAGES OF INDIVIDUALIZATION OF DOSING PATTERN

- Individualization of dosage regimen help in development of dosage regimen which is specific for the patient.
- Leads to decrease in toxicity and side effects and increase in pharmacological drug efficacy.
- Leads to decrease in allergic reactions of the patient for the drug if any.
- Patient compliance increases.

SOURCES OF VARIABILITY

1. Pharmacokinetic Variability: Due to difference in drug concentration at the site of action (as reflected from plasma drug concentration) because of individual differences in drug absorption, distribution, metabolism and excretion. Major causes are genetics, disease, age, body wt. & drug-drug interactions.

2. Pharmacodynamics Variability : which is attributed to differences in effect produced by a given drug concentration.

3. Disease condition : It affects the dose pattern of the patient like in renal, hepatic diseases, etc.

STEPS OF DOSING PATTERN

Based on the assumption that all patients require the same plasma conc. range for therapeutic effectiveness, the steps involved in the individualization of dosage regimen are :

- Estimation of pharmacokinetic parameters in individual patients and to evaluate the degree of variability.
- Attributing the variability to some measurable characteristics such as hepatic or renal diseases, Age, weight etc.
- Designing the new dosage regimen from the collected data.

- The design of new dosage regimen involves –
  1. Adjustment of dosage or
  2. Adjustment of dosing interval or
  3. Adjustment of both dosage and dosing interval.

A: Dosing of Drugs In Obese Patients

- The apparent volume of distribution is greatly affected by changes in body weight since the latter is directly related to vol. of various body fluids.
- The Ideal Body Weight (IBW) for men and women can be calculated from following formulae:

IBW (Men) = 50 kg +/- 1kg/2.5cm above or below 150cm in height. IBW (Women) = 45kg +/- 1kg/2.5cm above or below 150cm in height.

- Any person whose body Weight is more than 25% above the IBW is considered Obese.

B: Dosing of Drugs in Neonates, Infants and Children

- Neonates, Infants and children require different dosages than that of adults because of differences in the body surface area, TBW and ECF on per kg body weight basis.
- Dose for such patients are calculated on the basis of their body surface area not on body weight basis.
- The surface area in such patients are calculated by **Mosteller's equation** :

$$SA\ (\text{in } m^2) = \frac{(\text{Height} \times \text{Weight})^{1/2}}{60}$$

- Infants and children require larger mg/kg doses than adults because:
  - Their body surface area per kg body weight is larger and hence
  - Larger volume of distribution (particularly TBW : Total body water and fluid.

B: Dosing of Drugs in Neonates, Infants and Children

- The child's Maintenance dose can be calculated from adult dose by the following by the following equation :

$$\text{Child's dose} = \frac{\text{SA of child in } m^2}{1.73} \times \text{Adult dose}$$

Where 1.73 is surface area in m^2 of an avg. 70kg adult.

- Since the surface area of a child is in proportion to the body weight according to the following equation:

$$SA(\text{in } m^2) = \text{Body weight (in kg)}$$

The following relationship can also be written for child's dose

$$\text{Child dose} = \frac{\text{Wt. of child in kg} \times \text{Adult dose}}{70}$$

C: Dosing of Drugs in elderly

- Drug dose should be reduced in elderly patients because of general decline in body function with age.
- The lean body mass decreases and body fat increases by almost 100% in elderly persons as compared to adults.
- V_d of water soluble drugs may decrease and that of lipid soluble drugs like diazepam increases with age.
- Age related changes in renal and hepatic functions greatly alters the clearance of drugs.

$$\text{Patients dose} = \frac{(\text{weight in Kg})\,(140 - \text{age in years}) \times \text{adult dose}}{1660}$$

D: Dosing of Drugs in hepatic diseases

- Disease is a major source of variations in drug response. Both pharmacokinetics and pharmacodynamics of many drugs are altered by diseases other than the one which is being treated.
- The influence of hepatic disorder on drug availability and disposition is unpredictable because of the multiple effects that liver disease produces **– effects on drug metabolizing enzymes, on drug binding and on hepatic blood flow**.
- Other ways of metabolization are available. Therefore the drug dosage should be reduced in patients with hepatic dysfunction since clearance is reduced and availability is increased in such a situation.

E: Dosing of Drugs in renal failure

- Drug in patients with renal impairment have altered pharmacokinetic profile.
- Their renal clearance and elimination rate are reduced, the elimination half- life is increased and apparent volume of distribution altered.
- Since dose must be altered depending upon renal function in such patient.

- To calculate dose in case of renal failure , the regimen may be adjusted by reduction in dosage or increase dosing interval or a combination of both