DESIGN OF DOSAGE REGIMEN

K.P. ARUN
LECTURER

DEPARTMENT OF PHARMACY PRACTICE
JSS COLLEGE OF PHARMACY
OOTY
Dosage regimen design is the selection of drug dosage, route, and frequency of administration in an informed manner to achieve therapeutic objectives.

Deliberate planning of drug therapy is necessary because the administration of drugs usually involves risk of untoward effects.

Specific drugs have inherently different risks associated with their use and a dosage regimen should be selected which will maximize safety.

At the same time, the variability among patients in pharmacodynamic response demands individualized dosing to assure maximum efficacy.
INTRODUCTION...

Factors to consider in Design of Drug Dosage Regimens

I. Route of Administration:
   1. Drug absorption characteristics
   2. Presence of presystemic elimination
   3. Accumulation of drug at absorption site, e.g. intramuscular depots
   4. Need for immediate onset of action
   5. Ease of administration
   6. Half-life: infusion may be necessary for drugs with short $t_{1/2}$ or sustained release formulation
   7. Patient acceptance of route and dosage form
INTRODUCTION…

Factors to consider in Design of Drug Dosage Regimens…

II. Dose:

1. Therapeutic index: if high, consider benefits of loading dose

2. Volume of distribution: to estimate peak plasma concentration

3. Documented nonlinearity of pharmacokinetics

4. Cost of medication

5. Half-life: tapering of dose may not be necessary for some drugs with long $t_{1/2}$

6. Availability of treatment for overdose

7. Existence of a therapeutic or toxic concentration range
Factors to consider in Design of Drug Dosage Regimens…

III. Dosage interval:

1. Half-life: dosage interval can generally be extended in relation to half-life

2. Therapeutic index: the higher the TI, the longer an interval can be spaced with higher doses

3. Body clearance: to evaluate accumulation

4. Side effects which may require special administration times, e.g. bedtime to avoid sedation
INTRODUCTION...
Factors to consider in Design of Drug Dosage Regimens...

IV. Complications:

1. Analytical methodology and reliability in monitoring $C_p$
2. Active metabolites
3. Changing pathophysiology
4. Drug interactions
5. Auto or exogenous enzyme induction
6. Development of pharmacodynamic tolerance
7. Side effects not dose or concentration related
8. Need for baseline con. data with recent history of drug use
Several methods may be used to design a dosage regimen

- Individualized dosage regimen
- Dosage regimen based on population average
- Dosage regimen based on partial pharmacokinetic parameters
- Empirical dosage regimen
Individualized Dosage Regimen:

- Most accurate approach
- Dose calculated based on the pharmacokinetics of the drug in the individual patient derived from measurement of serum/plasma drug levels
- Not feasible for calculation of the initial dose, however, readjustment of the dose is quite possible
- Most dosing program record the patient’s age and weight and calculate the individual dose based on creatinine clearance and lean body mass

Dosage Regimens based on Population Averages:

- Dosage regimen is calculated based on average pharmacokinetic parameters obtained from clinical studies published in the drug literature
Dosage Regimens based on Population Averages…

- There are two approaches followed
  - Fixed model
  - Adaptive model

**Fixed Model:**

- Assumes that population average pharmacokinetic parameters may be used directly to calculate a dosage regimen for the patient, without any alteration

- The practitioner may use the usual dosage suggested by the literature and then make a small adjustment of the dosage based on the patient’s weight and / or age
Fixed Model…

- Usually, pharmacokinetic parameters such as $K_a$, $F$, $V_d$, $k$ are assumed remain constant and most often drug is assumed to follow one compartment open model

- When a multiple dose regimen is designed, multiple dosage equations based on the principle of superposition are used to evaluate the dose

Adaptive Model:

- This approach attempts to adapt or modify dosage regimen according to the need of the patient

- Uses patient variable such as weight, age, sex, body surface area, and known patient’s pathophysiology such as, renal disease, as well as known population average pharmacokinetic parameters of the drug
Adaptive model…

- This model generally assumes that pharmacokinetic parameters such as drug clearance do not change from one dose to the next.

- However, some adaptive models allow for continuously adaptive change with time in order to simulate more closely the changing process of drug disposition in the patient, especially during a disease state.

Dosage Regimen based on Partial Pharmacokinetic Parameters:

- For many drugs, the entire pharmacokinetic profile for the drug is unknown or unavailable.

- Therefore, the pharmacokineticist needs to make some assumptions in order to calculate the dosage regimen.

- These assumptions will depend on the safety, efficacy, and therapeutic range of the drug.
Dosage Regimen based on Partial Pharmacokinetic Parameters…

- The use of population pharmacokinetics uses average patient population characteristics and only a few serum / plasma concentration from the patient.

- Population pharmacokinetic approaches to therapeutic drug monitoring have increased with the increased availability of computerized data bases and development of statistical tools for the analysis of observational data.

Empirical Dosage Regimens:

- In many cases, physician selects a dosage regimen of the patient without using any pharmacokinetic variables.

- The physician makes the decision based on empirical clinical data, personal experience and clinical observations.
A nomogram typically has three scales: two scales represent known values and one scale is the scale where the result is read off.

The known scales are placed on the outside; i.e. the result scale is in the center.

Each known value of the calculation is marked on the outer scales and a line is drawn between each mark.

Where the line and the inside scale intersects is the result.

Examples include, height – BMI – weight, total clearance – maintenance dose – lean body weight, etc.
NOMOGRAMS AND TABULATIONS IN DESIGNING DOSAGE REGIMENS

- For ease of calculation of dosage regimens, many clinicians rely on nomograms to calculate the proper dosage regimen for their patients.

- The use of nomogram may give a quick dosage regimen adjustment for patients with characteristics requiring adjustments such as age, body weight, and physiologic state.

- In general, nomogram of a drug is based on population pharmacokinetic data collected and analyzed using a specific pharmacokinetic model.
In order to keep the dosage regimen calculation simple, complicated equations are often solved and their results displayed diagrammatically on special scaled axes to produce a simple dose recommendation based on patient information.

Some nomograms make use of certain physiologic parameters, such as serum creatinine concentration, to help modify the dosage regimen according to renal function.

For many marketed drugs, the manufacturer provides tabulated general guidelines for use in establishing a dosage regimen for patients, including loading and maintenance doses.
NOMOGRAMS AND TABULATIONS IN DESIGNING DOSAGE REGIMENS...

- Examples of drugs for which nomograms are being used for designing dosage regimen:
  - Digoxin
  - Warfarin
  - Heparin
  - Vancomycin
  - Tacrolimus
  - Phenytoin
  - Clozapine