Unit –V

APPLICATIONS OF PHARMACOKINETICS

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CONTENTS

INTRODUCTION

- Drug research encompasses several diverse disciplines united by a common goal, namely the development of novel therapeutic agents.
- The search for new drugs can be divided functionally into two stages: discovery and development.
- The former consists of setting up a working hypothesis of the target enzyme or receptor for a particular disease, establishing suitable models (or surrogate markers) to test biological activities, and screening the new drug molecules for in vitro and/or in vivo biological activities.
- In the development stage, efforts are focused on evaluation of the toxicity and efficacy of new drug candidates.

PHARMACOKINETICS

- Study and characterization of the time course of drug absorption, distribution, metabolism and excretion, and relationship of these processes to the intensity and time course of therapeutic and toxicology effects of drug.

- It describes the process where by a specific mode and by a specific dose is handled by the body, leading to the specific drug concentrations in different tissues/organs.

- Part of drug will reach the site(s) of action and exerts its pharmaco dynamic action.

- Another way it can be said as what body does to drug.

  Pharmacokinetics is used in the clinical setting to enhance safe and effective therapeutic management of the individual patient. This application is termed as Clinical pharmacokinetics.

PRINCIPLES:

- Design and development of new drugs for improving therapeutic effectiveness.
- Design and development of an optimum formulation for better use of the drug.
- Design and development of controlled/targeted release formulation.
- Select the appropriate route for drug administration.
- Select the right drug for a particular illness.

- Predict and explain drug-food and drug-drug interactions.
- Design an appropriate multiple dosage regimen.
- Therapeutic drug monitoring in individual patients.
- Dosage adjustments in situations of altered physiology and drug interactions.

APPLICATIONS OF PHARMACOKINETICS

- Drug Development
- Formulation Development
- Deciding Dosage Regimen
- Designing Rational Dose, Frequency and Duration
- Rational Drug Design (QSPKR)
- Clinical Pharmacy
- ADME study, Bioavailability and Bioequivalence studies
- *In Vitro –In Vivo* correlation studies
- Pharmacokinetics, Pharmacodynamics Relationship

PHARMACOKINETIC PARAMETERS

- Overall first order elimination rate constant(K)
- Half life($t_{1/2}$)
- Clearance (Total. Renal, Hepatic etc.(Cl)
- Effective concentration range
- Absorption rate constant(K_a)
- Extent of bioavailability(F)
- Fraction of dose excreted unchanged in urine ($X_{u\,\alpha}$)
- Blood -Plasma concentration ratio
- Apparent volume of distribution (V_d)
- Fraction of protein binding(F_b)
- Peak concentration(C_p)
- Time to reach peak concentration(t_p)
- Toxic concentrations

APPROACHES FOR DESIGN OF SAFER DRUGS

- From toxicological and pharmacological points of view, it is desirable to design a "safer" drug that undergoes no metabolism.
- Hard drugs: The concept of nonmetabolisable drugs called hard drugs. Drugs are excreted primarily through either bile or kidney.

  Eg: Bisphosphonates, enalaprilat, lisinopril

- Soft drugs: It is pharmacologically active, it undergoes a predictable and controllable metabolism to nontoxic and inactive metabolites.
  - The main concept is to avoid oxidative metabolism as much as possible and to use hydrolytic enzymes to achieve predictable and controllable drug metabolism. Eg: Atracurium, Remifentanil etc.

- Active metabolites: The metabolites of some drugs are pharmacologically active being used as a source of new drug candidates. Eg: Acetaminophen which is an O-deethylated metabolite of Phenacetin.

ADME CHARACTERS

- **Absorption:** It is a process in which the unchanged proceeds from site of administration to the site of measurement with in the body.

  Eg Bisphosphonates
- **Distribution:** The transfer of drug from blood to the extravascular fluids (i.e extracellular and intra cellular water) and tissues. It is a rapid and reversible process.
- **Metabolism:** it is the biochemical conversion of drug into another chemical form.
- **Elimination:** It is the irreversible loss of drug from the site of measurement.
- **Excretion:** It is the irreversible loss of chemically unchanged drug by various routes. This can occur through urine, biliary secretion, saliva. sweat, milk, respiratory route.

PHARMACOKINETIC CHARACTERIZATION OF THE DRUG FOR SELECTION OF SUITABLE DELIVERY SYSTEMS

- Compartment model
- Elimination rate constant and terminal half life ($t_{1/2}$)
- Area under the concentration-time curve (AUC)
- Total clearance (Cl_T)
- Apparent volume of distribution (V_d)
- Mean steady state concentration (C_{SS})
- Mean residence time
- First-pass effect
- Intrinsic absorption rate constant
- Relative areas
- Dosage form index

DESIGN OF CONTROLLED RELEASE FORMULATION

- C_T is the target concentration to be maintained for T hour.

- Rate of elimination = $K.C_T.V_d$ or $\frac{0.693}{t_{1/2}} C_T.V_d$

- Where K is the eliminnation rate constant of the drug.
- V is the apparent volume of distribution.

- Rate of absorption, $K_a X_a$ should be equal to the rate of elimination to maintain constant concentration. So ,

$$K_a X_a = K. C_T V_d$$

- Then rate of release should be equal to the rate of absorption and rate of elimination. So,

$$\text{Rate of release, } K_r = K. C_T V_d$$

So,

Maintainence dose = rate of release x duration to be maintained

$$= K.\ C_T\ V_d\ T$$

$$t_{max} = \frac{2.303}{K - K_a} \text{Log} \frac{K_a}{K}$$

Where K_a is absorption rate constant

$$\text{Loading dose} = \frac{C_T\ V_d\ e^{-Ktmax}}{F}$$

- Where F is bioavailability (fraction)
- Above is on the basis that drug confers one compartment distribution

- Equation to express plasma concentration of controlled release product administered

$$C = \frac{K_0 (e^{-KT} - 1) e^{-Kt}}{K V_d}$$

- Where K_0 is zero order release rate
- 'T' is time of total release
- 't' is anytime at which concentration is measured
- 't' can be less than or equal or more than 'T'

APPLICATIONS OF PHARMACOKINETICS IN NDDS

- To understand the process of absorption, distribution, elimination of drug, which affects onset and intensity of biological response.
- To access plasma drug concentration response to given dose which is considered as more appropriate parameter than intrinsic pharmacological activity.
- In design and utilization of *In-vitro* model that can evaluate dissolution characteristics of new compound formulated as new drug formulations and establish meaningful IVIVC.
- In design and development of new drug and their appropriate dosage regimen.
- In safe and effective management of patients by improving drug therapy.

- To understand the concept of bioavailability which has been used to evaluate and monitor *in vivo* performance of new dosage forms and generic formulations.
- To carry out the bioavailability and bioequivalence tests.
- We can use the pharmacokinetic principles in the development of the various NDDS.

Eg: The drug with short half life about 2-6 hrs can be formulated as controlled release drugs by using polymers.

The lower bioavailability of the drugs can be increased by using several components like ß-cyclodextrin.

- List of drug carriers in NDDS:

Nanosomes, Liposomes, Niosomes, Proniosomes, Vesicular drug delivery system, Cubisomes, Aquasomes, Pharmacosomes, Miscelles, Nanoparticles, Nanosphere, Microsphere, Microparticle, Dendrimer, Microemulsion, Transferosomes, Nanosuspension, Dendrosomes etc.

DESIGN OF DOSAGE REGIMENS

- Dosage regimen is defined as the manner in which a drug is taken.

- An optimal multiple dosage regimen is the one in which the drug is administered in suitable doses (by a suitable route), with sufficient frequency that ensures maintenance of plasma concentration within the therapeutic window(without excessive fluctuations and drug accumulation) for the entire duration of therapy.

APPROACHES TO DESIGN OF DOSAGE REGIMEN

1. **Empirical Dosage Regimen:** It is designed by physician based on empirical clinical data, personal experience and clinical observations.

2. **Individualised Dosage Regimen:** it is based on the pharmacokinetics of drug in the individual patient.

   Suitable for hospitalised patients.

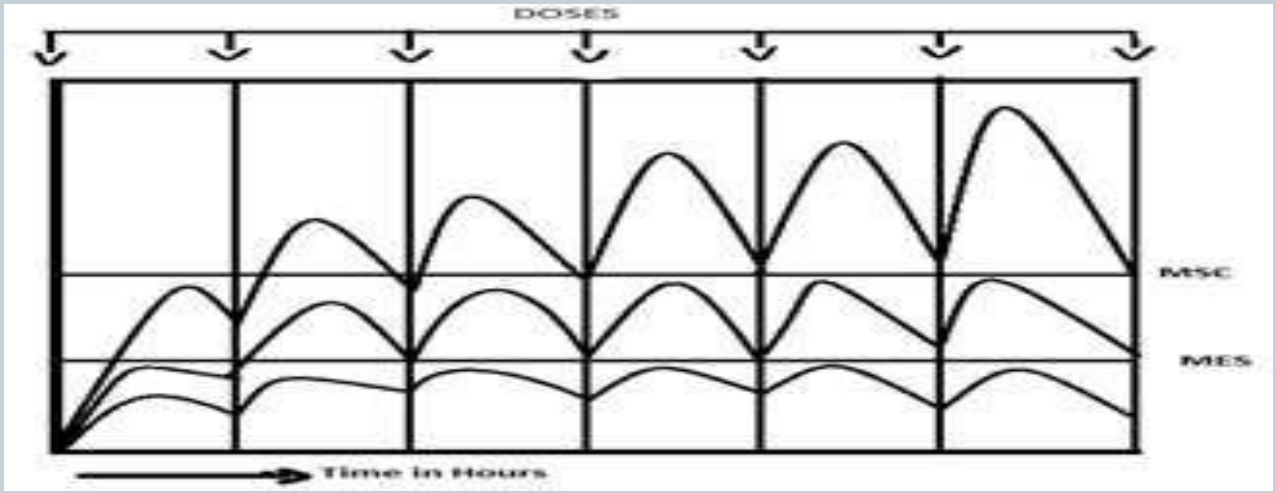
3. **Dosage Regimen on population Averages:** It is based on one of the two models-

i) Fixed model: Population average pharmacokinetic parameters are used directly to calculate the dosage regimen.

ii) Adaptive model: Based on both population average pharmacokinetic parameters of the drug as well as patient variables such as weight,

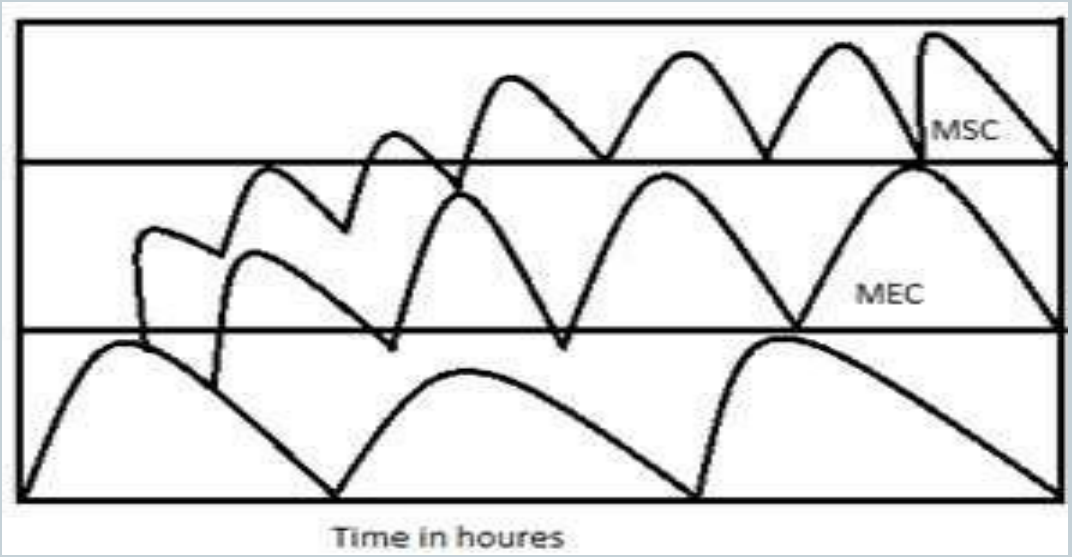
DOSE SIZE:

- The magnitude of both therapeutic and toxic responses depends on dose size.
- Dose size calculation also requires 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,greater chances of toxicity.



DOSING FREQUENCY:

- The dosing 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, Cmax, Cmin & Cav decrease but the ratio Cmax/Cmin increases.
- Opposite is observed when dosing interval is reduced or dosing frequency increased.



MONITORING DRUG THERAPY

- Depending upon the drug and the disease to be treated, management of drug therapy in individual patient can be accomplished by:

- Monitoring therapeutic effect-therapeutic monitoring

- Monitoring pharmacologic actions- pharmacodynamic monitoring .

- Monitoring plasma drug concentration - pharmacokinetic monitoring.

PHARMACOKINETICS OF DRUG INTERACTIONS

- **Bioavailability**

  Complexation / chelation: Calcium, magnesium, or aluminum and iron salts with tetracycline complexes with divalent cations, causing a decreased bioavailability.\

- **Distribution**

  Protein binding of Warfarin – phenylbutazone leads to displacement of warfarin from binding.

INDIVIDUALIZATION OF DRUG DOSAGE REGIMENS:

- **Therapeutic Drug Monitoring:**

In administering potent drugs to patients, the physician must maintain the plasma drug level within a narrow range of therapeutic concentrations.

The functions of a TDM service are listed below:

- Select drug.
- Design dosage regimen.
- Evaluate patient response.
- Determine need for measuring serum drug concentrations.
- Assay for drug concentration in biological fluids.
- Perform pharmacokinetic evaluation of drug concentrations.
- Readjust dosage regimen, if necessary.
- Monitor serum drug concentrations.

Drug Selection:

- The choice of drug and drug therapy is usually made by the physician.
- Pharmacokinetics and pharmacodynamics are part of the overall considerations in the selection of a drug for inclusion into the drug formulary (DF).
- Drugs with similar therapeutic indications may differ in dose and pharmacokinetics.

Dosage Regimen Design:

- The overall objective of dosage regimen design is to achieve a *target* drug concentration at the receptor site.
- The usual pharmacokinetics of the drug—including its absorption, distribution, and elimination profile—are considered in the patient.
- Pathophysiologic conditions, such as renal dysfunction, hepatic disease, or congestive heart failure, may change the normal pharmacokinetic profile of the drug, and the dose must be carefully adjusted.

- **Drug Dosage Form (Drug Product):**
  - Affect drug bioavailability.
  - The rate of absorption.
  - The route of drug administration and the desired onset will affect the choice of drug dosage form.
- **Patient Compliance:**
  - Cost of the medication.
  - Complicated instructions.
  - Multiple daily doses.
  - Difficulty in swallowing.
  - Adverse drug reactions.
- **Evaluation of Patient's Response:**
  - Practitioner should evaluate the patient's response clinically.
  - If the patient is not responding to drug therapy as expected, then the drug and dosage regimen should be reviewed.

Measurement of Serum Drug Concentrations:

- A major assumption made by the practitioner is that serum drug concentrations relate to the therapeutic and/or toxic effects of the drug.

- A single blood sample gives insufficient information. Several blood samples are often needed to clarify the adequacy of the dosage regimen.

- The pharmacokineticist should be aware of the usual therapeutic range of serum concentrations from the literature.

Dosage Adjustment:

- The new dosage regimen should be calculated using the pharmacokinetic parameters derived from the *patient's* serum drug concentrations.

DOSING OF DRUG IN OBESE PATIENTS

- Ideal body weight (IBW) is calculated as follows:

IBW $_{Men}$= 50 kg ± 1 kg /2.5 cm above or below 150cm in height … [1]

IBW $_{Women}$= 45 kg ± 1 kg/2.5 cm above or below 150cm in height…[2]

Any person is considered as obese if the body weight is more than 25% above the IBW.

DOSAGE CALCULATION IN NEONATES INFANTS AND CHILDREN:

- Formula:
  - Young's rule (For children 2 years and above): $\left(\frac{\text{Age (yr)}}{\text{Age (yr)}+12}\right) \times$ adult dose
  - Clark's rule: $\left(\frac{\text{Weight (lb)}}{150}\right) \times$ Adult dose
  - Fried's rule (For infants upto 2 years old): $\left(\frac{\text{Age (month)}}{150}\right) \times$ adult dose
  - Square meter surface area OR Mosteller's equation: $\text{SA in } m^2 = \sqrt{\frac{\text{height} \times \text{weight}}{60}}$

- The child's maintenance dose can be calculated from adult dose by using 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 average 70 Kg adult .

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

$$\text{SA (in } m^2\text{)} = \text{Body weight (in Kg)}^{0.7}$$

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

$$\text{Child's Dose} = \left[\frac{\text{Weight of child in Kg}}{70}\right]^{0.7} \times \text{Adult dose}$$

DOSING OF DRUG IN ELDERLY

- A general equation that allows calculation of maintenance dose for a patient of any age (except neonates and infants) when maintenance of same $C_{ss,av}$ is desired is :

- Patient's Dose :

$$= \frac{(\text{weight in Kg})^{0.7}\ (140 - \text{Age in years})}{1660} \times \text{Adult dose}$$

DOSING OF DRUG IN HEPATIC DISEASE

- The influence of hepatic disorder on drug availability and disposition in unpredictable as of the multiple effect that liver disease produce effects on the drug metabolizing enzyme, binding and hepatic blood flow.

DOSING OF DRUGS IN RENAL DISEASE

Dose adjustment based on total body clearance :

The parameters to be adjusted in renal Insufficiency are shown below:

$$C_{ss,av} = F \times \frac{1}{Cl_T} \times \frac{(X_0)}{\tau}$$

To be kept Normal	assumed constant	decrease due to disease	needs adjustment

CONCLUSION

- It is very important to have complete knowledge of pharmacokinetic characters of drug and factors effecting them for designing an effective and useful drug delivery systems.
- Pharmacokinetic study is also important to identify variables that are important in determining the potential success of drug delivery systems
- It can be used to evaluate the products or delivery systems.
- Selection/design of proper experimental protocol is very important. Suitable analytical method is necessary for proper estimation.
- Iv-Iv correlation and PK /PD relationship are useful for better design.

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Thank
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