# UNIT:1– INTRODUCTION TO CLINICAL PHARMACOKINETICS

## SHORT ANSWERS:

### 1) Give the importance of clinical pharmacokinetics ?

Clinical Pharmacokinetics can be defined as the study of the relationship between drug dosage regimens and the concentration time profiles. There are three basic parameters that govern these relationships. They are:

● Clearance i.e. the volume of the fluid that is cleared out completely from the drug per unit time

● Distribution volume i.e. the apparent volume in which the drug has been distributed to make the measured concentration

● Elimination half-life i.e. the time that is required for 50 percent of the drug to be completely eradicated.

The knowledge of distribution volume is helpful in estimating a loading dose in order to quickly attain a target concentration. On the other hand the knowledge of clearance can be helpful in calculating the dose rate needed to retain a target concentration. Furthermore, elimination half-time helps in determining the time needed for a drug to completely blend and eliminate from the body. It also indicates the time taken to attain a steady state and can be further used to gauge the optimum dosage interval for producing the target peak to channel the difference

### 2)Define apparent volume of distribution and give the mathematical equation to calculate this parameter?

- The Volume of distribution (VD), also known as Apparent volume of distribution, is used to quantify the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing.
- It is called as Apparent Volume because all parts of the body equilibrated with the drug do not have equal concentration.
  Vd = dose of the drug given (Q)/ concentration of drug in plasma (Cp)

### 3)Define non-linear pharmacokinetics?

It is also known as capacity-limited, dose-dependent, or saturation pharmacokinetics. At lower dose, drug shows first order kinetics but at higher dose, it shows zero order due to saturation, so it is also known as Mixed Order Kinetics. Nonlinear pharmacokinetics do not follow first-order kinetics as the dose increases. Nonlinear pharmacokinetics may result from the saturation of an enzyme- or carrier-mediated system.

**4) Describe the difference between first and zero order elimination and how each order appears graphically**.

First order elimination kinetics: a constant proportion (eg- a percentage) of drug is eliminated per unit time.

Zero order elimination kinetics: a constant amount (eg- so many milligrams) of drug is eliminated per unit time.

First order kinetics is a concentration dependent process (i.e. the higher the concentration, the faster the clearance), whereas zero order elimination is independent of concentration.

Non-linear elimination kinetics is the term which describes drug clearance by Michaelis-Menten processes, where a drug at low concentration is cleared by first order kinetics and at high concentrations by zero order kinetics (eg- phenytoin or ethanol)

**5) Define biological half life and give its equation with units.**

Biological half-life also known as elimination half-life, pharmacologic half life of a biological substance such as medication is the time takes from its maximum concentration to half maximum concentration in the human body, and it is denoted by t1/2.

Biological half life:

The biological half life ($t_{1/2}$) is determined using the equation

$t_{1/2} = 0.693/b$

**6) Give the relationship between half-life and elimination rate constant.**

Half-life is the time taken for the drug concentration to fall to one half of its original value whereas the elimination rate constant (k) is the fraction of drug in the body which is removed per unit time.

Generally, a drug will be completely eliminated after 6 half lives

- After 1 half-life the conc. will be 50%
- After 2 half-lives it will be 25%
- After 3 half-lives 12.5%
- After 4 half-lives 6.25%
- After 5 half-lives 3.125%
- After 6 half-lives 1.56%

**7)What is clearance? Give the relationship between the clearance, drug dosage**

- Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process, instead of describing the drug elimination rate in terms of amount of drug removed per unit time (eg- mg/min).
- Drug clearance is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit time and the units for the clearance are volume /time.

If the drug concentration in the blood (Ca) entering is greater than the drug concentration of blood (Cv) leaving the organ, then some of the drug has been extracted by the organ. The ER is Ca-Cv divided by the entering drug concentration (Ca).

ER=Ca-Cv /Ca

**8) Give the assumptions of compartment model.**

- The body is represented as a series of compartment arranged in series or parallel to each other.
- The rate of drug movement between compartment is described by first order kinetics.
- Rate constants are used to represent rate of entry into and exit from compartment.

- A statistical analysis of plasma concentration time data is another method used to find out number of compartments.

**9) Define pharmacokinetics. Name and define three pharmacokinetic parameter that describes typical plasma level time curve.**

Pharmacokinetics refers on how the body acts on the drug and it involves the study of absorption, distribution, metabolism (biotransformation) and drug excretion.

Three important parameters useful in assessing the bioavailability of a drug from its formulation are:

1. **Peak plasma concentration** (cmax) the point at which, maximum concentration of drug in plasma.
   Units: µg/ml
   • Peak conc. Related to the intensity of pharmacological response, it should be above MEC but less than MSC.
   • The peak level depends on administered dose and rate of absorption and elimination.
2. **Time of peak concentration** (tmax) the time for the drug to reach peak concentration in plasma (after extra vascular administration).
   Units: hrs
   • Useful in estimating onset of action and rate of absorption.
   • Important in assessing the efficacy of single dose drugs used to treat acute conditions (pain, insomnia).
3. **Area under curve (AUC)**It represents the total integrated area under the plasma level-time profile and expresses the total amount of the drug that comes into systemic circulation after its administration.
   Units: µg/ml x hrs
   • Represents extent of absorption – evaluating the bioavailability of drug from its dosage form.
   • Important for drugs administered repetitively for treatment of chronic conditions (asthma or epilepsy).

**10) Define loading dose and maintenance dose. Give equation to calculate the same**.

Loading dose- For drugs with long half-lives, the time to reach steady state might be long. It takes about 5 half- lives to reach steady state. In a such cases the plateau can be achieved by administering a dose that gives the desired steady-state. Such an initial/ first dose is called as Loading dose.

$X_{o,L} = C_{ss,av} * V_d / F$

Maintenance dose- After the loading dose is given another dose (I.V) is given to maintain the steady- state drug conc. Or plateau. Such dose is known as maintenance dose i.e., maintain the response of drug by replacing drug lost during dosing interval.

Maintenance dose = loading dose x $(1- e^{-k\tau})$

**11) Give any four applications of clinical pharmacokinetics.**

- Design and development of targeted and controlled release formulation
- Design of multiple dosage regimen
- Selection of appropriate route of administration
- Select of right drug for particular illness
- Predict interactions
- TDM

5 marks

**13) Explain the process and clinical significance of conversion from intravenous to oral dosing.**

- The ideal route of administration for any medication is one that achieves serum concentrations sufficient to produce the desired effect without producing undesired effects.
- In the past, patients were switched to oral (PO) therapy to continue treatment after an already adequate course of intravenous (IV) therapy was administered
- Today, it is not uncommon to convert a patient to PO therapy as part of the initial treatment course.
- The available oral formulations on the market are easier to administer, safe, and achieve desired therapeutic concentrations, thus making the PO route an ideal choice.
- Patients are more comfortable if they do not have an IV catheter in place.

- Attachment to an IV pole can restrict movement, which can hinder early and/or frequent ambulation.
- Patients who continue to receive parenteral therapy are at an increased risk for infusion-related adverse events.
- In addition, the presence of an IV catheter provides a portal for bacterial and fungal growth.
- These secondary infections can lead to additional antibiotic therapy, prosthesis failures, sepsis, and in a small number of cases, death.
- Using PO therapy also reduces hidden expenses such as the cost of IV sets and pumps, laboratory monitoring, and nursing and pharmacy personnel time.
- Most significantly, early use of PO therapy may allow for earlier discharge from the hospital.

**TYPES OF IV TO PO THERAPY CONVERSIONS**

There are three types of IV to PO therapy conversions

1. Sequential Therapy
2. Switch Therapy
3. Step-down Therapy

**Sequential Therapy:** Refers to the act of replacing a parenteral version of a medication with its oral counterpart ¬ An example is the conversion of famotidine 20 mg IV to famotidine 20 mg PO ¬ There are many classes of medications that have oral dosage forms that are therapeutically equivalent to the parenteral form of the same medication.

**Switch Therapy**: Used to describe a conversion from an IV medication to the PO equivalent that may be within the same class and have the level of potency, but is a different compound. An example is the conversion of IV pantoprazole to rapidly dissolving lansoprazole tablets or omeprazole capsules.

**Step-down Therapy**: Refers to converting from an injectable medication to an oral agent in another class or to a different medication within the same class where the frequency, dose, and the spectrum of activity (in the case of antibiotics) may not be exactly the same. Converting from ampicillin 3 g IV q 6 hr to amoxicillin 875 mg PO q 12 hr is an example of step-down therapy. Proper identification of patients, diagnoses, medications, and contraindications to oral therapy are all essential aspects for a successful IV to PO therapy conversion program. It is very important that the pharmacist conduct a thorough and complete review of these areas so only the most appropriate

patients are converted. Doing so is a benefit to both patient care and professional credibility

The criteria used to determine whether or not the patient is eligible for PO therapy vary from hospital to hospital, but they generally encompass four key areas:

- Intact and functioning gastrointestinal (GI) tract
- Improving clinical status
- Does not meet any exclusion criteria
- Others

**46. What is the BEER's criteria for drugs to be used in geriatric patients?**

- The criteria are used in geriatrics clinical care to monitor and improve the quality of care.
- They are also used in training, research, and healthcare policy to assist in developing performance measures and document outcomes.
- These criteria include lists of medications in which the potential risks may be greater than the potential benefits for people 65 and older.
- By considering this information, practitioners may be able to reduce harmful side effects caused by such medications.
- The Beers Criteria are intended to serve as a guide for clinicians and not as a substitute for professional judgment in prescribing decisions.
- The criteria may be used in conjunction with other information to guide clinicians about safe prescribing in older adults.

# CHAPTER-1 DESIGN OF DOSAGE REGIMEN

**Q.12 (10M) Explain the various factors considered in the** design of dosage regimen for geriatric and obese patients

- ❖ The geriatric population is often arbitarily defined as patients who are older than 65years and many of these people live active and healthy lives.
- ❖ In addition there is an increasing number of people who are living more than 85 years ,who are often considered as the older elderly population.
- ❖ The aging process is more often associated with physiological changes during aging rather than purely chronological age.

Chronologically , the elderly have been classified as;

1. YOUNG OLD (age 65-75yrs)
2. THE OLD(75-8 yrs)
3. The OLD-OLD(age above 85 yrs)

- ❖ Performance capacity and the loss of homeostatic reserve decreases with advanced age but occurs to a different degree in each organ in each patient.
- ❖ Physiologic and cognitive functions tend to change with the aging process and can affect compliance and the therapeutic safety and efficacy of a prescribed drug .
- ❖ The elderly also tend to be on multiple drug therapy due to concomitant illness.

Decreased cognitive function due to:

- Complicated drug dosage schedules.
- High cost of drug therapy .

- ❖ Several vital physiologic functions related to age as measured by markers. Shows that renal plasma flow, glomerular filtration, cardiac output and breathing capacity can drop from 10% to 30% in elderly subjects compared to those at age 30.

- ❖ The physiologic changes due to aging may necessitate special considerations in administering drugs in the elderly which is due to an age dependent increase in adverse drug reactions or toxicity may be observed.
- ❖ This apparent increased drug sensitivity in the elderly may due to pharmacokinetic and pharmacodynamic changes.
- ❖ The pharmacodynamics hypothesis assumes that age causes alteration in the quantity and quality of target drug receptors leading to enhanced drug response.
- ❖ Quantitatively, the number of drug receptors may decline with age, whereas quantitatively, a change in the affinity for the drug may occur.
- ❖ The pharmacokinetic hypothesis assumes that age dependent increase in adverse drug reactions are due to physiologic changes in drug ADME .
- ❖ Age dependent alterations in DRUG ABSORPTION may include:
  - Decline in the splanchnic blood flow.
  - Altered gastrointestinal motility.
  - Increase in gastric PH .
  - Alteration in the gastrointestinal absorptive surface.
- ❖ Age dependent alterations in DRUG DISTRIBUTION may include:
  - Decreased drug protein binding in the plasma as a result of decrease in the albumin concentration.
  - Change in the apparent volume of distribution due to decrease in the muscle mass and increase in body fat.
  - Renal drug excreation may generally declines with age as a result of decrease in GFR and active tubular secreation.
  - The activity of enzymes responsible for drug biotransformation may decrease with age , leading to decline in hepatic -drug clearance.

Patient's dose= (weight in Kg) 0.7x (140- age in years)

_____ xadult dose

1660

<u>DOSING IN OBESE PATIENTS:</u>

- ❖ Obesity is a major problem in the united states and is also becoming a problem in other countries.

- ❖ Obesity has been associated with increased mortality resulting from increase in the incidence of hypertension, atherosclerosis, coronary artery disease, diabetes and other conditions compared to non obese patients.
- ❖ A patient is considered obese if actual body weight exceeds ideal or desirable body weight by 20% according to metropolitan life insurance data.
- ❖ Ideal or desirable body weights are based on average body weights and hights for males and females considering age.
- ❖ Athlets who have greater body weight due to greater muscle mass are not considered obese.
- ❖ Obesity often defined by BODY MASS INDEX(BMI), a value that normalizes body weight based on height.
- ❖ BMI is expressed as body weight (kg) divided by the square of the person's height (meters)or $Kg/^{m2}$

$$BMI = \frac{\text{weight in pounds}}{(\text{Height in inches})\text{x (height in meters)}} \text{x703}$$

$$BMI = \frac{\text{weight in kg}}{(\text{height in meters})\text{x (height in meters)}}$$

- The obese patient (BMI>30) has greater accumulation of fat tissue than is necessary for normal body functions.
- Adipose(fat) tissue has a smaller proportion of water compared to muscle tissue. Thus the obese patient has a smaller proportion of total body water compared to the patient of ideal body weight , which can affect the apparent volume of distribution of the drug.
- In addition to differences in the total body water per kilogram body weight in the obese patients, the greater proportion of body fat in these patients could lead to distributional changes in the drug's pharmacokinetics due to partitioning of the drug b/w lipid and aqueous environments.
- Drugs such as digoxin and gentamicin are very polar and tend to distribute into water rather than into fat tissue , although lipophilic drugs associated with larger volumes of distribution in obese patients compared to hydrophilic drugs.

- Other pharmacokinetic parameters may be altered in the obese patients as a result of physiologic alterations such as fatty infiltration of the liver affecting biotransformation and cardiovascular changes that may affect renal blood flow and renal excretion.
- Dosing by actual body weight may result in overdosing of drugs such as aminoglycosides, ( eg: gentamicin), which are very polar and are distributed in extracellular fluids. dosing of these drugs are based on ideal body weight.
- Lean body weight has been estimated by several empirical equations based on the patient's height and actual (total body weight).
- The following equations have been used for estimating lean body weight ,particularly for adjustment of dosage in renally impaired patients.

Lean body weight (LBW)-males =50kg +2.3kg each inch over

5ft

LBW= 45.5 kg +2.3kg for each inch over 5ft.

EXAMPLE:

Calculate the lean body weight for an adult male patient who is 5ft 9 in (175.3cm) tall and weight 264lb (120kg).

Solution:

LBW:50+(2.3x9)=70.7kg.

**Q .NO 14(5m)**

**What are nomograms? Explain their applications in pharmacokinetic studies with examples. give their advantages and disadvantages.**

- A nomogram is a graphical calculating device. a two dimentional diagram designed to allow the approximate graphical computation of a function.
- A nomogram typically has 3 scales:
- 2 scales represent known values and one scale is the where the result read off

- The scales may be linear , logerithamic and have some more complex relationship.
- 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 adjustments for patients with characteristics requiring adjustments such as age, body weight and physiological state.
- In general, the 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 the result 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 concentrations to help modify the dosage regimen according to renal function

APPLICATIONS OF NOMOGRAMS:

- Quick dosing regimen adjustments for patients
- Calculating proper dosage regimen for individualized patients
- Quick dosage regimen adjustment for patients requiring dosage adjustment
- Make simple dose recommendations based on patient information
- Modify dosage regimen according to renal function through use of certain parameters

ADVANTAGES:

- The advantage of nomogram is that it can be easily mass produced, distributed and evaluated while providing the some information as the logistic regression it represent.
- Nomograms are typically used in applications where the level of accuracy they offer is sufficient and useful.
- Provides risk estimation on 0 to 100% scale which is easier to understand and operation
- Validated in large patient population and are highly generalized.
- Provide most objectives evidence based individualized risk estimation.
- Empower patients and allow them to better understand diseases.
- Assist physicians with difficult clinical decision making and provide consistant and reliable predictions.

- Calculate proper dosage regimen for individual patients.
- Quick dosage regimen for patients with required adjustment.
- Make simple dose recommendation based on patient information.
- Modify dosage regimen according to renal function through use of certain parameters of creatinie clearanc

DISADVANTAGES:

- Scale is always a limitation regarding frequency reduction- it does not provide an accurate reduction ranking.
- Cumulative issues and evaluations are difficult to show in a transparent manner.
- There can be a strong tendency to try and provide a greater level of accuracy than what is capable.
- It's accuracy is limited to how well one can read the scales some scales run down rather up which can easily lead to pilot error
- Nomograms don't provide significant digits result as electronic devices.
- Graphical calculating devices-graph 3 coplanar curves each graduated 4 different variable cutting there intersect related values of each variable.

## Q.15 (5m) Explain in detail the determination of dose and dosing interval of a drug

DETERMINATION OF DOSE:

- Drug dose is estimated to deliver a desirable therapeutic level of drug to the body.
- Dose of a drug is estimated with the objective of delivering a designate therapeutic level of drug in body
- For many drugs desirable therapeutic drug levels and pharmacokinetic parameters are available in some cases may not yield complete drug information or information available may be poorly
- For a drug that is given in multiple doses for an extended period of time, the dosage regimens calculated so that average steady state blood level is within therapeutic range.
- Doses can be calculated which express $C_{av,}$ in terms of dose(Do) dosing interval (T), volume of distribution ($v_d$) and elimination half life of drug ($t_{1/2}$).
- F is the fraction of drug absorbed and is equal to 1 for drug administered IV

- DOSE=dosing route x dosing interval

$$C_{av}^{\infty} = \frac{1.44 D_O T_{1/2} F}{V_0 I}$$

DOSING INTERVAL:

- It is the frequency of intermitent during administration based on drug half life.
- If the dosing interval is increased and dose is unchanged $c_{max}$ $C_{MIN}$ and $c_{av}$ decreases but ratio $c_{max}/c_{min}$ increases.
- Opposite is observed when DI is decreased or dosing frequency increased.
- It also results in greater drug accumulation in body and toxicity.
- The proper balance between both dose and dose interval and dosing frequency is often desired to attain steady state concentration with minimum fluctuation and to ensure therapeutic efficacy and safety.

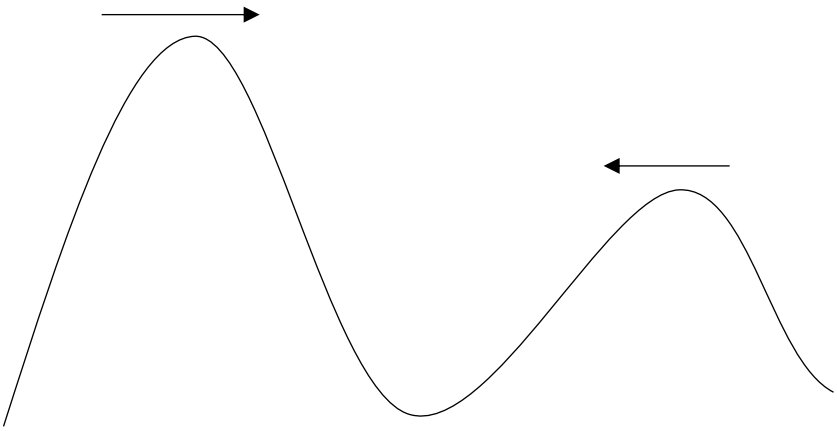
**16.Describe the principle of superposition and how it applies to multiple drug dosing?**

Ans. The principle of superposition states that when 2 or more waves of the same type cross at some point; the resultant displacement at that point is equal to the sum of the displacement due to each individual wave.

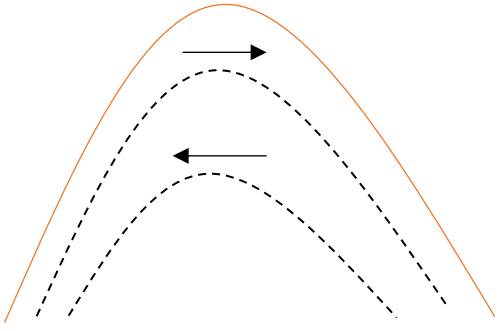
The principle of superposition can be used when all the PK processes are linear.

**Basic Assumptions:**

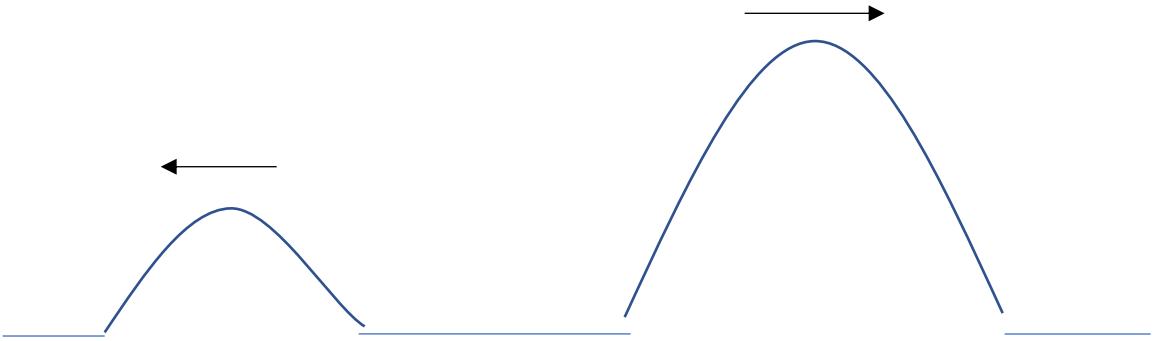
- That the drug is eliminated by first-order kinetics
- That the pharmacokinetics of the drug after a single dose, are not altered after taking multiple doses.



Before Superimposition



Superimposition



After superimposition

**In Multiple dosage regimen**

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.

To calculate multiple dose regimen. It is necessary to decide whether successive dose of the drug will have any effect on the previous dose.

The principle of superposition assumes that early doses of drug do not affect the peak of the subsequent doses therefore the blood levels after second ,third on nth dose will overlay or superimpose the blood level.

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**17. Explain the role of nomograms and tabulation in the design of dosage regimen.**

Ans: Pharmaceutical manufacturers provide dosage recommendation in the approved label for many marketed drugs in the form of a table or as a nomogram.

- **Nomogram** is a graph having 3 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, ie the result is in the centre.Each known value of the calculation is marked on the outer scale and a line is

drawn between each mark, where the line and inside scales intersects is the result.

Ex: height- BMI- weight ,Total clearance -maintenance dose-lean body weight

**Application:**

1.For ease of calculation of dosage regimen many clinicians depend on nomograms to calculate the proper dosage regimen for their patients.

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

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

**Advantages**

1.Help in risk estimation

2.Help in better understanding of the disease

3.Assist clinicians in decision making

**Disadvantages**

1.Accuracy are limited

2.Doesnt provide significant digit for result like electronic device.

**Tabulation**

For many marketed drugs,the manufacturer provides tabulated general guidelines for use in establishing a dosage regimen for patients, including loading and maintenance doses.

For drugs with a narrow therapeutic range such as theophylline, a guide for monitoring serum drug concentration is given .

Another example is aminoglycoside antibiotic tobramycin sulfate which is eliminated primarily by renal clearance. Thus the dosage of tobramycin sulfate should be reduced in creatinine clearance.

**18. Explain the different methods of conversion intravenous to per oral dosing.**

Ans: **Introduction:**

The ideal route of administration of any medication is one that achieves serum concentrations sufficient to produce the desired effect without producing undesired effects.

In the past, patients were switched to oral (PO) therapy to continue treatment after an adequate course of therapeutic concentrations, thus making the PO route an ideal choice

Patients are more comfortable if they do not have an IV catheter in place. Attachment to IV pole can restrict movement which can hinder early and frequent ambulation. Patients who continuously receive IV treatment are at a increased risk of infusion related adverse events.

Using PO therapy reduces the expenses such as the cost cost of IV sets and pumps.

**Types of IV to PO therapy**

There are 3 types :

1.Sequential therapy:

2.Switch therapy

3.Step down load

1.**Sequential therapy**:

It refers to the act of replacing the parenteral version of the medication to oral counterpart.

Eg: conversion of Famotidine 20 mg IV to famotidine 20mg PO

2.**Switch therapy:**

It refers to the conversion from IV medication PO equivalent that maybe within the same class and have the level of potency, but is a different compound.

Eg: Conversion of IV Pantoprazole to rapidly dissolving Lansoprazole tablets or Omeprazole.

3. **Step down therapy:**

It refers to converting from an IV medication to an PO medication in another class or to a different medication of the same class where the frequency,dose and the spectrum of activity( in the case of antibiotics) may not be the same.

Eg: Converting from ampicillin sulbactum 3g IV 6hr to amoxicillin clavunate 875 mg PO 12 hr.

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**42. Mention any 4 factors considered in dosing paediatric patients.**

1. Total body water

2.Age based dosing

3. Body weight based

4.Physiology based pK

1) **Explain various factors considered in designing the Dosage regimen for Geriatric patients?**

## Dosage In elderly patient.

The geriatric population is often arbitrarily defined as patients who are older than 65 years and many of these people live active and healthy lives

*In addition, there is an increasing number of people who are living more than 85 years, who are often considered as the older elderly population.

The aging process is more often associated with physiological changes during aging rather than purely chronological age.

*Chronologically , the elderly have been classified as:

1. Young old (ages 65 – 75 years)

2. The old (ages 75 – 85 years)

3. The old-old (age above 85 years)

*Performance capacity and the loss of homeostatic reserve decreases with advanced age but occurs to a different degree in each organ and in each patient.

*physiologic and cognitive functions tent to change with the aging process and can affect compliance and the therapeutic safety and efficacy of a prescribed drug.

* The elderly also tend to be on multiple drug therapy due to concomitant illness.

*Decreased cognitive function

*Complicated drug dosage schedules

*High cost of drug therapy several vital physiologic functions related to age as measured by markers show that renal plasma flow, glomerular filtration, cardiac output and breathing capacity can drop from 10% to 30% in elderly subjects compared to those at age 30.

*The physiologic changes due to aging may necessitate special considerations in administering drugs in the elderly which is due to an age dependent increase in adverse drug reactions or toxicity may be observed.

*This apparent increased drug sensitivity in the elderly may be due to pharmacodynamic and pharmacokinetic changes.

*The pharmacodynamic hypothesis assumes that age causes alterations in the quantity and quality of target drug receptors leading to enhanced drug response.

*Quantitatively, the number of drug receptors may decline with age, where as qualitatively, a change in the affinity for the drug may occur.

*The pharmacokinetic hypothesis assumes that age dependent increase in adverse drug reactions are due to physiologic changes in drug ADME.

- Age dependent alterations in drug absorption may include.

- Decline in the Splanchnic blood flow

- Altered gastrointestinal motility

- Increase in gastric PH

- Alteration in the gastrointestinal absorptive surface.

Age dependent alterations in drug distribution may include.

*Decreased drug protein binding in the plasma as a result of decrease in the albumin concentration.

*Change in the apparent volume of distribution due to decrease in muscle mass and increase in body fat.

*Renal drug excretion also generally declines with age as a result of decrease in GFR and active tubular secretion.

*The activity of enzymes responsible for drug biotransformation may decrease with age, leading to a decline in hepatic drug clearance.

Patients = $\frac{\text{(weight,kg) } 0.7\text{x(140-age,year)} \times \text{ adult dose}}{\text{Dose} \qquad 1660}$

**2)Explain the factors considered in the design of dosage regimen for pediatric patients. Give any 2 formulae for the calculations of child Dose**.

*Dosing of drugs in this population requires a thorough consideration of the differences in the pharmacokinetics and pharmacology of a specific drug.

* Unfortunately the pharmacokinetic and pharmacodynamic of most drugs are not well known in children under 12 years of age.

* The variation in body composition and the maturity of liver and kidney function are potential sources of differences in pharmacokinetic with respect to age.

* Infants are defined as children 0-2 years of age . However, within this group, special considerations is necessary for Infants less than 4 weeks (1 month ) old because their ability to handle drugs often differs from that of more mature Infants.

* In addition to different dosing requirements of the pediatric population, there is a need to consider the use of pediatric dosage forms that permit more accurate dosing and patient compliance.

* For example, liquid pediatric drug products may come with calibrated dropper or a premeasured teaspoon 5ml for accurate dosing and have a cherry flavor for pediatric patient compliance.

* Pediatric drug formulations may also contain different drug concentration compared to the adult drug formulations.

* In general, complete hepatic function is not attained until the 3rd week of life and oxidative process are fairly well developed in Infants, but there is a deficiency of conjugative enzymes .

* In addition, many drugs exhibit reduced binding to plasma albumin in Infants.

* Newborns only show 30% -50% of the renal activity of adults on the basis activity per unit of body weight and drugs that are heavily dependent on renal excretion will have a sharply Decreased Elimination half life .

For ex , the penicillins are excreted for the most part through the kidney and Elimination half life of such drugs are much reduced in Infants.

* Different methods to calculate the dose of drugs for Infants and children are :

- Based on the age

- Based on the body weight
- Based on the body surface area

*Depending upon whether the dose was calculated for an Infants or a child, the method use the age in year for the child and age in month for the infant

These methods are :

1) Fried's rule : for Infants and children up to 2 years

$$\text{DOSE} = \frac{\text{AGE in months} \times \text{adult dose}}{150}$$

2) YOUNG's rule : for children upto 1 -12 years

$$\text{DOSE} = \frac{\text{AGE in year} \times \text{adult dose}}{\text{Age} + 12}$$

3) CLARK's rule:

$$\text{DOSE} = \frac{\text{WEIGHT in lb} \times \text{adult dose}}{150}$$

4) COWLING's rule :

DOSE = AGE in birthday × adult dose

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24

5) AUGUS BERGER METHOD

CD = AD ×1.5 × (CW+10)

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100

6) CRAWFORD TERRY ROURKE METHOD:

Based on body surface area of Infants and children:

BSA = AD × body surface area of child

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1.73 m2

* Methods such as YOUNG's rule or CLARK's rule for dose adjustment are at best used approximation in that they take into account only body age and size change attributable to growth and to not consider the rate of drug Elimination.

* Other method which is based on the body surface area has the advantage of avoiding bias due to obesity or unusual body weight , because the height and weight of the patient are both considered.

**3) Explain various factors considered in designing the Dosage regimen for obese patients.**

* Obesity is a major problem in the United States and is also becoming a problem in other countries.

* Obesity has been associated with increased mortality resulting from increase in the incidence of HTN, atherosclerosis, coronary arteries disease, diabetes and other condition compared to non obese patients

* A patient is considered dose if actual body weight exceeds ideal or desirable body weight by 20% according to metropolitan life insurance company data.

* ideal or desirable body weight are based on average body weights and heights for males and for females considering age.

* Atletes who have a greater body weight due to greater muscle mass are not considered obese.

* Obesity often defined by body mass index BMI

a value that normalizes body weight based on height.

* BMI is expressed as body weight (kg) divided by the surface of the person's height (meters) or kg/m2

$$BMI = \frac{\text{WEIGHT in pounds} \times 703}{\text{Height in inches} \times \text{heights in inches}}$$

$$BMI = \frac{\text{WEIGHT in kg}}{\text{Height in inches} \times \text{heights in inches}}$$

Height in meters × height in meters

* The obese patients [BMI >30] has a greater accumulation of fat tissue than in necessary for normal body functions.

* Adipose tissue has a smaller proportion of water compared to muscle tissue. Thus, the obese patient has a smaller proportion of total body water to total body weight compared to the Patient of ideal body weight compared to the patient of ideal body weight compared to the Patient of ideal body weight ,which can affect the apparent volume of distribution of the drug.

* In addition to differences in total body water per kilogram body weight in the obese patients, the greatest proportion of body fat in these patients could lead to distributional changes in the drug's pharmacokinetic due to partitioning of the drug between lipid and aqueous environments.

* Drug such as digoxin and gentamicin are very polar and tend to distribute into water rather than into fat tissue, although lipophilic drugs are associated with larger volumes of distribution in obese Patient compared to hydrophilic drugs.

* Other pharmacokinetic parameters may be altered in the obese patient as a result of physiologic alterations such as fatty infiltration of the liver affecting biotransformation and cardiovascular changes that may affect renal blood flow and renal excretion.

* Dosing by actual body weight may result in overdosing of drugs such as aminoglycosides ( gentamicin) ,which are very polar and are distributed in extracellular fluids .

* Lean body weight has been estimated by several empirical equations based on the patient's height and actual total body weight.

* The following equation have been used for estimating lean body weight,particularly for adjustment of dosage In renally impaired patients.

LBW (Males)=50kg +2.3kg for each inch over 5ft

LBW ( Females) = 45.5kg +2.3kg for each inch over 5 ft

**Clinical Pharmacokinetics and Pharmacotherapeutic Drug Monitoring**

**Unit -2**

## A. Design of dosage regimens

**SHORT ESSAY:**

### 25. Explain in detail determination of dose and dosing interval of a drug.

**Introduction:**

- The dose of a drug is the amount at the time of administration to obtain a desired therapeutic response
- Dosage regimen refers to the schedule of dosing
- Since, several factors affecting the dose of a drug, the exact amount of a drug to be administered is decided by the health care professionals
- The inter and intra subject variations to the effects of drugs can be avoided by tailoring a dose (or a dosage regimen) to a given patient through the use of clinical pharmacokinetics
- For an optimal therapeutic response, we must select a suitable drug and determine an appropriate dose with the available strengths and a convenient dosing interval
- To meet this responsibility, the serum or plasma drug concentrations have to be analysed, pharmacokinetic parameters have to be evaluated, the drug dose has to be adjusted and the dosing interval has to be determined.

**Pharmacokinetic-Based Design and Modification of Dosage Regimens:**

- Traditionally, drug information provided by pharmaceutical companies (such as package inserts and Physicians' Desk Reference) has contained information about the pharmacokinetics of drugs and the therapeutic range (if available)
- Depending on this information, the focus of design of dosage regimens has been the use of pharmacokinetic data

**IV Bolus Dosing:**

**STEP – 1: Estimation of a target average steady state concentration (Cave ∞):**

The following equation defines Cave ∞ the value based on the minimum (Cmin ∞) and maximum (Cmax ∞) steady state concentrations equal to MEC and MTC, respectively

$$Cave\ \infty = Cmax\ \infty - Cmin\ \infty / \ln (Cmax\ \infty / Cmin\ \infty)$$

**STEP – 2: Estimation of the dosing rate (dose/τ) necessary to achieve Cave ∞:**

For this calculation, one also needs clearance (Cl) and extent of systemic availability (F) of the drug

$$\text{Dose}/\tau = Cl.\ Cave\ \infty/F$$

For IV administration, F is equal to 1.

Therefore, $\text{Dose} / \tau = Cl.Cave\ \infty$

**STEP – 3: Estimation of the maximum allowable τ (τ max)**

The rate of decline in the plasma concentration from Cmax ∞ to Cmin ∞ is governed by the drug elimination half-life (t1/2 ) or elimination rate constant (K)

Therefore, we can estimate how long it would take for the plasma concentration to decline from a maximum to a minimum

$$Cmin\ \infty = Cmax\ \infty\ e^{-k\tau max}$$

The above equation can be rearranged to solve for τ max:

$$\tau\ max = \ln (Cmax\ \infty / Cmin\ \infty) / K$$

**STEP – 4: Estimation of the dose:**

Knowing the dosing rate (dose/τ) and dosage interval (τ), we can simply estimate the dose as,

Dose = Dosing Rate X Dosage Interval

**STEP – 5: Estimation of the loading dose (if needed):**

In some cases, administration of a loading dose may be necessary, particularly if the half-life of the drug is long and the immediate achievement of therapeutic concentrations is important

In these cases, the loading dose (DL) may be estimated by either of the following two methods

$$DL = DM.\ R$$

$$DL = Cmax\ \infty.\ V$$

Where, DM = maintenance dose; R = Accumulation factor; V = Volume of distribution

**Pharmacodynamic-Based Dosage Regimen Design:**

- Recently, very specific pharmacodynamic information such as maximum effect (Emax) and the plasma concentration producing half of Emax (EC50) are beginning used in dosage regimen design

- Therefore, it is possible to design dosage regimens for these drugs to achieve certain effects rather than certain concentrations
  $E = Emax . C / EC50+C$
  $C = EC50 . E / Emax – E$
  $Cmax \infty = EC50 . EUPPER / Emax – EUPPER$
  $Cmin \infty = EC50 . ELOWER / Emax – ELOWER$
- The estimated Cmax ∞ and Cmin ∞ values then can be used for the design of multiple dosing regimens as explained earlier
- Similarly, for the constant IV infusion, a target effect may be converted to a Css value and a constant infusion rate be estimated as explained earlier

**26. Enumerate the factors involved in calculation of drug dose in paediatric patients.**

Understanding the differences in physiology at different stages of development (Table 1), compared to adults, assists with designing dose regimens. Drugs with a wide safety margin are good options for treating children as pharmacokinetic changes are unlikely to result in toxicity or ineffectiveness.

**Table 1** Childhood age classes

| Class | Age |
|---|---|
| Neonate | 0–28 days |
| Infant | >28 days – 12 months |
| Toddler | > 12–23 months |
| Preschool child | 2–5 years |
| School age child | 6–11 years |
| Adolescent | 12–18 year |

**Absorption**

The composition of intestinal fluids and the permeability of the gut vary during childhood. Absorption of orally administered drugs is affected by changes in gastric pH which decreases during infancy to reach adult values by two years of age. Infants are at higher risk of toxicity via skin absorption due to a larger surface area to volume ratio and they also absorb more of a drug across skin due to their thinner stratum corneum.This explains why infants have an increased risk of methaemoglobinaemia with topical anaesthetics.

## Distribution

The volume of distribution changes throughout childhood as stores of fat and water change. Infants have a higher percentage of extracellular water, and stores of body fat increase throughout childhood. Changes in volume of distribution can alter the drug's half-life, requiring adjustment of the dosing interval, as seen with digoxin. Dosing information for obese children is limited and has been identified as an area for research. Obese children can be dosed using ideal body weight and the dose adjusted based on clinical effect. They are at higher risk of toxicity from drugs such as paracetamol that do not distribute into fat, if actual weight is used to calculate the dose. Infants have lower concentrations of circulating plasma proteins reducing protein binding.This results in higher distribution and lower peak concentrations of protein-bound drugs such as cefazolin. **Metabolism**

The metabolism of drugs is the most complex difference between adults and children. Cytochrome P450 (CYP) enzymes are active in the fetus. Enzyme activity begins to increase during the later stages of pregnancy with different rates of individual enzyme development seen in infants who are born preterm.9 The pattern of active enzymes changes over the first few months of life to reach or exceed adult levels at around two years of age.7 While most enzymes increase in activity over the first few months of life, some such as CYP3A7 are replaced by other enzymes, in this case CYP3A4. The development of metabolic processes, such as glucuronidation, is less clear, but is thought to take at least three years to achieve full activity. Liver blood flow may be relatively high in infants. This could affect first-pass metabolism particularly for drugs with a high extraction ratio, like propranolol.

## Elimination

Excretion is an important step in the final removal of the drug and any metabolites from the body. It relies on effective renal and hepatic function that develop over time. Preterm neonates develop renal excretion pathways more slowly than term neonates. Glomerular filtration rates reach adult levels by about two years of age.

## Dosing and development

The change from treating children and neonates as little adults has occurred gradually. Previously size and gestational age were viewed as the main determinants of drug clearance, but this has been replaced with the view that the capacity and functions of individual organs and the development of biochemical pathways are of greater importance. The development of drug metabolism and

clearance pathways begins in the foetus and continues throughout childhood. A study by the FDA examined different methods of predicting paediatric clearance of drugs based on adult values, and concluded that no single method of prediction is suitable for all drugs or age groups. Dosage regimens based entirely on age are often inaccurate and may lead to adverse effects, toxicity or lack of clinical effect. There is a lack of pharmacokinetic studies in children of different ages. Dosing information is difficult to determine in children as traditional pharmacokinetic studies are hard to conduct in children and are subject to a greater range of ethical considerations. These studies require large amounts of blood to be taken over periods of time and this is not considered ethical in children. The development of population pharmacokinetic modelling has allowed paediatric-specific dosing information to be developed. These new techniques will assist in developing safer dosing information for children over time by reducing the burden of pharmacokinetic studies. Although improving, no mathematical method of dose estimation can replace clinical studies using actual outcomes, surrogate measures or therapeutic drug monitoring.

**27. Discuss the factors to be considered during the design of dosage regimen.**

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.

Some of the factors affecting the dose of a drug include:

**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 t1/2 or sustained release formulation

7. Patient acceptance of route and dosage form

**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 t1/2

6. Availability of treatment for overdose

7. Existence of a therapeutic or toxic concentration range

**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

**IV. Complications:**

1. Analytical methodology and reliability in monitoring Cp

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

**45. What are the factors considered in the conversion of IV to oral dosing?**

Proper identification of patients, diagnoses, medications, and contraindications to oral therapy are all essential aspects for a successful IV to PO therapy conversion program. It is very important that the pharmacist conduct a thorough and complete review of these areas so only the most appropriate patients are converted. Doing so is a benefit to both patient care and professional credibility.

The criteria used to determine whether or not the patient is eligible for PO therapy vary from hospital to hospital, but they generally encompass four key areas:

1. Intact and functioning gastrointestional (GI) tract

2. Improving clinical status

3. Does not meet any exclusion criteria

1. **Explain the reasons for converting IV dose to oral dose. Add a note on START and STOP criteria for drugs to be used in patients.**

It has many benefits for the patient and the hospital.

- Improved patient comfort and mobility
- Reduced exposure to nosocomial pathogens through the IV site
- Decreased risk of phlebitis
- Reduced preparation and administration time
- Lower costs (drug cost, IV tubing, syringes, IV pumps)
- Decreased length of stay
- It’s an upcoming CMS requirement.
- The facility has a system in place to identify patients currently receiving intravenous antibiotics who might be eligible to receive oral antibiotic treatment.

START and STOP criteria

Aims of STOP/START

- Provide explicit, evidence based rules of avoidance of commonly encountered instances of potentially inappropriate prescribing and potential prescribing omissions –
- Improve medication appropriateness
- Prevent adverse drug events
- Reduce drug cost

**Contents of STOPP**

| Physiological System | Number of criteria |
|---|---|
| Cardiovascular system | 17 |
| Central nervous system | 13 |
| Gastro-intestinal system | 5 |
| Musculoskeletal system | 8 |
| Respiratory system | 3 |
| Urogenital system | 6 |
| Endocrine system | 4 |
| Drugs that adversely affect fallers | 5 |
| Analgesics | 3 |
| Duplicate drug classes | 1 |

## Contents of start

| Physiological System | Number of criteria |
|---|---|
| Cardiovascular system | 8 |
| Respiratory system | 3 |
| Central nervous system | 2 |
| Gastro-intestinal system | 2 |
| Musculoskeletal system | 3 |
| Endocrine system | 4 |

Prevalence of Potentially Inappropriate Prescribing using STOPP/START

- Primary Care
  - Potentially inappropriate prescribing (STOPP): 21.4%
  - Potential prescribing omissions (START): 22.7%

  Ryan C *et al.* Br J Clin Pharmacol 2009
- Secondary Care
  - Potentially inappropriate prescribing (STOPP): 34.5%
  - Potential prescribing omissions (START): 57.9%

  Gallagher *et al.* Age Ageing 2008
  Barry PJ *et al.* Age Ageing 2007
- Nursing Home
  - Potentially inappropriate prescribing (STOPP): 55-49.8%

  Ryan C *et al.* Ir J Med Sci 2009
  O'Sullivan D *et al.* Eur Ger Med 2010

2 MARKS

1. **Write the different formulae for calculating child dose**

A) **Young's rule**: For children over 1 year of age up to 12 years

$$\text{Child's dose} = \frac{\text{Age of child in years}}{\text{Age of child in years} + 12} \times \text{Adult dose}$$

B) **Clark's rule**: it is calculated according to weight of the child, therefore it can be used for children's of all age.

$$\text{Child's dose} = \frac{\text{Weight of child in pounds}}{150} \times \text{Adult dose}$$

C) **Fried's rule:** for children under 1 year of age

$$\text{Child's dose} = \frac{\text{Age of child in months}}{150} \times \text{Adult dose}$$

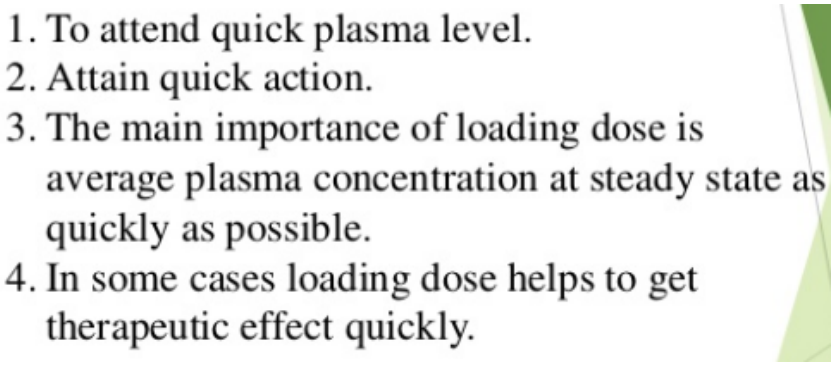


2. **BEERs criteria for drugs to be used in geriatric patients**

The AGS Beers Criteria® include the same five main categories as in 2015: (1) potentially inappropriate medications in older adults; (2) potentially inappropriate medications to avoid in older adults with certain conditions; (3) medications to be used with considerable caution in older adults; (4) medication combinations that

may lead to harmful interactions; and (5) a list of medications that should be avoided or dosed differently for those with poor renal function.

3. **Importance of loading dose in finding drug dosing intervals**




4. **Relationship between elimination half life and drug dosing interval**

The half-life equal to the dosing interval at steady-state where the maximum concentration at steady-state is twice the maximum concentration found for the first dose and where the fall off to the trough concentration from the maximum concentration is consistent with this half-life

5. **Define nomograms and tabulations**

a diagram representing the relations between three or more variable quantities by means of a number of scales, so arranged that the value of one variable can be found by a simple geometrical construction

**Tabulation** is a systematic and logical representation of numeric data in rows and columns to facilitate comparison and statistical analysis. ... In other words, the method of placing organised data into a tabular form is known as **tabulation**. It may be complex, double, or simple, depending upon the nature of categorisation.

**6. Advantage and disadvantage of nomograms**

- The advantages of the two-stage method are its simplicity, the use of standard data analysis, individual estimates of pharmacokinetic parameters, and controlled experimental conditions allowing unbiased definition of relationships between pharmacokinetic parameters.

- It has limitations such as its high cost, necessitating inclusion of only a small number of patients, and ethical problems of extensively studying patients who may not directly benefit from the study.

**7. Factors affecting the drug distrubution in obese patients**

The main **factors that affect** the tissue **distribution** of **drugs** are body composition, regional blood flow and the affinity of the **drug** for plasma proteins and/or tissue components. **Obese** people have larger absolute lean body masses as well as **fat** masses than non-**obese individuals** of the same age, gender and height.

## LONG ASSAY

47.Explain the necessity and process of TDM in patients receiving cyclosporine and Carbamazepine.

### CYCLOSPORINE:

■ It's a potent immune-suppresant agent.
■ The drug finds application in organ transplant patient to prevent organ rejections by supressing immune system.

### Monitoring of pharmacokinetics parameter and TDM information:

■Pharmacokinetics parameter vary from person to person , a mild is observed with cyclosporine in pharmacokinetics parameter.
■ When cyclosporine is administered orally
1) Varies from 2-5%
2) Peak plasma levels (Tmax ) are achieved within 2-6 hours .
3) It is metabolized in liver , elimination through bile to the feces at also through renal (less than 1%)
4) $T_{1/2}$ is then 5.6 +- 2 hrs
5) Therapeutic range of cyclosporine is 50-300 mg permit in plasma.

### Dosing of Cyclosporine:

15 mg once daily dose this is intimated for 4-14 hours prior the transplantation
And continued for 1-2 hours.

### Sampling of TDM :

■ Plasma drug concentration of cyclosporine is most useful information for TDM several blood sample between 2-6 hours dosing can be obtained to minimize variation in bioavailability .
■ Cyclosporine level should be monitored 2-3 hours a week and more frequent monitoring is required if the patient has clinical problem that can cyclosporine pharmacokinetics.

### Toxicity (Adverse effect)

■ Severe headache
■ Histatin
■ Visual disturbance
■Hypertension
■ Tremors
■ Convulsions
■Mesological Toxicity
■ The above adverse effect may vary with the dosage of cyclosporine and its concentration should be estimated in blood.

### Factor affecting plasma level :

■ Food is high fat meals may increase plasma level
■Children below in years to years may decreased the level of plasma because they have a Level of plasma because they have a large volume of faster body clearance .
■ Drugs which decrease cyclosporine level are carbamazepine , pheno-barbiturate, Phenytoin.

■ Physiological disorder : fever and increase fraction of unbonded cyclosporine.

## CARBAMAZEPINE:

■ Its an anti convulsions and mood stabilizing drug used priority in the treatment of epilepsy and bipolar us well as trigeminal neuralgia.

### Pharmacokinetic parameter and TDM information:

| | |
|---|---|
| 1 ) Elimination half life T1/2 | 1 ) 25-40 hours ( single dose in normal )<br>2) 15-24 hours ( mono therapy in chronic condition)<br>3) 6-14 hours (poly therapy in chronic condition)<br>4) 2.5-15 hours |
| 2 ) Potent body clearance | 1)2+- 5 (single dose normal )<br>2) 25+-25 (mono therapy ) |
| 3) Volume of distribution | 1) 1-2 liters |
| 4) Plasma drug binding | 1) 4-12 mg/l |
| 5)Therapeutic drugs | 3.5-10.4mg /l |
| 6) landing dose | 3.5-10.5 mg/l |
| 7) Mesetumance dose | 7.15 mg/l |
| | |

■ The absorption -1 cbz is very and irregular maximum activity ( T max ) is observed in 4-8 Hours but prolonged to as 24 hours

■ The plasma protein binding is 40-90% and converted important metabolites episode which is also active in active variant animals later it is metabolized compound and execrated

As glucuronamides these drug can hepatic enzymes hence half (T1/2) varies with repeated administration .

■ Clearance and plasma cbz is more than 75% by condition with other antiepileptic drug therapy .

### Monitoring of cbz toxicity:

■ Generally ADR includes nausea , vomiting ,dizziness skin rashes ,impaired vision and confusion.

■ Serious facility includes obstructive jaundice aplastic anemia , respiratory depression.

### Available dosage :

■Tablets 100-200mg

■ Chewable tablets 100mg

■Suspension 100mg 5 ml

### Factor affecting plasma level

■ food decreased plasma level parameter cbz is given as a form of suspensions.

■Drugs : likes phenytoin , warfarin , valproate, nulaperidol, isoniazid

## 48. List out the indications for TDM. Explain the necessity and process of TDM in patients receiving digoxin and phenytoin.

**NECESSITY/INDICATIONSOFTDM:**

Which drugs required monitoring and where it is indicated?

1. Pharmacokinetic variability e.g.aspirin,digoxin.
2. Conc. Related therapeutic and adverse effects e.g.phenytoin:ataxia,vertigo, drowsiness
3. Narrow Therapeutic Index:digoxin
4. Effect difficult to monitor.
5. Interindividual variations in metabolism.
6. Saturation kinetics : omeprazole : P4502C19
7. Difficult to recognized toxicity clinically : cyclosporin, Seizures
8. Hepatic andrenal diseases : aminoglycosside
9. Multiple drug therapy and drug interaction ,Probenicid increases level of penicillin
10. Doubtful patients compliance.

Drug assays are costly, so the reason for monitoring and the additional information to be gained (if any) should be carefullyconsidered. For some drugs, therapeutic drug monitoring helps toincrease efficacy (vancomycin), to decrease toxicity (paracetamol)and to assist diagnosis (salicylates). Routine monitoring is notadvocated for most drugs. Only clinically meaningful tests shouldbeperformed.

Theappropriateindicationsfortherapeuticdrugmonitoring(andexamples)include:

- **Toxicity**
    - -diagnosing toxicity when the clinical syndrome is undifferentiated (unexplained nausea in a patient takingdigoxin)
    - -avoiding toxicity(aminoglycosides,cyclosporin)
- **Dosing**
    - -after dose adjustment(usuallyafterreachingasteadystate)
    - Assessment of adequate loadingdose (afterstartingphenytointreatment)
    - Dose forecasting to help predict patient's dose requirements(aminoglycosides)
- **Monitoring**
- -assessing compliance (anticonvulsant concentrations inpatient shaving frequent seizures)
- -diagnosing under treatment (particularly important for prophylactic drugs such as anticonvulsants, immunosuppressants)
- diagnosing failed therapy (therapeutic drug monitoring can help distinguish between ineffective drug treatment,non compliance and adverse effects that mimic the

underlying disease).

**TDM FOR DIGOXIN**

- Digoxin continues to have an important role in the control of ventricular rate with atrial fibrillation,and as positive in tropicagentin heart failure.
- Digoxin inotropic effect is the basis for its use of treatment in CHF.
- While its chronotropic effects are the basis for treatment of atrial arrhythmias such as atrial fibrillation , atrial flutter and atrial tachycardia.

**INDICATIONS FOR THERAPEUTIC DRUG MONITORING OF DIGOXIN**

- Confirmation of toxicity
- Assessing the effect of factors altering
- Assessing the effect of factors altering pharmacokinetics
- Therapeutic failure
- Medication compliance

- Absorption: food decreases the rate but not the extent of absorption of digoxin.
- Distribution and protein binding: Digoxin has been reported to be 5 to 60% bound to plasma proteins.
- Metabolism and excretion :Although digoxinis reported to be excreted mainly unchanged in the urine there is evidence to suggest that metabolism may sometimes be extensive. Metabolites that have been detected in the urine include digoxigenin, dihydrodigoxigeninetc.
- Therapeutic range:–.0005-.002mg/dl.
- Plasma concentration range:The generally accepted therapeutic plasma concentration range is 0.5 to 2.0 nanograms/mL.

<0.5 μcg/L :-no clinical effect

• 0.7 μcg/L :-some positive inotropic and conduction blocking effects.

• 0.8-2μcg/L :-optimum therapeutic range (0.5 - 0.9 μcg/L in patients >65)

• 2-2.5 μcg/L :-increased risk of toxicity, although tolerated in some patients

• > 2.5 μcg/L :-gastro-intestinal , cadiovascular system and CNS toxicity.

- Elimination Half life:–It has an elimination half-life of 1.5 to 2 days.

**APPROPRIATE SAMPLING TIME**

- Digoxin concentrations should be measured at least eight hours following an oral dose of digoxin and ideally when concentrations have reached steady-state
- Understanding of the reasons behind these recommendations requires an understanding of the pharmacokinetic profile of digoxin

- Digoxin is well absorbed, with peak serum concentrations occurring within one hour
- A large volume of distribution(4–7l/kg)reflectsthatdigoxinconcentrates inthetissues,withtheactivesitebeingwithinmyocardialandothercells
- Redistribution from serum issue takes atleast six to eight hours
- Steady state conditions of digoxin had to have been reached (defined as 5 half-lives after digoxinwas initiated or after digoxin dose adjustment; i.e. 7 days in patients with normal renal function; t½: 36 hrs; 4-6 days in RF)
- Samples taken within eight hours of a dose will falsely imply elevated serum concentrations ,and in appropriate dose reduction may result.

**DOSAGE ADJUSTMENT**

- A change in dose will normally result in a proportional change in digoxin concentration, e.g.: doubling the dose will double the digoxin concentration, and halving the dose will halve the concentration (assuming stable renal function and no new drug interactions).

**SPECIMEN COLLECTION METHOD**

- Serum or plasma , anticoagulated with heparin or EDTA , may be used seum separator tubes should be avoided .
- Samples are stable for 24hrs at 2degreeCelsius- 8 degree Celsius and 1-2 weeks at -20 degree Celsius.

**ASSAY METHODS**

- Digoxinis almost exclusively assayed by EIA and FPIA for the purpose of TDM.
- The commonly used immunoassays may not distinguish digoxin from other drugs e.g. spironolactone and its from other drugs e.g. spironolactone and its metabolites and there is substantial cross reactivity with digoxin metabolites.
- The assays for digoxinare also unreliable for 10 days or more following administration of digoxin antibodies .

**TDM FOR PHENYTOIN**

- Phenytoin is a hydantoin compound related to the barbiturates that are used for the treatment of seizures.
- It is an effective anticonvulsant for the chronic treatment of tonic-clonic or partial seizures and the acute treatment of generalized status epilepticus.

**NEED FOR TDM**

- At the initiation of therapy , inorder to achieve a plasma concentration within the therapeutic range .
- When there is intercurrent illness ( AIDS , Renal impairment , or hypoalbuminaemia ) or a change in physiological state exists .
- When drug toxicity is suspected
- When the therapy is about to be withdrawn
- Narrow therapeutic index
- Highly protein bound , drud-drug interactions

- Inter-individual variability in enzyme saturation
- Non-linear pharmacokinetics even within the therapeutic range .

**THERAPEUTIC AND TOXIC CONCENTRATION**

- The generally accepted therapeutic range for unbound phenytoin concentrations is 1–2 μg/mL.
- The usual therapeutic range for total (unbound + bound) phenytoin serum concentrations when the drug is used in the treatment of seizures is 10–20 μg/mL.
- In the upper end of the therapeutic range (>15 μg/mL) some patients will experience minor central nervous system depression side effects such as drowsiness or fatigue.
- Phenytoin concentrations above 20 μg/mL, nystagmus may occur
- When total concentrations exceed 30 μg/mL, ataxia, slurred speech, and/or incoordination similar to ethanol intoxication can be observed.
- If total phenytoin concentrations are above 40 μg/mL, mental status changes, severe confusion or lethargy, and coma are possible.
- Drug-induced seizure activity has been observed at concentrations over 50–60 μg/mL.

**Absorption :**

Bioavailability

1) Intramuscular: 99% to 100%
2) Intravenous: 99% to 100%

Absorption of phenytoin by oral route is slow because of its poor aqueous solubility

**DISTRIBUTION**

A) Distribution Sites

1) Protein Binding 95% to 99%

2) Tissues

Unbound PHENYTOIN enters all tissues and is bound to phospholipids and proteins.

**Metabolism :**

PHENYTOIN is metabolized extensively (95%) in the liver by hydroxylation and glucuronide conjugation.

**Excretion**

- mostly by Bile
- Only 5% unchanged phenytoin is excreted in urine.
- Half life 12- 24 hours progressively increases up to 60 hrs when plasma concentration rises above 10 mcg/ml as metabolizing enzymes get saturated. Maintaining of plasma concentration is very helpful in tailoring dosage

**DOSAGE RECOMMENDATIONS**

- Phenytoin exhibits nonlinear behavioue following therapeutic doses
- Thus increase in dose rate will produce greater than proportional increase in the average serum concentration during the dosing interval
- Nomograms can be used to estimate individual dosage requirements .

**Specimens**

- Serum or plasma concentration are generally recommended for total phenytoin measurments .
- Use of anticoagulants are recommended
- Saliva is proposed for children
- Saliva is useful for monitoring unbound phenytoin concentration.

**Collection methods and assays**

- Immunoassays are most common methods of measurements

- Immunoassay that use monoclonal antibodies or HPLC can be used in samples from patients with renal impairment.

## 49. Explain the necessity and process of TDM in patients receiving lithium and methotrexate.

**TDM FOR LITHIUM**

- **Lithium is used for the treatment and prophylaxis of mania, bipolar disorder and recurrent depression.**
- **Aggressive or self-mutilatingbehavior.**

**NEED FOR TDM**

Wide availability variation between preparations; changing therapy should be monitored as for initiation of therapy.

Lithium competes with sodium for reabsorption in renal tubes- altered sodium balance or fluid intake may precipitate toxicity.

**USUAL DOSE AND DOSE INTERVAL:**

Lithium carbonate is the typical salt used: 400-1200mg daily initially with serum concentration monitoring 12 hours post-dose to fall within the target range; adjust as required.

Elderly usually require lower dose.

Once dose stabilized, switch from divided to single doses.

**Plasma concentration response relationship**

0.4mmol/L : Little therapeutic effect

0.4 to 1 mmol/L : Optimum range for prophylaxis of mania

0.8 to 1.2 mmol/L : Causes possible renal impairment

1.5 to 3 mmol/L : Renal impairment, drowsiness, thirst and diarrhea

3 to 5 mmol/L : Confusion, spasticity, convulsions, coma and death

**Optimum sampling time**: 12 hours post-dose

**Time to peak**: 2-4 hours (longer with sustained-release form)

**Route of elimination**: renal excretion only

**Elimination half-life**: 10-35 hours (elderly have decreased renal function and typically longer half-lives)

**Time to steady state**: 3-7 days of chronic dosing

**Protein binding**: 0%

**TOXIC EFFECTS OF LITHIUM**

- Renal impairment
- Hypothyroidism
- Nephrogenic diabetes insipidus

- Hyponatremia
- Hyperparathyroidism(rarely)
- CNS disturbances(ataxia, tremors, lethargy, sedation, dysarthria, confusion, seizures)

**DOSAGE ADJUSTMENT**

- The starting dose is normally 400mg/450mg at night (200mg/250mg in the elderly). Lithium plasma concentration should be checked 5-7 days (depending on renal function) after starting or changing dose and then weekly until two similar results are obtained at the same dose.
- The blood taken for lithium should be taken 10-14(ideally 12 hours) after the last dose administered. To assist sampling, lithium is usually given as a bedtime dose so that blood can be taken the following morning.
- Doses should be adjusted to achieve serum lithium concentration between 0.4-1.0 mmol/L. In people prescribed it for first time, a range of between 0.6 and 0.8 mmol should be used. The lower end of the range is usually the target for maintenance therapy and treatment of elderly patients.

**ASSAY METHODS**

- POTENTIOMETRIC [ion-selective electrode(ISE)] OR SPECTROPHOTOMETRIC METHOD
- The spectrophotometric methods can be divided into 2 groups: a dry chemistry method using reflectance spectrophotometry(RSM) or a wet chemistry method using spectrophotometry(SM)
- The RSM is performed as dry chemistry methodology on a multilayered analytical slide using spectrophotometer as detector.
- Serum lithium binds and reacts with a crown-ether azo dye incorporated in the slide and thereby quantitatively changes the absorption of the dye.
- Using SM methodology, lithium reacts with an alkaline-substituted porphynin (heterocyclic macrocycle organic compound) capable of decreasing the absorbance of the sample solution quantitatively.

## 50. Enumerate and explain various factors in individualizing drug dosage regimen?

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 t1/2 or sustained release formulation

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 t1/2 6. Availability of treatment for overdose

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

V. Complications:
1. Analytical methodology and reliability in monitoring Clinical pharmacy
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 data with recent history of drug use.

## 51. Explain in detail pharmacokinetic/pharmacodynamic correlation in drug therapy.

Most pharmacological responses are due to non covalent interaction between drug and receptor . nature of interaction is assumed to be reversible and conforms to law of mass action.

[drug]+[receptor] $\rightleftharpoons$ [drug.receptor complex] $\longrightarrow$ response

This scheme explains occupation theory and following assumptions are made,

1. Binding is fully reversible.
2. Assumes a single type of receptor binding site which one binding site per receptor molecule.
3. Drug combines with receptor as a bimolecular association and resulting drug receptor complex disassociates as unimolecular entity.

- Basically 3 types of responses may occur at the receptor:

1. Agonist elicits maximal pharmacologic response .
2. Partial agonist elicit partial response.
3. Antagonist elicit no response from the receptor but inhibits the receptor interaction of a second agent.

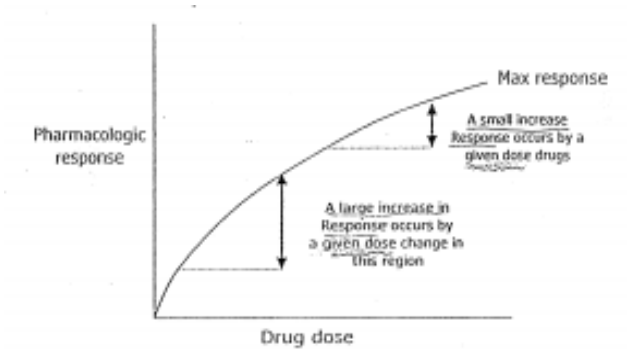
**Rate theory**

States that the pharmacological response is not depended on drug receptor complex concentration but rather depends on the rate of association of drug and receptor each time adrug molecule hits a receptor, a response is produced.

Rate theory predicts that an agonist will associate rapidly to form a receptor complex, which dissociate rapidly to produce response. Antagonist associates rpidly to form a receptor drug complex and dissociates slowly to maintain the antagonist response.

**i. Relation of dose to pharmacologic effect:**

- Onset intensity and duration of effect depend on the dose and pharmacokinetics of drug.
- As dose increases, drug concentration at receptor site increases and response upto a maximum effect.
- A plot of pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum effect at plateau.
- When plotted as log linear scale, results in a sigmoid curve.




- Plot of a pharmacologic response versus dose on a linear scale.


- Mathematically, the relationship may be expressed by the following equation,

  E=mLogC+e

  E: Drug Effect
  C: Drug concentration
  M: Slope and e-extrapolated intercept for log C yields

$$\text{Log } C = \frac{E-e}{m}$$

- After IV dose, the concentration of drug in the body in a one compartment open model is described as follows:

$$\text{Log } C = \text{Log } C0 - kt/2.3$$

$$E - e = \frac{E0-e}{m} = kt/2.3$$

$$E = E0 - Kmt/2.3$$

E0 = Effect at concentration C0

**ii. Relation between dose and duration of activity, single IV injection**

- After an IV dose, assuming one compartment model, the time needed for any drug to decline to a concentration C is given by following equation, assuming the drug takes effect immediate.

$$T = 2.3 \left( \frac{\text{Log } C0 - \text{Log } C}{} \right)$$

K

Using Ceff to represent the minimum effective concentration duration of action can be obtained as follows.

$$Teff = \frac{2.3[\ Log\ (D0/VD) - Log\ Ceff]}{K}$$

For example, a doubling of the dose will not result in doubling of the effective duration of duration of pharmacological action, on the other hand doubling of t1/2 or corresponding decrease in K will result in a proportion increase in duration of action.

**Effect of both dose and elimination half life on duration of activity:**

A single equation can be desired to describe the relationship of dose D0 and the elimination half life (t1/2) on the effective time for therapeutic activity (teff) . This expression is derived below

$LnCeff = LnC0 - Kteff$

$LnCeff = Ln[D0/Ceff] - Kteff$

Substitute C0=D0/VD

$$Teff = \frac{1}{K} Ln \frac{[D0/VD\ ]}{Ceff}$$

- **Effect of elimination half life on duration of activity:**

  Because elimination of drugs is due to the process of excretion and metabolism, an alteration of any of these elimination process will effect the t1/2 of the drug .

  Substituting $K = \frac{0.693}{t1/2}$

  $$teff = 1.44\ t1/2\ Ln\ [\ D0/VD\ Ceff]$$

- Pathophysiologic changes in hepatic and renal function decrease elimination thus prolonging t1/2. This in turn will lead to retention of drug in body, thereby increasing possibility of drug toxicity.
- To improve the antibiotic therapy with the pencillin and cephalopod clinicians have intentionally prolonged the elimination of these drugs by giving a second drug probenecid which competitively inhibits the renal excretion of the antibiotic.

**Rate of drug absorption and pharmacodynamic response**

Rate of drug absorption influences rate in which drug gets to the receptor and subsequent pharmacologic effect. For drugs that exert an acute pharmacological effect , usually directly acting drug agonist, extremely rapid drug absorption may have an intense and possibly deterimental effect.

Eg : Niacin is a vitamin given in large doses to decrease elevated plasma cholesterol and triglycerides. Rapid systemic absorption of Niacin when given as immediate release tablet will cause vasodilation, leading to flushing postural hypotension. Extended release products are preferred because more slowly absorbed Niacin allows the baroreceptors to adjust to the vasodialation and hypotensive effects of drug.

**Drug Tolerance:**

Drug tolerance is a quantitative change in sensitivity of drug and is demonstrated by decrease in pharmacodynamic effect after repeated exposure to same drug . It depends on dose and frequency of drug.
Ex : Opioids

**Physical Dependency:**

Appearance of withdrawal symptoms after cessation of the drug.
Ex : Workers exposed to volatile organic nitrates in work place may initially develop headaches and dizziness followed by tolerance with continuous exposure.after leaving workplace for few days workers may demonstrate nitrate withdrawal symptoms.

# SHORT ASSAY

## 52. Explain effect of age and bodyweight in individualization of drug dosage regimen.

### Age:-

- The factors that affect drug absorption, including gastric pH, gastric emptying, intestinal motility, and blood flow change with age.
- Thus, in the neonate a condition of achlorhydria persists for the first week of life, and only after 3 years of age gastric acid secretion approaches the adult value.
- Gastric emptying is also prolonged and peristalsis is irregular during the early months of life Skeletal muscle mass is also much reduced, and muscle contractions, which tend to promote both blood flow and spreading of an intramuscularly administered drug, are relatively feeble.
- An elevated gastric pH, a delay in gastric emptying, and both diminished intestinal motility and blood flow are also seen in the elderly.
- Differences in drug absorption among adults, the very young and the elderly, are therefore expected.
- Generally changes in rate rather than in extent of absorption are found.
- These changes tend to be less apparent in the elderly than in the very young.
- Children often appear to absorb drugs as completely and, if anything more rapidly than adults.
- Accordingly, in subsequent calculations of dosage, extent of absorption is assumed not to vary with age.
- A major exception is for some first-pass drugs given to the elderly, where oral bioavailability increase with age
- The half life is shortest around 1 year of age; it is longest in both newborn and elderly patients
- In premature newborns, the urinary excretion is even more depressed per kilogram of body weight than in full-term neonates
- Metabolic activity may take months to mature, the time required for full maturation varies with the enzyme system
- A decrease in unbound metabolic clearance in the elderly patient has been demonstrated for an increasing number of drugs, especially those principally by oxidation
- These changes may be associated in part, with the decrease in the size of the liver, as a proportion of body weight, from 25% in the young adult to 16 % at 90 years of age

### Body Weight :-

- One aspect of aging is body weight.
- Weight, 3.5 kg at birth, increases rapidly in childhood and adolescence and then declines slowly in the elderly.

- As body water spaces, muscle mass, organ blood flow, and organ functionare related to body weight, the volume of distribution, clearance and hence dosage regimens of drugs also depend on body weight.
- However, a weight adjustment is generally thought necessary only if the weight of an individual differs by more than 30% from the average adult weight (70kg).
- In practice, then, adjustments for weight are made only for the child and for the adult who is small thin, big or obese.
- A dose correction must be considered for thin and obese patients
- The difference in loading dose may not be as great as anticipated from body weight alone
- Because, distribution get age-related changes and much depends on the
- physicochemical properties of the drug
- In contrast, total body weight may be more relevant for a drug that is highly lipid soluble
- Though renal and hepatic functions are related to body size, obesity may not produce a corresponding increase in hepatic function.
- Consequently, the use of total body weight to determine a drug dosage regimen could result in toxic effects of the patient is grossly obese.
- Thus, though many drug doses are based on the body weight of the patient (expressed as me/ka), the influence of obesity or malnourishments is not always considered.

## 53. Explain role of geneties and disease condition in the individualization of drug dosage regimen.

### Genetics:

- Genetic polymorphism that lead to the production of isoenzyme with reduced or no activity of to multiple copies of an enzyme with high activity make a major contribution to the variability in the dose requirements of drugs that eliminated by hepatic metabolism.
- Cytochrome P450 (CYP 450) enzymes, P-Blycoproteins are increasingly being recognized for their importance to pharmacokinetic variability
- Most of these genetic differences are complex and are difficult to determine with any degree of certainty, but a few genetic differences are well documented (oxidation, S-methylation, and acetylation)
- Probe drugs approved by US FDA for genetic phenotyping:
    - Omeprazole / Pantoprazole (Phenotyping for CYP2C19)
    - Lovastatin (Phenotyping for CYP3A4)
    - Dextromethorphan (Phenotyping for CYP206)

**Disease Conditions:**

- Disease is a major source of variability in drug response
- The PK and PD of some drugs have been shown to be influenced by the presence of concurrent diseases other than the one for which a drug is used
- There are also occasions when the pharmacokinetics of a drug is altered in the disease for which it is used
- Diseases of the kidney, liver, cardiovascular system, respiratory system, gastrointestinal system and endocrine system are the major cause that warrant individualized drug therapy
- The influence of Hepatic disorder on the drug bioavailability & disposition is unpredictable because of the multiple effects that liver produces.

- The altered response to drugs in liver disease could be due to decreased metabolizing capacity of the hepatocytes, impaired biliary elimination, due to biliary obstruction le g. Rifampicin accumulation in obstruction jaundice)
- In patient with renal failure, the half life of the drug is increase and its clearance drastically decreases if it is predominantly eliminated by way of excretion
- Hence, dosage adjustment should take into account the renal function ofthe patient and the fraction of unchanged drug excreted in urine.
- There are two additional method for dose adjustment in renal insufficiency the Vd change is assumed to be negligble.
- The adjustment of drug dosage in case of renal disease are carried out by mainly three approaches:
    1. Dose adjustment based on Total body clearance
    2. Dose adjustment based on Elimination rate constant or Half life.
    3. Dose adjustment in renal failure

## 54. Explain role of co-existing diseases and interacting drugs in the individualization of drug dosage regimen.

### Co-existing diseases:

- Disease is a major source of variability in drug response.
- The PK and PD of some drugs have been shown to be influenced by the presence of concurrent diseases other than the one for which a drug is used.
- There are also occasions when the pharmacokinetics of a drug is altered in the disease for which it is used.

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- Dose adjustment based on Total body clearance.

- Dose adjustment based on Elimination rate constant or Half life.
- Dose adjustment in renal failure

### Role of interacting drug

1. Many of the clinically significant interactions between drugs are pharmacokinetic in origin, often due to induction and inhibition of metabolizing enzymes or transporter proteins.
2. However, interactions can also occur between drugs and food supplements or herbal remedies
3. Interactions involving competitive inhibition often occur within two to three days whereas induction may take anything form hours to weeks
4. If the interacting drug has a long elimination half life, the interaction may persist for sometime after it has been discontinued

## Absorption:

- Studies have demonstrated the importance of intestinal CYP3A4 and P–glycoprotein in drug absorption
- Induction of these mechanisms by rifampicin and by St John's wort have been shown to reduce the BA of Digoxin
- Absorptioncanalsobealteredbydruginteractionswithinthegutthatresultfrombindingtootherdrugs,suchascholestyramineor antacids, or to enteral feeds, as in thecaseofPhenytoin

## Distribution:

- Drug distribution can be altered by interactions that cause displacement from plasma protein binding
- But,these donot normally alter maintenance dose requirements unless there is also a reduction in the clearance of unbound drug.

## Metabolism:

- Metabolism can be altered by enzyme induction or inhibition
- Due to wide variability in enzyme activity, the clinical significance of an interaction is often difficult to predict on an individual basis
- These interactions are often dose-dependent and the time scale of the offset and onset of the effect depends notonly on thePK of two (or more) drugs concerned, but also the isoenzyme(s) responsible for their metabolism

## Excretion:

- Probenecid reduces the renal excretion of many antibiotics by competing for anion

secretion transport mechanism

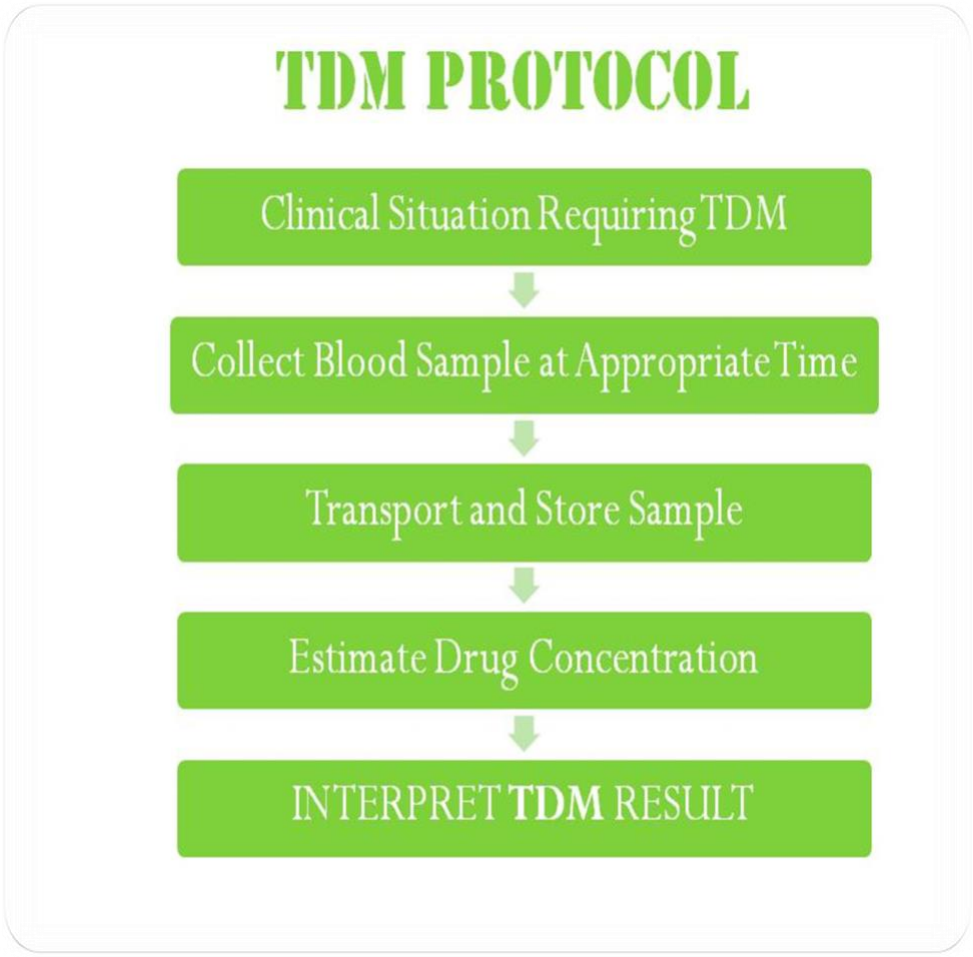
- Changesinbiliarysecretionandentero-hepaticcirculationcanalsoplayarole
- For example, Penicillins can impair there circulation for all contraceptives by altering the bacterial flora of the gut.

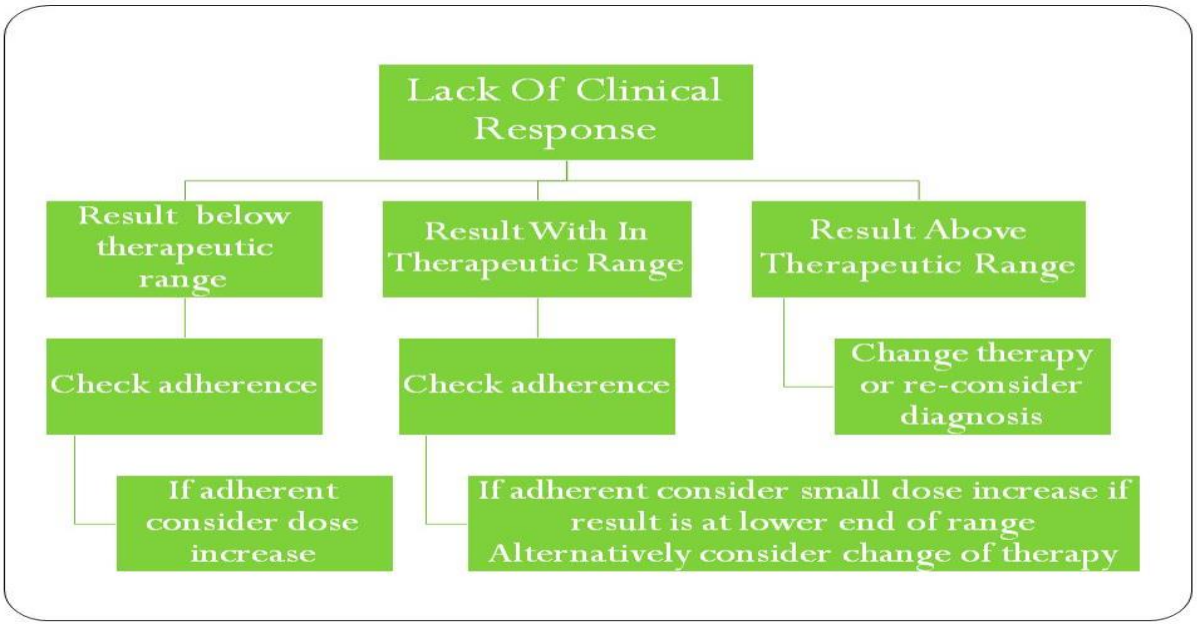
## 55. Describe the protocol for TDM of a drug.

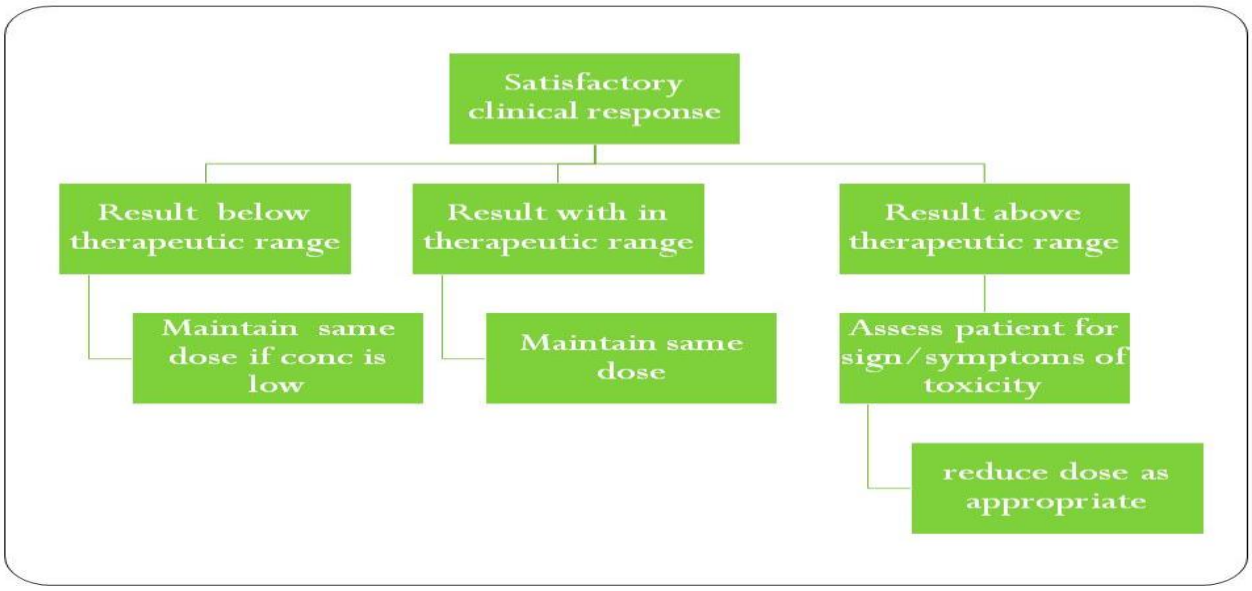
Therapeutic drug monitoring(TDM) is the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's blood stream, there by optimizing individual dosage regimens.

### STUDY PROTOCOL FOR TDM:

1) **Title of the study/project**
2) **Investigators**
    1. Chief investigator
    2. Joint investigator
    3. Co-investigator — a) Clinical b) Research fellow
3) **Place of study**
4) **Patient recruitment place**
5) **Need for TDM study**
6) **Objective for study**
7) **Criteria for selection of patients**
8) **Patient History**
9) **Withdrawal of blood sample and storage**
10) **Instrument for**
    a) Measurement of drug levels
    b) Measurement of clinical parameters (ECG, EEG ,Respiration etc.)
11) **Report preparation**
12) **Clinical interpretation**


TDM PROTOCOL
Clinical Situation Requiring TDM
Collect Blood Sample at Appropriate Time
Transport and Store Sample
Estimate Drug Concentration
INTERPRET TDM RESULT


Lack Of Clinical Response
Result below therapeutic range
Result With In Therapeutic Range
Result Above Therapeutic Range
Check adherence
Check adherence
Change therapy or re-consider diagnosis
If adherent consider dose increase
If adherent consider small dose increase if result is at lower end of range Alternatively consider change of therapy




## 57. Explain the role of clinical pharmacist in TDM

A Clinical pharmacist with adequate pharmacokinetic background can play a vital role in helping the physician for individualizing drug therapy.

### The role of clinical pharmacist in TDM:

- Contribute to monitoring decisions
- **Advise multidisciplinary healthcare team(doctors , nurses)**
- When TDM is required and suggest time to take TDM samples.
- How to interpret TDM results and suggest drug therapy options

E.g.: reduce dose /frequency or possibly change drug

- **Determine what factors may contribute to unexpected TDM levels**
- Unusual timing of doses
- Other drug involvement
- Initial selection of drug regimen : decisions about drug choice , dosing , dosing interval , route of administration and dosage form of drug considering age , sex , weight , race , metabolism , renal function , plasma albumin concentration , use of other drugs and laboratory results.
- Refinement and adjustment of the dosage regimen based on TDM results and the patient's clinical response.
- Assessment of possible causes for unexpected results, such as non-compliance, bioavailability problems, medication errors, drug interactions, or pharmacogenetic variability.
- Dosage adjustment for patients on haemodialysis or peritoneal dialysis
- Research activities.
- Provision of poison information

## 58. Explain the relationship between dose and pharmacological effect of a drug?

**Dose response relationship:**

The pharmacological effect of a drug depend on its concentration at the site of action, which in turn is determined by the dose of the drug administered. Such a relationship is called dose-response relationship.

**Types of dose-response curves**

Graded dose response:

As the concentration of a drug increases, its pharmacological effect also gradually increases until all the receptors are occupied (the maximum effect).

Quantal dose response curve:

Certain pharmacological effects which cannot be quantified but can only be said to be present or absent.

Therapeutic index:

The relationship between the doses of a drug required to produce desired and undesired effect.

**Therapeutic index =LD50/ED50**

LD50: It is the dose of a drug, which produce the desired effect in 50% of the population.

ED50: It is the dose of the drug, which produce the desire effect in 50% of the population.

Drug potency:

- The amount of a drug required to produce a desired response, the lower the dose required for a given response.
- The dose or concentration of a drug required to produce a given effect or the activity per unit weight of drug is called potency.

**Drug efficacy:**

It is the maximum effect of drug, it depend on the number of drug receptor complex formed and the efficiency with which the activated receptor produce a cellular function.

**Therapeutic window:**

The range of dosage of a drug or of its concentration in a bodily system that provides safe effective therapy.

**Combined effects of drugs:**

- **Additive effect**: It is the overall consequence which is the result of two chemicals acting together and which is the simple sum of the effectsof the chemicals acting independently.
- **Synergistic effects**: are nonlinear cumulative effects of two active ingredients with similar or related outcomes of their different activities, or active ingredients with sequential or supplemental activities.
- **Potentiation: It** is an interaction between two or more drugs or agents resulting in a pharmacologic response greater than the sum of individual responses to each drug or agent, e.g. combination of sedative drugs with alcohol.
- **Antagonism effect:**A receptor antagonist is a type of receptor ligand or drug that blocks or dampens a biological response by binding to and blocking a receptor rather than activating it like an agonist. Antagonistdrugs interfere in the natural operation of receptor proteins.

  **A) Physiological antagonism**: bind to two different receptors and produce opposite effects.
  For example, insulin and glucagon are physiological antagonists of one another.

  b) **Chemical Antagonists:**It is a type of antagonist that binds to a drug or ligand and renders it ineffective. A chemical antagonist does so by causing certain chemical changes in the ligand it binds.

  For example, **protaminesulfate** is a positively charged drug. When it is given IV, it binds to heparin; a negatively charged drug, forming an inactive complex. As a result, heparin cannot perform its function

c) **Physical antagonism:** It is a type of antagonist that is based on the physical property of the drug. It can bind to the agonist and prevent its action. For example, when charcoal is used in case of poison ingestion, such as alkaloid poisons; it acts as a physical antagonist. It has the ability to absorb the poison.

## 59. Explain the relationship between dose and duration of activity of a drug?

**Dose-response relationship**, effect on an organism or, more specifically, on the risk of a defined outcome produced by a given amount of an agent or a level of exposure.

- A dose-response relationship is one in which increasing levels of exposure are associated with either an increasing or a decreasing risk of the outcome.

- Demonstration of a dose-response relationship is considered strong evidence for a causal relationship between the exposure and the outcome. The chance of a causal relationship cannot be disregarded, however, even when a dose-response relationship is absent

- Exposure in investigations of dose-response relationships can be characterized in different ways, including peak exposure; duration of exposure at or above a set level; average exposure, which is a time-weighted average of exposure; or cumulative exposure, which is the sum of time-weighted exposures. In any of those instances, the increase in exposure can be in its intensity or its duration.

- Dose-response relationships can be affected significantly by time.

  For example, the time to response when examining the relationship of the exposure to the outcome can be influenced by a latent period between exposure and the outcome. If the effects are measured too soon after the exposure, no effect will be seen, even in the case where the exposure causes the outcome. One example of this is the increased risk of leukemia after exposure to radiation, which can have a latent period of between 2 and 20 years, depending on the nature of the exposure.

## 60. Explain with suitable examples how elimination half life of a drug influence the duration of activity.

There's obiviosly a correlation between the half-life of a drug and the duration of it's effects. The longer the halflife, the longer the effect.

- The amount of time a drug stays in the body is measured by the elimination half-life.
- This is the time required for the concentration of the drug in the blood to decrease by 50%.
- Half-life affects the frequency of administration
- Drugs with short half-lives are quickly eliminated from the body longer (Ex: PCN given several X per day).
- Drugs with longer half-lives stay in the body longer(Ex: Digoxin given once a day).

- **Effect of elimination half life on duration of activity**

Because elimination of drugs is due to the process of excretion and metabolism an alteration of any of these elimination process will effect the t half of the drug.

Substituting k=o.693/t1/2

teff = 1.44t1/2Ln [DO/VDCeff ]

- Pathophysiological changes in hepatic and renal function decrease elimination, thus prolonging t1/2. This in turn will lead to retention of drug in the body,therby increasing duration of activity of drug as well as increasing possibility of drug toxicity.
- To improve the antibiotic therpy with the pencillin and cephalopod clinicians have intentionally prolonged the elimination of these drugs by giving a second drug prescribed which competitive inhibits the renal excretion of the antibiotic.

## 61. Write about Emax model.

**Emax model:**

Receptor occupancy theory forms the basis of pharmacodynamic response evaluation and is routinely employed to describe concentration–effect/exposure-response relationship in drug discovery and development. The origins of the fundamental PD models can be derived using the receptor occupancy theory. The theory and derivation are described in detail as follows. In general, as the drug is administered, one or more drug molecules may interact with a receptor to form a complex that in turn elicits a pharmacodynamic response.

**R+C↔RC**

The rate of change of the drug–receptor (RC) complex is given by the following equation:

**$[RC]\ DT$ =kon .(RT-RC) . C-koff .**

Where RT is the maximum receptor density, C is the concentration of the drug at the site of action, kon is the second-order association rate constant, and koff is the first-order dissociation rate constant. The term (RT - RC) represents the free receptors, R, available as the total number of receptors, or the maximum receptor density can be written as RT = R + RC.

Under equilibrium conditions, that is, when $[RC]\ dt$ =0, the above equation becomes:

kon . (RT-RC) . C=koff . RC

Upon further rearrangement we get

kon . RT . C= RC . (kon . C+ koff)

$$RC = \frac{k_{on} \cdot R_T \cdot C}{k_{off} + k_{on} \cdot C}$$

$$RC = \frac{R_T \cdot C}{\frac{k_{off}}{k_{on}} + C}$$

$$RC = \frac{R_T \cdot C}{K_D + C}$$

Where KD is the equilibrium dissociation constant ( off/ $kon$ ). Under the assumption that the magnitude of effect, E, is proportional to the [RC] complex, the fraction of maximum possible effect, Emax, is equal to the fractional occupancy, fb= $E$ / , of the receptor, which can be described as

$$f_b = \frac{E}{E_{max}} = \frac{[RC]}{R_T}$$

Hence,

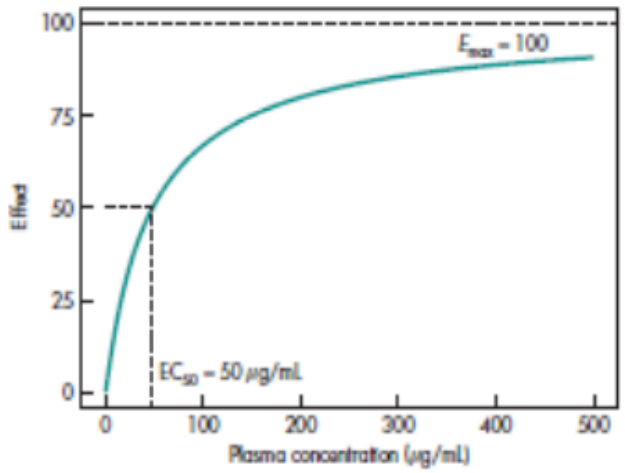
$$E = E_{max} \cdot \frac{\frac{R_T \cdot C}{K_D + C}}{R_T}$$

$$E = \frac{E_{max} \cdot C}{k_D + C}$$

Here, KD has the units of concentration and represents the concentration at which 50% of Emax is achieved. On substituting KD= EC50 yields the classical Emax concentration–effect relationship as below:

$$E = \frac{E_{max} \cdot C}{EC_{50} + C}$$

Emax refers to the maximum possible effect that can be produced by a drug and EC50 is the sensitivity parameter or the potency parameter representing the drug concentration producing 50% of Emax. As the fundamental PK parameters of a drug are clearance (Cl) and volume of distribution (VD), Emax and EC50 are the fundamental PD parameters for a drug, and hence they define the pharmacodynamic properties of the drug. From the above equation, it can be inferred that the typical effect–concentration relationship is curvilinear with parameters as Emax= 100 and EC50=50µg/ml.




- This model incorporates the observation known as law of diminishing returns.
- This law shows that an increase in drug concentration near the maximum pharmacological response produces a disproportionality smaller increase in the pharmacological response.
- This model model describes the drug action in the terms of :
  - Emax(maximum effect).
  - EC50 ( The drug concentration that produce 50% maximum pharmacological effect).

$$E = \frac{E_{max} C}{EC_{50} + C}$$

# Short Answers

## 2 marks

### 63.Enlist various types of samples used for analysis in TDM.

Ans : a) Plasma or serum is commonly used for drug assays.

b) Whole blood for cyclosporine , tacrolimus , sirolimus as there are large shifts of drug between red cells and plasma with storage and temperature change.

c) Saliva , which gives a measure of the unbound drug concentration, may be a useful alternative when blood samples are difficult to collect .

Ex: Phenytoin, Lithium, Amitryptyline

### 64.What do you understand by drug tolerance and physical dependency?

**Drug tolerance :** is a pharmacological concept describing subjects reduced Reactions to a drug following its repeated use. Increasing its dosage may reamplify The drug's effects. Drugs tolerance is indicative of drug use but is use but is not Necessarily associated with drug dependence or addictions .

**Physical dependence :** is a physical condition caused by chronic use of a tolerance forming drug, in which abrupt or gradual drug withdrawal causes unpleasant symptoms . Physical dependence can develop from low- dose therapeutic use of therapeutic use of certain medications such as benzodiazepines, opioids, and antidepressants, as well as the recreational misuse of drugs such as alcohol, opioids and benzodiazepines.

### 65.Define narrow therapeutic index with suitable examples.

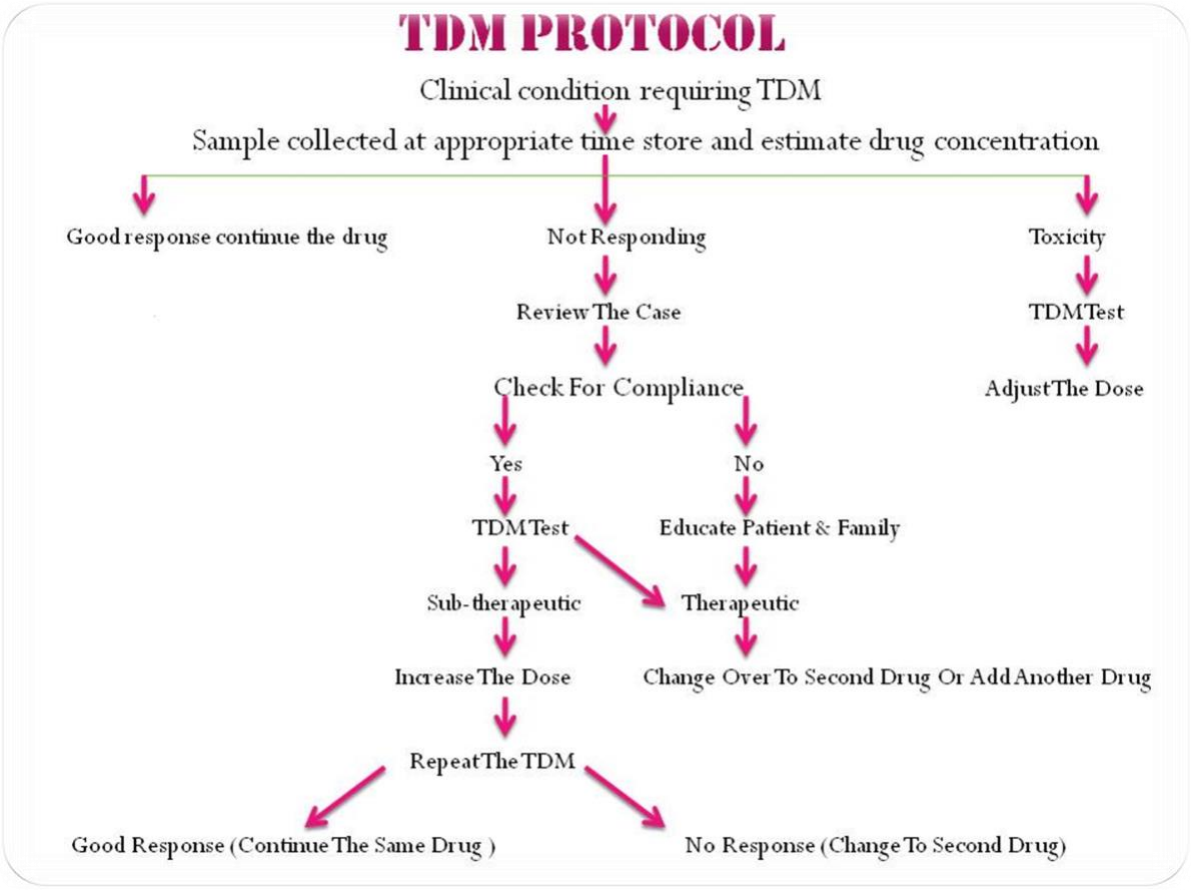
Narrow therapeutic index is a very close margin between the concentration in the blood circulation of a drug that is therapeutic and the concentration that is lethal .
Eg. Quinidine , carbamazepine , levothyroxine digoxin

### 66. Define TDM. Name any four drugs that require TDM.

Therapeutic drug monitoring(TDM)is the clinical practice of measuring specific drugs at designated intervals to maintain as optimizing individual dosage regimens.

Eg: Digoxin, Amikacin , lithium , theophylline

## 67. Write the protocol for TDM of a drug




## 68. Give any four indications for TDM.

- Monitoring compliance
- Individualizing therapy
- during early therapy
- during dosage changes
- Diagnosing undertreatment
- Avoiding toxicity
- Monitoring and detecting drug interactions

## 69. Why is TDM necessary for Digitoxin?

Digitoxin is a cardio active drug with a narrow therapeutic range. Therapeutic drug monitoring is essential in clinical practice for efficacy as well as to avoid Digitoxin toxicity. Immunoassays are commonly used in clinical laboratories for determination of serum or plasma Digitoxin concentrations.

## 70. Why is TDM necessary for methotrexate?

Fewer activated inflammatory cells means a reduction in clinical symptoms ad pain in disease. Therapeuticdrug monitoring of MTX aims to measure the levels of MTX-PGs in the blood cells of patients with rheumatoid arthritis and to correlate these levels with their response to therapy.

## 71. Give the necessity for TDM of lithium.

- Can be measured in blood, saliva, RBC and tears.
- In general only serum or plasma concentrations are measured.
- Narrow therapeutic window.

## 72. Why is TDM necessary for phenytoin.

- TDM is necessary a guide to dosage adjustment.
- Also necessary as the drug exhibits non linear kinetics.
- Necessary as phenytoin has a low therapeutic index.
- The relative rate of elimination is slower at higher concentrations than of lower concentration of the drug.
- Highly protein-bound; drug-drug interactions, drug-disease interactions
- Inter-individual variability in enzyme saturation, Approximately 90% of phenytoin is bound to albumin. Thus, phenytoin levels must be corrected according to albumin levels.

## 73. Why is TDM necessary for phenytoin.

a) TDM is necessary a guide to dosage adjustment.
b) Also necessary as drug exhibits non linear kinetics.
c) Necessary as phenytoin has a low therapeutic index.
d) The relative rate of elimination is slower at higher concentrations than of lower concentrations of the drug.
e) Highly protein-bound drug interactions , drug-disease interactions.
f) Inter-individual variability in enzyme saturation, Approximately 90% of phenytoin is is bound to albumin. Thus, phenytoin levels must be corrected according to albumin levels.

## 74. Explain the reasons for monitoring drug levels.

- These tests are used to monitor blood concentrations of particular drugs that have a narrow dose range in which the drug is effective but not toxic .
- In addition , some drugs require monitoring because the amount of drug administered does not correlate well with the amount of drug that reaches the bloodstream.
- For selected drugs therapeutic drug monitoring aims to enhance drug efficacy , reduce toxicity or assist with diagnosis.

# UNIT III : PHARMACOKINETIC DRUG INTERACTIONS

## SHORT ESSAY

## 75.Explain the various pharmacokinetic drug interactions with suitable examples

Pharmacokinetic interactions are those in which one drug alters the rate or extent of absorption, distribution or elimination (metabolism and/or excretion) of another drug.

This is most commonly measured by a change in one or more kinetic parameters, such as maximum serum concentration, area under the concentration-time curve, half-life, and total amount of drug excreted in the urine.

**VARIOUS PHARMACOKINETIC INTERACTION**

- **ABSORPTION INTERACTION**
  Drug interaction can affect the rate and the extent of systemic drug absorption (bioavailability) from the absorption site, resulting in increased or decreased drug bioavailability.
- **DISTRIBUTION INTERACTION**
  Drug distribution may be altered by displacement of the drug from plasma protein or other binding sites due to competition for the same binding site.
- **HEPATIC ELIMINATION INTERACTION**
  Drugs that share the same drug-metabolizing enzymes have a potential for a drug interaction.
- **RENAL CLEARANCE INTERACTION**
  Drugs that compete for active renal secretion may decrease renal clearance of the first drug. Probenecid blocks the active renal secretion of penicillin drugs.

## Table 20.10 Pharmacokinetic Drug Interactions

| Drug Interaction | Examples (Precipitant Drugs) | Effect (Object Drugs) |
|---|---|---|
| **Bioavailability** | | |
| Complexation/chelation | Calcium, magnesium, or aluminum and iron salts | Tetracycline complexes with divalent cations, causing a decreased bioavailability |
| Adsorption binding/ionic interaction | Cholestyramine resin (anion-exchange resin binding) | Decreased bioavailability of thyroxine, and digoxin; binds anionic drugs and reduces absorption |
| Adsorption | Antacids (adsorption) | Decreased bioavailability of antibiotics |
| | Charcoal, antidiarrheals | Decreased bioavailability of many drugs |
| Increased GI motility | Laxatives, cathartics | Increases GI motility, decreases bioavailability for drugs which are absorbed slowly; may also affect the bioavailability of drugs from controlled-release products |
| **Distribution** | | |
| Protein binding | Warfarinâ€"phenylbutazone | Displacement of warfarin from binding |
| | Phenytoinâ€"valproic acid | Displacement of phenytoin from binding |
| **Hepatic elimination** | | |
| Enzyme induction | Smoking (polycyclic aromatic hydrocarbons) | Smoking increases theophylline clearance |
| | Barbiturates | Phenobarbital increases the metabolism of warfarin |
| Enzyme inhibition | Cimetidine | Decreased theophylline, diazepam metabolism |
| Mixed-function oxidase | | |
| | Fluvoxamine | Diazepam $t_{1/2}$ longer |
| | Quinidine | Decreased nifedipine metabolism |
| | Fluconazole | Increased levels of phenytoin, warfarin |
| Other enzymes | Monoamine oxidase inhibitors, MAO-I (eg, pargyline, tranylcypromine) | Serious hypertensive crisis may occur following ingestion of foods with a high content of tyramine or other pressor substances (eg, cheddar cheese, red wines) |
| Inhibition of biliary secretion | Verapamil | Decreased biliary secretion of digoxin causing increased digoxin levels |

| Drug Interaction | Examples (Precipitant Drugs) | Effect (Object Drugs) |
|---|---|---|
| Decreased GI motility | Anticholinergic agents | Propantheline decreases the gastric emptying of acetaminophen (APAP), delaying APAP absorption from the small intestine |
| Alteration of gastric pH | H-2 blockers, antacids | Both H-2 blockers and antacids increase gastric pH; the dissolution of ketoconazole is reduced, causing decreased drug absorption |
| Alteration of intestinal flora | Antibiotics (eg, tetracyclines, penicillin) | Digoxin has better bioavailability after erythromycin; erythromycin administration reduces bacterial inactivation of digoxin |
| Inhibition of drug metabolism in intestinal cells | Monoamine oxidase inhibitors (MAO-I) (eg, tranylcypromine, phenelzine) | Hypertensive crisis may occur in patients treated with MAO-I and foods containing tyramine |
| **Distribution** | | |
| Protein binding | Warfarinâ€"phenylbutazone | Displacement of warfarin from binding |
| | Phenytoinâ€"valproic acid | Displacement of phenytoin from binding |
| **Hepatic elimination** | | |
| Enzyme induction | Smoking (polycyclic aromatic hydrocarbons) | Smoking increases theophylline clearance |
| | Barbiturates | Phenobarbital increases the metabolism of warfarin |
| Enzyme inhibition | Cimetidine | Decreased theophylline, diazepam metabolism |

## RENAL CLEARANCE

### Glomerular filtration rate (GFR) and renal blood flow

Eg:Methylxanthines (eg, caffeine, theobromine)(percipitant drug)

Increased renal blood flow and GFR will decrease time for reabsorption of various drugs, leading to more rapid urinary drug excretion

### Active tubular secretion

Eg :Probenecid(percipitant drug) Probenecid blocks the active tubular secretion of penicillin and some cephalosporin antibiotics

### Tubular reabsorption and urine pH

- Antacids, sodium bicarbonate(percipitant drug) Alkalinization of the urine increases the reabsorption of amphetamine and decreases its clearance
- Alkalinization of urine pH increases the ionization of salicylates, decreases reabsorption, and increases its clearance .

## 76. Explain the influence of drug interaction on drug absorption with examples?

- **Drug-drug interactions** occur when two or more drugs react with each other. This drug-druginteraction may cause you to experience an unexpected side effect.

- Drugs Interacting at Sites of Absorption;

- Interactions affecting rate of absorption:

- The rate of absorption determines how fast drug enters the blood and the peak concentrations obtained. Absorption rate is usually not critically important, since patients requiring immediate therapy usually receive the drug parenterally.

- Interactions affecting extent of absorption:

- Extent of absorption affects the total amount available systemically. Interactions of this type will alter the relationship between the dose administered and serum concentrations achieved, requiring alterations in the dosage regimen. A decreased extent of absorption can result in a substantial decrease in circulating serum concentrations of a drug, thereby compromising therapy. An increase in absorption, though unusual, could subject the patient to drug toxicity.

- Types of Interactions:

- Formation of drug complexes due to absorption; chelation, or binding

- Interactions before Administration:
- Phenytoin precipitates in dextrose solutions (e.g. D5W), Amphotericin precipitates in saline, Gentamicin is physically/chemically incompatible with most beta-lactams, resulting in loss of antibiotic effect.
-
- In the GI Tract:
- Sucralfate, some milk products, antacids, and oral iron preparations block absorption of quinolones, tetracycline, and azithromycin Cholestyramine binds raloxifene, thyroid hormone, and digoxin
-
- Alterations in gastric pH:
- Omeprazole, lansoprazole, H2-antagonists can reduce absorption of ketoconazole, or delavirdine Didanosine (given as a buffered tablet) can reduce ketoconazole absorption
- Altered GI Function and Presystemic Effects: This may not be an alteration is absorption, per se, but has the same net effect.
- Changes in GI motility
- Alterations in GI mucosal function
- Effects on GI metabolism
- Effects on membrane absorption sites
- Alterations in GI perfusion
- Examples:
- Gut transit and metabolism
- Intestinal wall CYP3A4 metabolizes a number of drugs
- Inhibition/induction results in altered bioavailability grapefruit juice inhibits intestinal CYP3A4
- Results in increased bioavailability of calcium channel blockers (dihydropyridine), cyclosporin, saquinavir (HIV-1 protease inhibitors), carbamazepine, lovastatin, terazosin, triazolam and midazolam.
- High intrinsic hepatic clearance dependent upon hepatic blood flow Inhibition results in increased bioavailabilty. Propranolol, metoprolol, labetalol, verapamil, hydralazine, felodipine, clhlorpromazine, imipramine, amitriptyline, morphine
-
- Monoamine Oxidase Inhibitors

- Intestinal MAO inhibited by nonselective irreversible agents and inhibit metabolism of dietary tyramine resulting in increased release of norepi from sympathetic postganglionic neurons less problematic for selective MAO B inhibitor selegiline and reversible agent moclobemide

## 77. Discuss drug interactions related to protein binding and metabolism.

### (a) Interaction affecting distribution of drugs:

Though several factors govern the distribution of drugs to various tissues, clinically significant interactions result due to competition between drugs for binding proteins/tissues and displacement of one drug by the other. Competitive displacements, which result when two drugs are capable of binding to the same site on the protein, cause the most significant interaction. Greater risk of interaction exists when the displaced drug is highly protein bound (more than 95%), has a small volume of distribution and has narrow therapeutic index (e.g. tolbutamide, warfarin and phenytoin), and when the displacer drug has a higher degree of affinity than the drug to be displaced. In such situation, displacements of even a small percent of drug results in a tremendous increase in the free form of the drug, which precipitates increased therapeutic or toxic-effects.

Drugs may also be displaced from binding site in tissues. An interesting example of this is oral hypoglycemic such as the sulphonylureas (tolbutamide, glibenclamide, etc.). These agents exert their therapeutic effects by displacing insulin from protein binding sites in pancreas, plasma and other region resulting in its elevated levels.

### (b) Interaction affecting metabolism of drugs:

The most important and most common cause of pharmacokinetic interaction is alteration in the rate of biotransformation of drugs. Major problems arise when one drug either induces or inhibits the metabolism of 18 anther drug.

Even the environmental chemical can bring about such an effect. The influence of enzyme inducers and inhibitors become more pronounced when drugs susceptible to first-pass hepatic metabolism are giving concurrently. The metabolic pathway usually affected is phase-1 oxidation.

Enzyme inducers reduce the blood level and clinical efficacy of co-administered drugs but may also enhance the toxicity of drugs having active metabolites. In contrast to enzyme induction, which is usually not hazardous, enzyme inhibition leads to accumulation of drug to toxic levels and serious adverse effects may be precipitated.

## 78. Describe the role of cytochrome P-450 enzymes in drug interactions. Add a note with suitable examples and their clinical significance.

**INDUCTION OF DRUG METABOLISM**

Cytochrome P-450 isozymes are often involved in the metabolic oxidation of many drugs. Many drugs can stimulate the production of hepatic enzymes. Therapeutic doses of phenobarbital andother barbiturates accelerate the metabolism of coumarin anticoagulants such as warfarin and substantially reduce the hypoprothrombinemic effect.

Fatal hemorrhagic episodes can result when phenobarbital is withdrawn and warfarin dosage maintained at its previous level. Other drugs known to stimulate drug metabolism include carbamazepine, rifampin, valproic acid, and phenytoin. Enzymatic stimulation can shorten the elimination half-life of the affected drug. For example, phenobarbital can result in lower levels of dexamethasone in asthmatic patients taking both drugs.

## 79. Explain the influence of drug interaction on drug metabolism with respect to enzyme induction and enzyme inhibition.

**INHIBITIONOFDRUGMETABOLISM**

- Numerous clinical instances of severe adverse reactions as a result of drug interaction involving a change in the rate of drug metabolism have been reported.
- Knowledge of pharmacokinetics allows the clinical pharmacist to evaluate the clinical significance of the drug interaction. Pharmacokinetic models help to determine the need for dose reduction or discontinuing a drug.
- In assessing the situation, the pathophysiology of the patient and the effect of chronic therapy on drug disposition in the patient must be considered.
- A severe drug reaction in a patient with liver impairment has resulted in near-fatal reaction in subjects taking otherwise safe doses of acetaminophen.
- In some patients within jury or severe cardio vascular disease, blood flow maybe impaired, resulting in delayed drug absorption and distribution.
- Many incidents of serious toxicity or accidents are caused by premature administration of a "booster dose" when the expected response is not immediately observed.
- Potent drugs such as morphine, midazolam ,lidocaine ,pentothal, and fentenyl can result in serious adverse reactions if the kinetics of multiple dosing are not carefully assessed.

**Examples**

**1.*Fluvoxamine doubles the half-life of diazepam:*** The effect of fluvoxamine on the pharmacokinetics of diazepam was investigated in healthy volunteers. Concurrent fluvoxamine intake increased mean peak plasma diazepam concentrations from 108 to 143 ng/mL, and oral diazepam clearance was reduced from 0.40 to 0.14 mL/min/kg.
The half- life of diazepam increased from 51 to 118 hours. The area under the plasma concentration time curve for the diazepam metabolite N-desmethyl diazepam was also significantly increased during fluvoxamine treatment. These data suggest that fluvoxamine inhibits the biotransformation of diazepam and its active N-demethylated metabolite.

**2.** ***Quinidine inhibits the metabolism of nifedipine and other calcium channel-blockingagents*:** Quinidine co administration significantly inhibited the aromatization of nifedipine to its major first-pass pyridine metabolite and prolonged the elimination half-life by about 40%. The interaction between quinidine and nifedipine supports the involvement of a common cytochrome P-450 (P450 3A4) in the metabolism of the two drugs

***3.Theophylline clearance is decreased by cimetidine***: Controlled studies have shown that cimetidine can decrease theophylline plasma clearance by 20 - 40% (apparently by inhibiting demethylation).Prolongation of half-life by as much as 70% was found in some patients. Elevated

theophylline plasma concentrations with toxicity may lead to nausea,vomiting,cardiovascular instability, and even seizure

**4.*Cimetidine and diazepam interaction*:** The administration of 800mg of cimetidine daily for 1 week increased the steady-state plasma diazepam and nor diazepam concentrations due to a cimetidine- induced impairment in microsomal oxidation of diazepam and nor diazepam. The concurrent administration of cimetidine caused a decrease in total metabolic clearance of diazepam and its metabolite, nor diazepam.

**INDUCTIONOFDRUGMETABOLISM**

- Cytochrome P-450 isozymes are often involved in the metabolic oxidation of many drugs.
- Many drugs can stimulate the production of hepatic enzymes.
- Therapeutic doses of Phenobarbital and other barbiturates accelerate the metabolism of coumarin anticoagulants such as warfarin and substantially reduce the hypoprothrombinemic effect. Fatal hemorrhagic episode scan result when Phenobarbital is withdrawn and warfarin dosage maintained at its previous level.
- Other drugs known to stimulate drug metabolism include carbamazepine, rifampin, valproic acid,and phenytoin.
- Enzymatic stimulation can shorten the elimination half-life of the affected drug. For example, Phenobarbital can result in lower levels of dexamethasone in asthmatic patients taking both drugs.

## 80. Explain the effect of inhibition of biliary excretion of drugs and list out the drug interactions which influence the biliary excretion.

**Drug interactions in biliary excretion**

- Drugs are conjugated and excreted in bile . Some drugs are excreted in bile without biotransformation .
- For examples, in humans , most water-soluble drugs and metabolites of relatively high molecular weight( more than about 450) are excreted largely in the bile.
- This excretion is mainly via transportes , and the possibility exists for drug interactions with concomitant adminstration.
- Conjugates such as glucuronides are often excreted in bile and then deconjugated in the intestinal tract and reabsorbed(enterohepatic circulation)
- Drug interactions in the process of biliary excretion may affect the residence time and AUC of the unchanged drug in plasma.

**HEPATOBILIARY DRUG INTERACTION:**

| Transporter | Drug | Inhibitor | Result of interaction |
|---|---|---|---|
| P-gp | Digoxin | Quinidine | ↓sed biliary excretion |
| MR1*2 | SN-38 | Probenicid | ↓sed biliary excretion ,results in |

| | | | |
|---|---|---|---|
| | | | ↑sed AUC |

**1.**The coadminstration of drugs which inhibit the co-transporter involved in biliary excretion can reduce the biliary excretion of drug which are substrates of transporter leading to elevated plasma concentration of drugs.

**2.** Irinotecan is a component in chemotherapy of advanced colorectal cancer , it is metabolized by carboxylase esterase 2 to SN-38 (Active metabolite) which is conjugated by uridine diphosphate glucoronide to SN-38 glucoronide . Probenicid inhibits MR1*2 transporter resulting in decreased biliary excretion and increased plasma drug concentration.

**INHIBITIONOFBILIARYEXCRETION**

- The interaction between digoxin and verapamil () was studied insix patients (mean age 61 ± 5 years) with chronic atrial fibrillation.
- The effects of adding verapamil (240mg/day) on steady-state plasma concentrations of digoxin were studied.
- Verapamil induced a 44% increase in steady-state plasma concentrations of digoxin.The biliary clearance of digoxin was determined by a duodenal perfusion technique.
- The biliary clearance of digoxin decreased by 43%, from 187 ± 89 to 101 ± 55 mL/min,where as the renal clearance was not significantly different(153±31versus173±51mL/min).

## DOSAGE ADJUSTMENT IN RENAL AND HEPATIC DISEASE

**10 MARKS**

**81. Explain in detail the general approaches for dosage adjustmentin renal disease.**

**88.How do you adjust dosage regimen in renal failure patients based on elimination half life of drug?( 5 marks)**

**Ans)**

## GENERAL APPROACHES FOR DOSE ADJUSTMENT IN RENAL DISEASE

Several approaches are available for estimating the appropriate dosage regimen fora patient with renal impairment. Each of these approaches has similar assumptions,as listed in . Most of these methods assume that the required therapeutic plasma drug concentration in uremic patients is similar to that required in patients with normal renal function. Uremic patients are maintained on the same $C_{av}^{\hat{a}}$ after multiple oral doses or multiple IV bolus injections. For IV infusions, the same $C_{SS}$ is maintained. ($C_{SS}$ is the same as $C_{av}^{\hat{a}}$ after the plasma drug concentration reaches steady state.)

**Table 21.2 Common Assumptions in Dosing Renal-Impaired Patients**

| Asumption | Comment |
|---|---|
| Creatinine clearance accurately measures the degree of renal impairment | Creatinine clearance estimates may be biased. Renal impairment should also be verified by physical diagnosis and other clinical tests. |
| Drug follows dose-independent pharmacokinetics | Pharmacokinetics should not be dose-dependent (nonlinear). |
| Nonrenal drug elimination remains constant | Renal disease may also affect the liver and cause a change in nonrenal drug elimination (drug metabolism). |
| Drug absorption remains constant | Unchanged drug absorption from gastrointestinal tract. |
| Drug clearance, $Cl_u$, declines linearly with creatinine clearance, $Cl_{Cr}$ | Normal drug clearance may include active secretion and passive filtration and may not decline linearly. |
| Unaltered drug protein binding | Drug protein binding may be altered due to accumulation of urea, nitrogenous wastes, and drug metabolites. |
| Target drug concentration remains constant | Changes in electrolyte composition such as potassium may affect sensitivity to the effect of digoxin. Accumulation of active metabolities may cause more intense pharmacodynamic response compared to parent drug alone. |

The design of dosage regimens for uremic patients is based on the pharmacokinetic changes that have occurred as a result of the uremic condition. Generally, drugs in patients with uremia or kidney impairment have prolonged elimination half-lives

and a change in the apparent volume of distribution. In less severe uremic conditions there may be neither edema nor a significant change in the apparent volume of distribution. Consequently, the methods for dose adjustment in uremic patients are based on an accurate estimation of the drug clearance in these patients.

Several specific clinical approaches for the calculation of drug clearance based on monitoring kidney function are presented later in this chapter. Two general pharmacokinetic approaches for dose adjustment include methods based on drug clearance and methods based on the elimination half-life.

## Dose Adjustment Based on Drug Clearance

Methods based on drug clearance try to maintain the desired $C_{av}^{\infty}$ after multiple oral doses or multiple IV bolus injections as total body clearance, $Cl_t$, changes. The calculation for $C_{av}^{\infty}$ is

$$C_{av}^{\infty} = \frac{FD_0}{Cl_T \tau} \quad (1)$$

For patients with a uremic condition or renal impairment, total body clearance of the uremic patient will change to a new value,$Cl^u_T$. Therefore, to maintain the samedesired $C_{av}^{\infty}$, the dose must be changed to a uremic dose, $D^u_0$ or the dosage interval must be changed to $\tau^u$, as shown in the following equation:

$$C_{av}^{\infty} = \underbrace{\frac{D_0^N}{Cl_T^N \tau^N}}_{\text{(normal)}} = \underbrace{\frac{D_0^u}{Cl_T^u \tau^u}}_{\text{(uremic)}} \quad (2)$$

where the superscripts N and u represent normal and uremic conditions, respectively. Rearranging Equation 2 and solving for $D^u_0$.

$$D_0^u = \frac{D_0^N Cl_T^u \tau^u}{Cl_T^N \tau^N} \quad (3)$$

If the dosage interval is kept constant, then the uremic dose $D^u_0$ is equal to afraction ($Cl^u_T/Cl^N_T$) of the normal dose, as shown in the equation

$$D_0^u = \frac{D_0^N Cl_T^u}{Cl_T^N} \quad (4)$$

For IV infusions the same desired $C_{SS}$ is maintained both for patients with normal renal function and for patients with renal impairment. Therefore, the rate of infusion, R, mustbe changed to a new value, $R^u$, for the uremic patient, as described by the equation

$$C_{SS} = \frac{R}{Cl_T^N} = \frac{R^u}{Cl_T^u}$$
(normal) (uremic)

**Dose Adjustment Based on Changes in the Elimination Rate Constant**The overall elimination rate constant for many drugs is reduced in the uremic patient. A dosage regimen may be designed for the uremic patient either by reducing the normal dose of the drug and keeping the frequency of dosing (dosage interval) constant, or by decreasing the frequency of dosing (prolonging the dosage interval) and keeping the dose constant. Doses of drugs with a narrow therapeutic range should be reduced particularly if the drug has accumulated in the patient prior to deterioration of kidney function.

The usual approach to estimating a multiple-dosage regimen in the normal patient isto maintain a desired $C_{av}$, as shown in Equation 1. Assuming the $V_D$ is the same in both normal and uremic patients and is constant, then the uremic dose $D_0^u$ is a fraction ($k^u/k^N$) of the normal dose :

$$D_0^u = \frac{D_0^N k^u}{k^N}$$

(6)

When the elimination rate constant for a drug in the uremic patient cannot be determined directly, indirect methods are available to calculate the predicted elimination rate constant based on the renal function of the patient. The assumptions on which these dosage regimens are calculated include the following.

1. The renal elimination rate constant ($k_R$) decreases proportionately as renal function decreases. (Note that $k_R$ is the same as $k_e$ as used.)
2. The nonrenal routes of elimination (primarily, the rate constant for metabolism) remain unchanged.
3. Changes in the renal clearance of the drug are reflected by changes in the creatinine clearance.

The overall elimination rate constant is the sum total of all the routes of eliminationin the body, including the renal rate and the nonrenal rate constants:

$$k^u = k_{nr} + k_R^u$$

(7)

where $k_{nr}$ is the nonrenal elimination rate constant and $k_R$ is the renal excretionrate constant.

Renal clearance is the product of the apparent volume of distribution and the rate constant for renal excretion:

$$Cl_R^u = k_R^u V_D^u$$

(8)

Rearrangement of Equation 8 gives

$$k_R^u = Cl_R^u \frac{1}{V_D^u}$$

(9)

Assuming that the apparent volume of distribution and nonrenal routes ofelimination do not change in uremia, then $k^u_{nr} = k^N_{nr}$ and $V^u_D = V^N_D$.

Substitution of Equation 9 into Equation 7 gives

$$k^u = k_{nr} + \frac{1}{V_D} Cl_R^u$$

(10)

From Equation 10, a change in the renal clearance, $Cl^u_R$, due to renal impairmentwill be reflected in a change in the overall elimination rate constant $k_u$. Because changes in the renal drug clearance cannot be assessed directly in the uremic patient, $Cl^u_R$ is usually related to a measurement of kidney function by the glomerular filtration rate (GFR), which in turn is estimated by changes in the patients creatinine clearance.

## 82)Explain in detail the different methods of extracorporealremoval of drugs.

Ans) EXTRACORPEAL METHODS OF DRUG REMOVAL

Extracorporeal therapy is a medical procedure which is performed outside the body . For patients with end-stage renal disease and drugoverdose to remove accumulated drug and its metabolites.

Objective:

To remove rapidly the undesirable drugs and metabolites from thebody
Methods available for drug removal

- Hemodialysis
- Peritoneal dialysis
- Hemofiltration
- Hemodiafiltration
- Hemoperfusion

Dialysis is the process of separating elements in a solution by diffusion across a semipermeable membrane down a conc.gradient

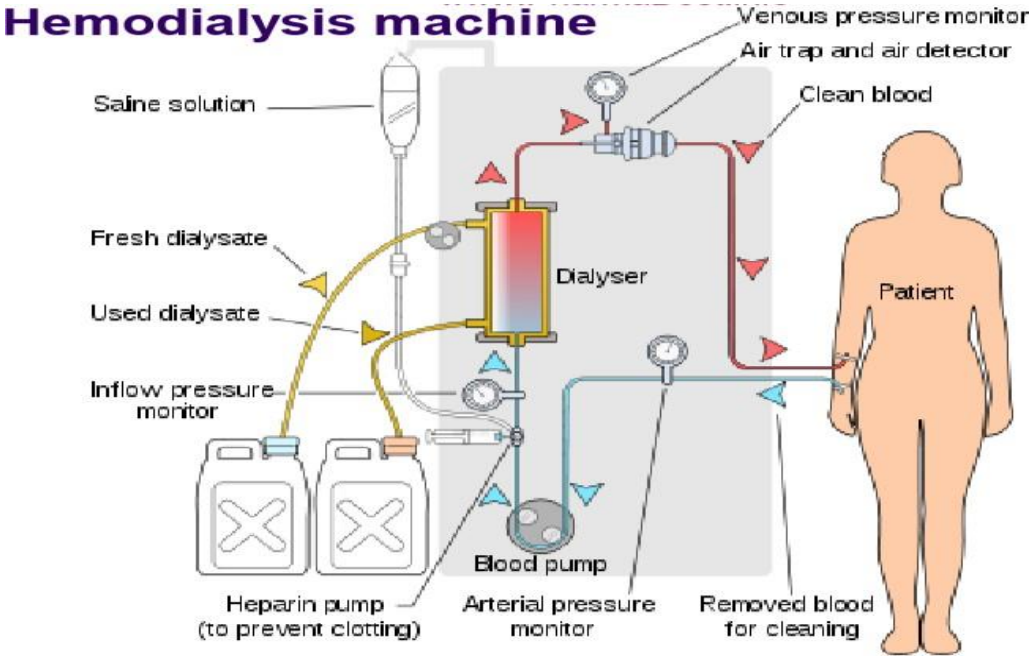
1) HEMODIALYSIS:

The method for removing waste products such as creatinine and urea, as well as free water from the blood when the kidneys are inrenal failure

**Principle:** involves diffusion of solutes across a semipermeable membrane

## How Does Hemodialysis Work?

- A dialysis machine pumps small blood out of the body, mixed with anticoagulant and circulated through a filter called dialyzer.
- inside the dialyzer, a porous artificial membrane separates blood from the dialysis fluid (dialysate)
- diffusion of extra fluid and wastes from the blood into the dialysate
- purified blood is then pumped back into the body.
- Membrane is permeable to water and small ions but is impermeable to blood cells,lipids, or plasma proteins
- utilizes counter current flow,ie. dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit.
- Counter-current flow maintains the conc. gradient across the membrane at a maximum and increases the efficiency of the dialysis.
- Pressure in the dialysate compartment is lower than blood compartment.



## TYPES OF HEMODIALYSIS ACCESS

- For temporary access
- a shunt is created in the arm, with one tube inserted in an artery and another in a vein.
- -tubes are joined above the skin
- For permanent access
- -an arterio-venous fistula or graft is created by a surgicalprocedure

## How is blood removed and replaced?

- An intravenous catheter
- An arteriovenous (AV) fistula
- A synthetic graft

## Types of hemodialysis

- Conventional hemodialysis
- Daily hemodialysis
- nocturnal hemodialysis

## Conventional hemodialysis

- Done 3 times per week, for about 3-4hrs for each treatment, during which patient's blood is drawn out through a tube at a rate of 3400cc/min.
- During treatment, the patient's entire blood volume circulates through the machine every 15 minutes

### Daily hemodialysis

- Used by patients who do their dialysis at home
- Usually done for 2 hours, six days a week

### Nocturnal hemodialysis

- Performed six nights a week and six-ten hours per session while the patient sleeps.

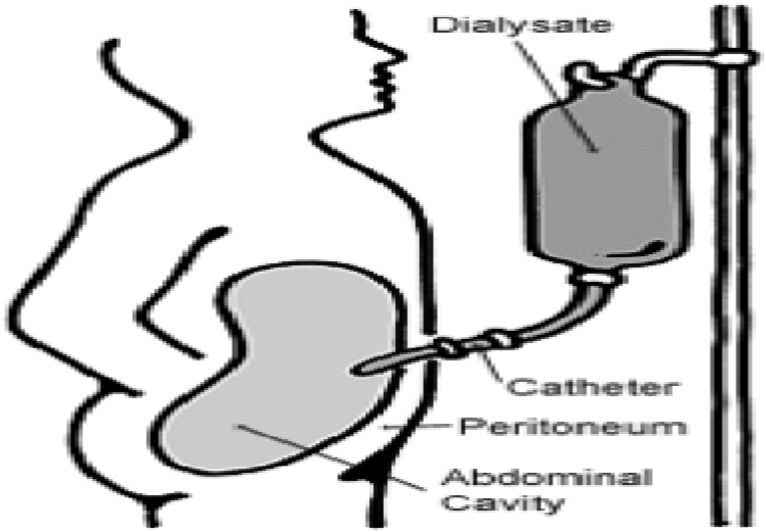
Applications

- Mainly used in chronic renal failure and in poisoning bycertain agents such as salicylates, phenobarbitone, methanol,ethylene glycol and lithium.

**2.** Peritoneal dialysis

Introducing dialyzing fluid into the peritoneal cavity via a catheterand after a period, the fluid is drained and discarded.

**Principle** : osmosis and diffusion




The process uses the patient's peritoneum in the abdomen as a membrane across which fluids and dissolved substances (electrolytes, urea, glucose, albumin and other small molecules) areexchanged from the blood.

Membrane restricts the movement of formed elements(eg.erythrocytes) and large molecules(eg.protein) butallows the movement of smaller molecules according to the conc.gradient.Techniques used for peritoneal dialysis

- Manual intermittent peri.dialysis
- Automated cycler intermittent peri.dialysis
- Continuous ambulatory peri.dialysis

Manual intermittent peri.dialysis

Bags containing fluid are warmed to body temp; fluid is infused for 10mins, allowed to remain there for 60 to 90 mins and then drainedin about 10 to 20mins

Automated cycler intermittent peri.dialysis

- Timed device, performed by people in their home.
- People set the cycler at bedtime so the dialysis takes placewhile they are sleeping
- Performed 6 or 7 nights a week

Continuous ambulatory peritoneal dialysis

- During the day by keeping 2l of fluid in the abdomen at alltimes
- Exchanging the fluids 4-6 times per day

Peritoneal Dialysis solution

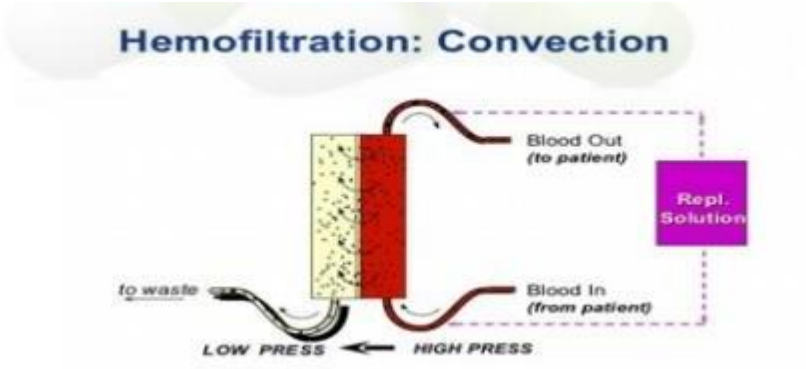
- Sodium chloride 5.6g
- Calcium chloride 0.26g
- Magnesium chloride 0.15g
- Sodium lactate 5.0g
- Anhydrous glucose 13.60g
- Water for inj. To 1000ml

Glucose increases osmotic pressure and thereby determines the rateof fluid transfer and facilitates ultra filtration

**3.** Hemofiltration

- Convective solute transport ie. Movemet of dissolved substances with fluid flow through filtering membrane

- blood is passed through a set of tubing (a filtration circuit) viaa machine to a semipermeable membrane (the filter) where waste products and water are removed.
- Replacement fluid is administered to the patient for volume replacement
- purified blood is returned to the patient.




- dialysate is not used.
- positive hydrostatic pressure drives water and solutes across the filter membrane from the blood to the filtrate compartment, from which it is drained.
- Removes nonprotein bound,small molecules from blood

TYPES OF HEMOFILTRATION

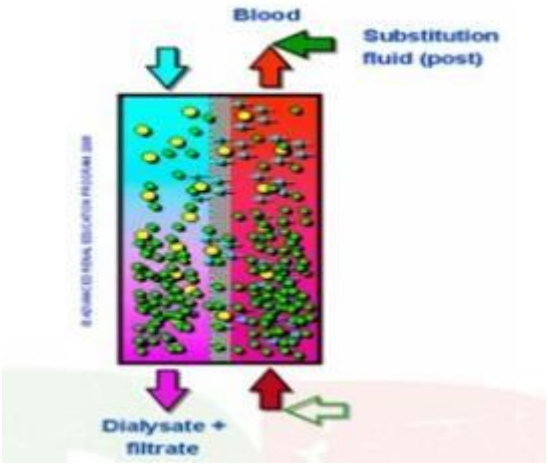
- Continous veno-venous hemofiltration
- hemofilter is placed between cannulated femoral, subclavian orinternal jugular veins
- Continous arteriovenous hemofiltration
- blood passes through a hemofilter that is placed between acannulated femoral artery and vein

**4)** Hemodiafiltration

Hemofiltration in combination with hemodialysis

- Blood is pumped through the blood compartment of a high flux dialyzer, and a high rate of ultrafiltration is used

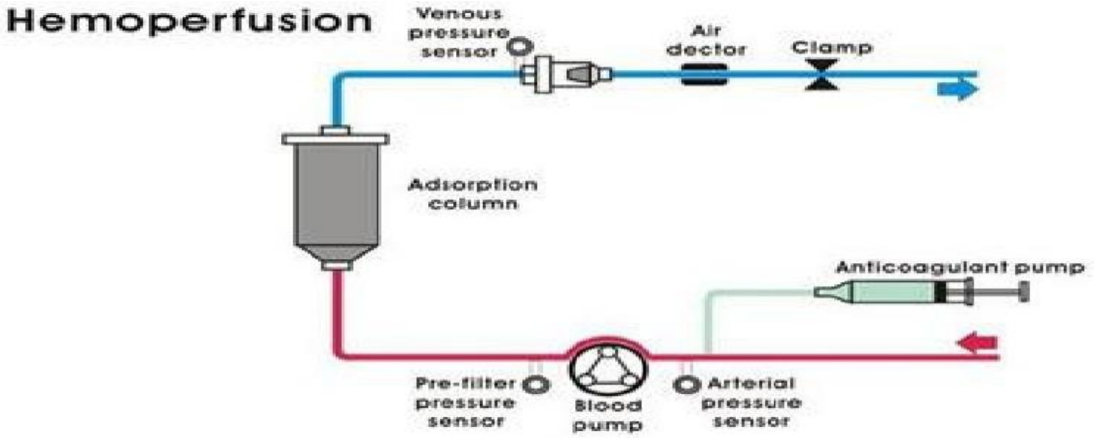
- So high rate of movement of water and solutes from blood to dialysate that must be replaced by substitution fluid that is infused directly into the blood line.
- Dialysis solution is also run through the dialysate compartment of the dialyzer




- Blood pump is used to drive blood flow through the filter Access is achieved through a catheter
- Good removal of both large and small mole.wgt solutes

5 )Hemoperfusion

- Blood is passed through an adsorbent material which attracts toxic substances.
- Adsorbent is fixed to a solid surface inside a column.
- Patient's blood is passed through the column and toxins bind to the adsorbent material, allowing cleansed blood to flow out of the column.



Adsorbents used:

a.Activated charcoal

b.Amberlite resin (Amberlite XAD-2/XAD-4)

- Activated charcoal adsorbs both polar and nonpolar drugs

-Amberlite resins are available as insoluble polymeric beads, each containing agglomerate of polystyrene microspheres; greater affinityfor nonpolar drugs

- heparin is given at the beginning of the procedure and at 15-20mins interval
- Treatment takes about 3 hrs
- Useful for rapid drug removal in accidental poisoning and reducing blood conc.of lipid soluble or protein-bound drugs such as medium and short-acting barbiturates and theophylline

Factors for drug removal by hemoperfusion

- Affinity of the drug for the adsorbent
- Surface area of the adsorbent
- Absorptive capacity of the adsorbent
- Rate of blood flow through the adsorbent
- Equilibration rate of the drug from the peripheral tissue into the blood

83)**Discuss various markers used in the measurement of glomerular filtration rate along with their advantages and disadvantages . Enumerate the various formula used for the measurement of creatinine clearance ?**

Several drugs and endogenous substances have been used as markers to measure GFR. These markers are carried to the kidney by the blood via the renal artery and are filtered at the glomerulus. Several criteria are necessary to use a drug to measure GFR

1. The drug must be freely filtered at the glomerulus.
2. The drug must not be reabsorbed nor actively secreted by the renal tubules.
3. The drug should not be metabolized.
4. The drug should not bind significantly to plasma proteins.
5. The drug should not have an effect on the filtration rate nor alter renal function.
6. The drug should be nontoxic.
7. The drug may be infused in a sufficient dose to permit simple and accurate

quantitation in plasma and in urine.

The commonly used markers for GFR measurement

a) Inulin
b) Creatinine
c) Blood urea nitrogen

- Inulin, a fructose polysaccharide, fulfills most of the criteria listed above and is therefore used as a standard reference for the measurement of GFR.
- In practice, however, the use of inulin involves a time-consuming procedure in which inulin is given by intravenous infusion until a constant steady-state plasma level is obtained.
- Clearance of inulin may then be measured by the rate of infusion divided by the steady-state plasma inulin concentration. Although this procedure gives an accurate value for GFR, inulin clearance is not used frequently in clinical practice.

Advantage

- Inulin freely filtered at the glomerulus
- Inulin is non toxic.
- It is used as the standerd reference for the measurement of GFR.

Disadvantage

- use of inulin involves a time-consuming procedure

b) creatinine clearance

- The clearance of creatinine is used most extensively as a measurement of GFR.
- Creatinine is an endogenous substance formed from creatine phosphate during muscle metabolism. Creatinine production varies with the age, weight, and gender of the individual.
- In humans, creatinine is filtered mainly at the glomerulus, with no tubular reabsorption.
- However, a small amount of creatinine may be actively secreted by the renal tubules, and the values of GFR obtained by the creatinine clearance tend to be higher than GFR measured by inulin clearance.
- Creatinine clearance tends to decrease in the elderly patient. As mentioned in , the physiologic changes due to aging may necessitate special considerations in administering drugs in the elderly

Advantage

It is most widely used marker when compared to others.
It fulfills all the crieteria to become a good marker

Disadvantage

It is altered by physiological changes.

C). Blood urea nitrogen (BUN)

- Blood urea nitrogen (BUN) is a commonly used clinical diagnostic laboratory test for renal disease.
- Urea is the end product of protein catabolism and is excreted through the kidney.
- Normal BUN levels range from 10 to 20 mg/dL. Higher BUN levels generally indicate the presence of renal disease. However, other factors, such as excessive protein intake, reduced renal blood flow, hemorrhagic shock, or gastric bleeding, may affect increased BUN levels.
- The renal clearance of urea is by glomerular filtration and partial reabsorption in the renal tubules. Therefore, the renal clearance of urea is less than creatinine or inulin clearance and does not give a quantitative measure of kidney function.

Advantage

It fulfills all the crieteria to become a good marker.

Disadvantages

It does not give a quantitative measure of kidney function.

FORMULAS FOR MEASUREMENT OF CREATININE CLEARENCE

- Creatinine clearance may be defined as the rate of urinary excretion of creatinine/serum creatinine.
- Creatinine clearance can be calculated directly by determining the patient's serum creatinine concentration and the rate of urinary excretion of creatinine,
- . Creatinine clearance is expressed in mL/min and serum creatinine concentration in mg/dL or mg%.
- The following equation is used to calculate creatinine clearance in mL/min when the serum creatinine concentration is known:

$$\text{Clcr} = \text{rate of } \frac{\text{urinary excretin of creatinine}}{\text{Serum concentration of creatinine}}$$

$$\text{Clcr} = \frac{\text{CuV} \times 100}{\text{Ccr} \times 1440}$$

where C Cr = creatinine concentration (mg/dL) of the serum taken at the 12th hour or at the midpoint of the urine-collection period, V = volume of urine excreted (mL) in 24 hours, C u = concentration of creatinine in urine (mg/mL), and Cl Cr = creatinine clearance in mL/min.

**OTHER METHOD TO CALCULATE CREATININE CLEARENCE.**

**ADULT**

The method is used to estimate creatinine clearance from serum creatinine concentration. This method considers both the age and the weight of the patient. For

males,

$$Clcr = [140 - agr\ (yr)] \times \frac{body\ weight\ (Kg)}{72\ (Ccr)}$$

For females, use 90% of the Cl Cr value obtained in males.

**CHILDREN**

The Method for calculation of creatinine clearance in children, based on body length and serum creatinine concentration.

$$Clcr = 0.55 \times \frac{body\ length\ (cm)}{Ccr}$$

where Cl Cr is given in mL/min/1.73 m2.

## 84] Enumerate various causes for renal impairment .Discuss in detail the pharmacokinetic considerations in the renal failure patients.

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people and more than 1 million of them are receiving kidney replacement therapy. The kidney is an important organ in regulating body fluids ,electrolyte balance, removal of metabolic waste and drug excretion from the body. Impairement or degeneration of kidney function affects the pharmacokinetics of drugs.

Acute diseases or trauma to the kidney can cause uremia ,in which glomerular filtration is impaired or reduced ,leading to accumulation of excessive fluid and blood nitrogenous products in the body. Uremia generally reduces glomerular filtration and active secretion ,which leads to decrease in renal drug excretion resulting in longer elimination half life of the administrated drug.

In addition to changing renal elimination directly ,uremia can affect drug pharmacokinetics in unexpected ways .For example ,declining renal function leads to disturbances in electrolyte and fluid balance ,resulting in physiologic and metabolic changes that may alter the pharmacokinetics and pharmacodynamics of a drug.

Pharmacokinetic process such as drug distribution (including both the volume of distribution and protein binding) and elimination (including both biotransformation and renal excretion) may also be altered as a result of changes in drug sensitivity at the receptor site. Overall, uremic patients have special dosing considerations to account for such pharmacokinetic and pharmacodynamic alterations.

Common Causes of Kidney Failure :

**Pyelonephritis :** Inflammation and deterioration of the pyelonephrons due to infection, antigens, or other idiopathic causes.

**Hypertension** : Chronic overloading of the kidney with fluid and electrolytes may lead to kidney insufficiency.

**Diabetes mellitus:** The disturbance of sugar metabolism and acid base balance may lead to or predispose a patient to degenerative renal disease.

**Nephrotoxic drugs/metals** : Certain drugs taken chronically may cause irreversible kidney damage -eg, the aminoglycosides, phenacetin, and heavy metals such as mercury and lead.

**Hypovolemia :**Any condition that causes a reduction in renal blood flow will eventually lead to renal ischemia and damage.

**Neophroallergens** : Certain compounds may produce an immune type of sensitivity reaction with nephritic syndrome -eg, quartan malaria and nephrotoxic serum.

## PHARMACOKINETIC CONSIDERATIONS :

Uremic patients may exhibits pharmacokinetic changes in bioavailability,volume of distribution and clearance.

- **Absorption :** The oral absorption of drug in severe uremia ,may decrease as a result of disease related changes in GI motility and pH caused by nausea,vomiting,diarrhea.

- **Bioavailability :** The oral bioavailability of drug such as propranolol [which has a high first pass effect],may be increase in patient with renal impairment as a result of decrease in first pass hepatic metabolism.

- **Volume of distribution :** It depends on drug protein binding in plasma or tissues and total body water. Renal impairment may alter distribution of drug as a result of change in fluid balance, drug protein binding or other factors.

- **Protein binding :** The plasma protein binding of weak acidic drugs in uremic patient is decreased and whereas protein binding of weak basic drugs less affected .The decrease in protein binding ,result I larger fraction of free drugs and increase in volume of distribution.

**Elimination half life :** The net elimination half life is generally increase as a result of dominant effect of reduced glomerular filtration. The clinical practices,estimation of drug dosage in renal impairment is based on an estimate of remaining renal function of patient and prediction of total body clearance.

**85. List out various factors for hepatic impairment. Discuss in detail the pharmacokinetic considerations in the hepatic disease patients.**

Ans:

## EFFECT OF HEPATIC DISEASE ON PHARMACOKINETICS:

Hepatic disease can alter drug pharmacokinetics including absorption and disposition as well as pharmacodynamics including efficacy and safety. Hepatic disease may include common hepatic diseases, such as alcoholic liver disease (cirrhosis) and chronic infections with hepatitis viruses B and C, and less common diseases, such as acute hepatitis D or E, primary biliary cirrhosis, primary sclerosing cholangitis, and a1-antitrypsin deficiency.

Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver. Drugs and metabolites may also be excreted by biliary secretion. Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration, and other effects including possible alteration in drug–protein binding. Liver disease may also alter kidney function.

The major difficulty in estimating hepatic clearance in patients with hepatic disease is the complexity and stratification of the liver enzyme systems. In contrast, creatinine clearance has been used successfully to measure kidney function and renal clearance of drugs. Clinical laboratory tests measure only a limited number of liver functions. Some clinical laboratory tests, such as the aspartate aminotransferase (AST) and alanine aminotransferases (ALT), are common serum enzyme tests that detect liver cell damage rather than liver function.

Other laboratory tests, such as serum bilirubin, are used to measure biliary obstruction or interference with bile flow. Presently, no single test accurately assesses the total liver function.

A few tests have been used to relate the severity of hepatic impairment to predicted changes in the pharmacokinetic profile of a drug (FDA Guidance for Industry, 2003).

Examples of these tests include the ability of the liver to eliminate marker drugs such as antipyrine, indocyanine green, monoethylglycine-xylidide, and galactose. Furthermore, endogenous substrates, such as albumin or bilirubin, or a functional measure, such as prothrombin time, has been used for the evaluation of liver impairment.

## Causes of hepatic impairment:

- Certain prescription medicines.
- Form herbal supplement.
- Toxins.
- Viral infections.
- Certain autoimmune disease.
- Chemicals.
- Metabolic disturbance.

- Immune system abnormality.
- Genetics.
- Cancer.
- Chronic alcohol abuse.

## Dosage Considerations in Hepatic Disease:

Several physiologic and pharmacokinetic factors are relevant in considering dosage of a drug in patients with hepatic disease. Chronic disease or tissue injury may change the accessibility of some enzymes as a result of redirection or detour of hepatic blood circulation.

Liver disease affects the quantitative and qualitative synthesis of albumin, globulins, and other circulating plasma proteins that subsequently affect plasma drug protein binding and distribution.

As mentioned, most liver function tests indicate only that the liver has been damaged; they do not assess the function of the cytochrome P-450 enzymes or intrinsic clearance by the liver.

## Considerations in Dosing Patients with Hepatic Impairment

1. Nature and severity of liver disease: Not all liver diseases affect the pharmacokinetics of the drugs to the same extent.
2. Drug elimination: Drugs eliminated by the liver >20% are less likely to be affected by liver disease. Drugs that are eliminated mainly via renal route will be least affected by liver disease.
3. Route of drug administration: Oral drug bioavailability may be increased by liver disease due to decreased first-pass effects.
4. Protein binding: Drug–protein binding may be altered due to alteration in hepatic synthesis of albumin.
5. Hepatic blood flow: Drugs with flow-dependent hepatic clearance will be more affected by change in hepatic blood flow.
6. Intrinsic clearance: Metabolism of drugs with high intrinsic clearance may be impaired.
7. Biliary obstruction: Biliary excretion of some drugs and metabolites, particularly glucuronide metabolites, may be impaired.
8. Pharmacodynamic changes: Tissue sensitivity to drug may be altered.
9. Therapeutic range: Drugs with a wide therapeutic range will be less affected by moderate hepatic impairment.

**Fraction of Drug Metabolized**: Drug elimination in the body may be divided into (1) fraction of drug excretion unchanged, $f_e$.
(2) fraction of drug metabolized.
The latter is usually estimated from $1 - f_e$; alternatively, the fraction of drug metabolized may be estimated from the ratio of $Cl_h/Cl$, where $Cl_h$ is hepatic clearance and Cl is total body clearance. Knowing the fraction of drug eliminated by the liver allows estimation of total body clearance when hepatic clearance is reduced. Drugs with low $f_e$ values (or, conversely, drugs with a higher fraction of metabolized drug) are more affected by a change in liver function due to hepatic disease.

$$Cl_h = Cl(1-f_e)$$

Assumes that drug metabolism occurs in the liver and the unchanged drug is excreted in the urine.

## Active Drug and the Metabolite:

For many drugs, both the drug and the metabolite contribute to the overall therapeutic response of the drug to the patient. The concentration of both the drug and the metabolite in the body should be known.
When the pharmacokinetic parameters of the metabolite and the drug are similar, the overall activity of the drug can become more or less potent as a result of a change in liver function; that is,
(1) when the drug is more potent than the metabolite, the overall pharmacologic activity will increase in the hepatic-impaired patient because the parent drug concentration will be higher.
(2) when the drug is less potent than the metabolite, the overall pharmacologic activity in the hepatic patient will decrease because less of the active metabolite is formed.
Changes in pharmacologic activity due to hepatic disease may be much more complex when both the pharmacokinetic parameters and the pharmacodynamics of the drug change as a result of the disease process.
In such cases, the overall pharmacodynamic response may be greatly modified, making it necessary to monitor the response change with the aid of a pharmacodynamic model.

## Hepatic Blood Flow and Intrinsic Clearance:

Blood flow changes can occur in patients with chronic liver disease (often due to viral hepatitis or chronic alcohol use). In some patients with severe liver cirrhosis, fibrosis of liver tissue may occur, resulting in intra- or extrahepatic shunt. Hepatic arterial-venous shunts may lead to reduced fraction of drug extracted and an increase in the bioavailability of drug.
In other patients, resistance to blood flow may be increased as a result of tissue damage and fibrosis, causing a reduction in intrinsic hepatic clearance.
The following equation may be applied to estimate hepatic clearance of a drug after assessing changes in blood flow and intrinsic clearance (Clint):

$$Cl_h = \frac{Q\ Cl_{int}}{Q + Cl_{int}}$$

Alternatively, when both Q and the extraction ratio, ER, are known in the patient, Cl may also be estimated:

$$Cl = Q\ (ER)$$

Unlike changes in renal disease, in which serum creatinine concentration may be used to monitor changes in renal function such as GFR, the above physiologic model equation may not be adequate for accurate prediction of changes in hepatic clearance. Calculations based on model equations must be corroborated by clinical assessment.

## Pathophysiologic Assessment:

In practice, patient information about changes in hepatic blood flow may not be available, because special electromagnetic (Nuxmalo et al, 1978) or ultrasound techniques are required to measure blood flow and are not routinely available. The clinician/ pharmacist may have to make an empirical estimate of the blood flow change after examining the patient and reviewing the available liver function tests. Various approaches have been used diagnostically to assess hepatic impairment. The Child–Pugh (or Child–Turcotte–Pugh) score assesses the overall hepatic impairment as mild, moderate, or severe (Figg et al, 1995; Lucey et al, 1997). The score employs five clinical measures of liver disease, including total bilirubin, serum albumin, International Normalized Ratio (INR), ascites, and hepatic encephalopathy.

While chronic hepatic disease is more likely to change the metabolism of a drug (Howden et al, 1989), acute hepatitis due to hepatotoxin or viral inflammation is often associated with marginal or less severe changes in metabolic drug clearance.

The clinician should make an assessment based on acceptable risk criteria on a case-by-case basis. In general, basic pharmacokinetics treats the body globally and more readily applies to dosing estimation. However, drug clearance based on individual eliminating organs is more informative and provides more insight into the pharmacokinetic changes in the disease process.

A practical method for dosing hepatic-impaired patients is still in the early stages of development. While the hepatic blood flow model (see Chapter 12) is useful for predicting changes in hepatic clearance resulting from alterations in hepatic blood flow, Qa and Qv, extrahepatic changes can also influence pharmacokinetics in hepatic-impaired patients. Global changes in distribution may occur outside the liver.

Extrahepatic metabolism and other hemodynamic changes may also occur and can be accounted for more completely by monitoring total body clearance of the drug using basic pharmacokinetics.

For example, lack of local change in hepatic drug clearance should not be prematurely interpreted as “no change” in overall drug clearance. Reduced albumin and AAG, for example, may change the volume of distribution of the drug and therefore, alter total body clearance on a global basis.

## Liver Function Tests and Hepatic Metabolic Markers:

Drug markers used to measure residual hepatic function may correlate well with hepatic clearance of one drug but correlate poorly with another substrate metabolized by a different enzyme within the same cytochrome P-450 subfamily. Some useful marker compounds are listed below.

**1. Aminotransferase (normal ALT: male, 10–55 U/L; female, 7–30 U/L; normal AST: male, 10–40 U/L; female, 9–25 U/L):** Aminotransferases are enzymes found in many tissues that include serum aspartate aminotransferase (AST, formerly SGOT) and alanine aminotransferase (ALT, formerly SGPT). ALT is liver specific, but AST is found in liver and many other tissues, including cardiac and skeletal muscles. Leakage of aminotransferases into the plasma is used as an indicator for many types of hepatic disease and hepatitis. The AST/ALT ratio is used in differential diagnosis. In acute liver injury, AST/ALT is ≤1, whereas in alcoholic hepatitis the AST/ALT > 2.

**2. Alkaline phosphatase (normal: male, 45–115 U/L; female, 30–100 U/L):** Like aminotransferase, alkaline phosphatase (AP) is normally present in many tissues, and it is also present on the canalicular domain of the hepatocyte plasma membrane. Plasma AP may be elevated in hepatic disease because of increased AP production and released into the serum. In cholestasis, or bile flow obstruction, AP release is facilitated by bile acid solubilization of the membranes. Marked AP elevations may indicate hepatic tumors or biliary obstruction in the liver, or disease in other tissues such as bone, placenta, or intestine.

**3. Bilirubin (normal total = 0–1.0 mg/dL: direct = 0–0.4 mg/dL):** Bilirubin consists of both a water-soluble, conjugated, "direct" fraction and a lipid-soluble, unconjugated, "indirect" fraction. The unconjugated form is bound to albumin and is, therefore, not filtered by the kidney. Since impaired biliary excretion results in increases in conjugated (filtered) bilirubin, hepatobiliary disease can result in increases in urinary bilirubin. Unconjugated hyperbilirubinemia results from either increased bilirubin production or defects in hepatic uptake or conjugation. Conjugated hyperbilirubinemia results from defects in hepatic excretion.

**4. Prothrombin time (PT; normal, 11.2–13.2 s):** With the exception of Factor VIII, all coagulation factors are synthesized by the liver. Therefore, hepatic disease can alter coagulation. Decreases in PT (the rate of conversion of prothrombin to thrombin) are suggestive of acute or chronic liver failure or biliary obstruction. Vitamin K is also important in coagulation, so vitamin K deficiency can also decrease PT.

## Hepatic Impairment and Dose Adjustment:

Hepatic impairment may not sufficiently alter the pharmacokinetics of some drugs to require dosage adjustment. Drugs that have the following properties are less likely to need dosage adjustment in patients with hepatic impairment:

- The drug is excreted entirely via renal routes of elimination with no involvement of the liver.
- The drug is metabolized in the liver to a small extent and the therapeutic range of the drug is wide, so that modest impairment of hepatic clearance will not lead to toxicity of the drug directly or by increasing its interaction with other drugs.

• The drug is gaseous or volatile, and the drug and its active metabolites are primarily eliminated via the lungs.

For each drug case, the physician needs to assess the degree of hepatic impairment and consider the known pharmacokinetics and pharmacodynamics of the drug.

**5 marks**

**86) List various formulae for measurement of glomerular filtration rate.**

**Ans)**

a. Renal function can be determined by measuring the GFR.
b. Creatinine clearance is used most as the measurement of GFR.
c. Creatinine clearance, the most useful clinical estimate of GFR, is defined as the volume of plasma that is cleared of creatinine by the kidney per unit of time.
d. It varies with age , gender , weight
e. Creatinine clearance is the rate of urinary excretion .

## Methods of estimation

## Direct method for determining creatinine clearance

Creatinine clearance may be defined as the rate of urinary excretion of creatinine/serum creatinine. Creatinine clearance can be calculated directly by determining the patient's serum creatinine concentration and the rate of urinary excretion of creatinine. The approach is similar to that used in the determination of drug clearance. In practice, the serum creatinine concentration is determined at the midpoint of the urinary collection period and the rate of urinary excretion of creatinine is measured for the entire day (24 hr) to obtain a reliable excretion rate. Creatinine clearance is expressed in mL/min and serum creatinine concentration in mg/dL or mg%. Other $Cl_{Cr}$ methods based solely on serum creatinine are generally compared to the creatinine clearance obtained from the 24-hour urinary creatinine excretion.

The following equation is used to calculate creatinine clearance in mL/min when theserum creatinine concentration is known:

$$Cl_{Cr} = \frac{\text{rate of urinary excretion of creatinine}}{\text{serum concentration of creatinine}} \qquad (21.11)$$

$$Cl_{Cr} = \frac{C_u V \times 100}{C_{Cr} \times 1440}$$

where $C_{Cr}$ = creatinine concentration (mg/dL) of the serum taken at the 12th hour or at the midpoint of the urine-collection period, $V$ = volume of urine excreted (mL) in 24 hours, $C_u$ = concentration of creatinine in urine (mg/mL), and $Cl_{Cr}$ = creatinine clearance in mL/min.

**ESTIMATION OF GFR** BY Cockraft and Gault's equation(for adults)

- For male :

CrCl = **(140 – Patient's age in years ) x (Body weight in kg )**
**(Serum creatinine in mg/dl x 72)**

- For Females:

CrCl = **(140 – Patient's age in years) x (Body weight in kg) x 0.85**
**(Serum creatinine in mg/dl x 72)**

- **ESTIMATION OF GFR BY Jellife equation**

**1- Jellife equation:**

*For males:* $CrCl = \frac{98 - 0.8 \times (patient\ 's\ age\ in\ years - 20)}{serum\ creatinine\ in\ mg\ /\ dl}$

*For females:* $CrCl = 0.9\ X\ CrCl\ determined\ using\ formula\ for\ males$

- **ESTIMATION OF GFR BY Levey Formula (MDRD formula)**

## Levey Formulae for Estimation of GFR

$GFR^{a} = 170 \times [P_{Cr}]^{-0.999} \times [age]^{-0.176} \times [0.762 \text{ if female}] \times [1.18 \text{ if black}] \times [BUN]^{-0.170} \times [albumin]^{0.318}$

$GFR^{b} = 186.3 \times [P_{Cr}]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if female}] \times [1.21 \text{ if black}]$

## Baseline Characteristics of the MDRD Participants

- Age: 51 (± 13) years
- GFR: 40 (± 21) mL/min/1.73m2
- Weight: 80 (± 17) kg
- Serum creatinine: 2.3 mg/dL
- White race: 88%
- Male: 60%
- Diabetes mellitus: 6%

## ➢ ESTIMATION OF GFR BY Schwartz equation

**CHILDREN**

There are a number of methods for calculation of creatinine clearance in children,based on body length and serum creatinine concentration. Equation 21.13 is a method developed by Schwartz et al (1976) :

$$Cl_{Cr} = \frac{0.55 \text{ body length (cm)}}{C_{Cr}}$$

where $Cl_{Cr}$ is given in mL/min/1.73 $m^2$.

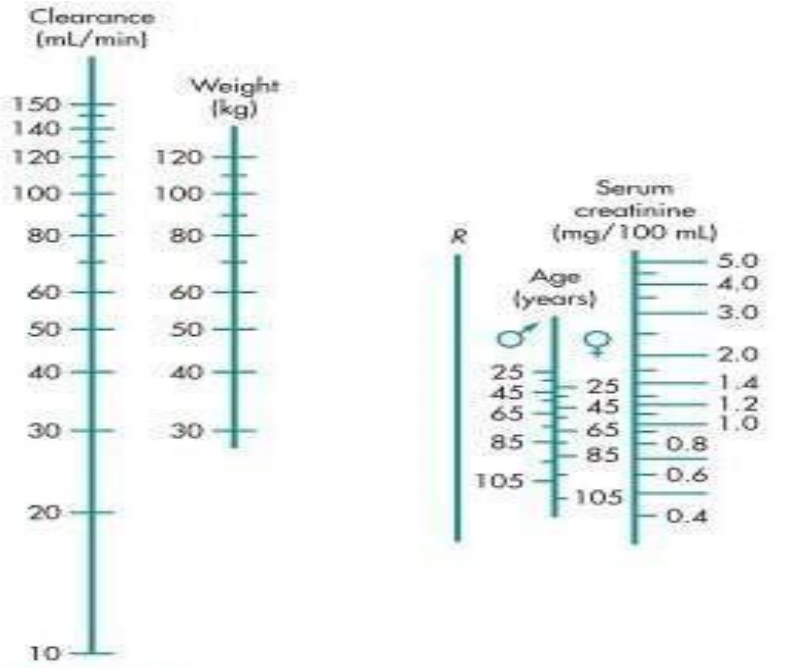



**FIGURE 24-1** Nomogram for evaluation of endogenous creatinine clearance. To use the nomogram, connect the patient's weight on the second line from the left with the patient's age on the fourth line with a ruler. Note the point of intersection on *R* and keep the ruler there. Turn the right part of the ruler to the appropriate serum creatinine value and the left side will indicate the clearance in mL/min. (Reproduced with permission from Kampmann J, et al: Rapid evaluation of creatinine clearance. *Lancet* **1**(7709):1133–1134, 1971.)

Another method of calculating creatinine clearance in children uses the nomogramof Traub and johnson (1980) shown in fig. . This nomogram is based on observations of 81 children aged 6 to 12 years and requires the patient's height andserum creatinine concentration.

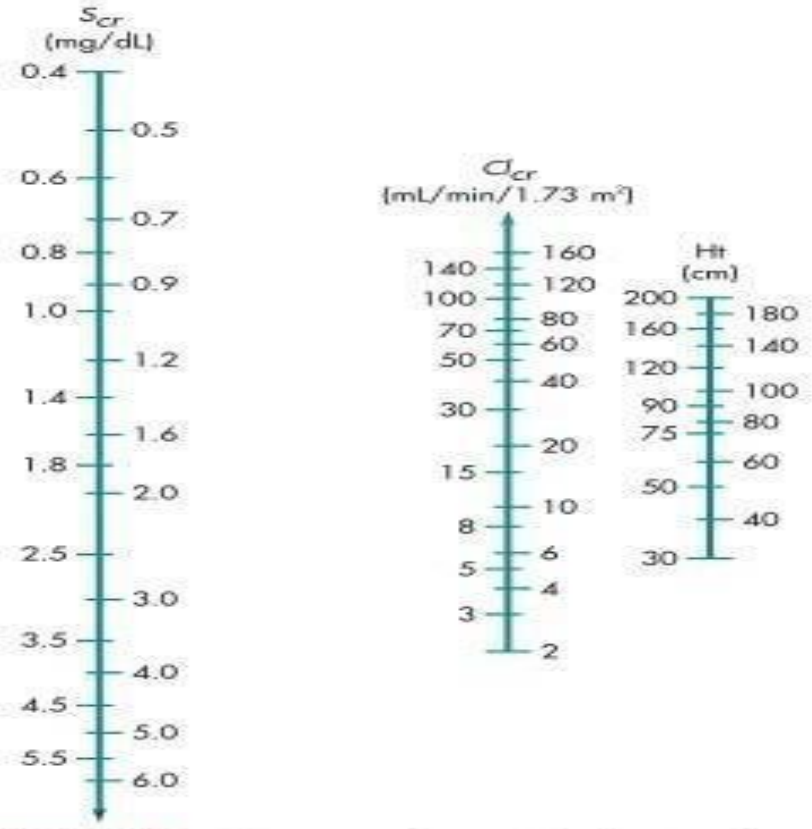



**FIGURE 24-2** Nomogram for rapid evaluation of endogenous creatinine clearance ($Cl_{cr}$) in pediatric patients (aged 6–12 years). To predict $Cl_{cr}$, connect the child's $S_{cr}$ (serum creatinine) and Ht (height) with a ruler and read the $Cl_{cr}$ where the ruler intersects the center line. (From Traub and Johnson, 1980, with permission.)

**87) Explain the various pharmacokinetic changes observed in therenally impaired patients.**

**Ans) PHARMACOKINETIC CONSIDERATIONS**

Uremic patients may exhibit pharmacokinetic changes in bioavailability, volume of distribution, and clearance. The oral bioavailability of a drug insevere uremia may be decreased as a result of disease-related changes ingastrointestinal motility and pH caused by nausea, vomiting, and diarrhea. Mesenteric blood flow may also be altered. However, the oral bioavailability of a drug such as propranolol (which has a high first-pass effect) may be increased in patients with renal impairment as a result of the decrease in first-pass hepatic metabolism .

The apparent volume of distribution depends largely on drug protein binding in plasma or tissues and total body water. Renal impairment mayalter the distribution of the drug as a result of changes in fluid balance, drug protein binding, or other factors that may cause changes in the apparent volume of distribution . The plasma protein binding of weak acidic drugs in uremic patients is decreased, whereas the protein bindingof weak basic drugs is less affected. The decrease in drug protein bindingresults in a larger fraction of free drug and an increase in the volume of distribution. However, the net elimination half-life is generally increased as a result of the dominant effect of reduced glomerular filtration.
Protein binding of the drug may be further compromised due to the accumulation of metabolites of the drug and accumulation of various biochemical metabolites, such as free fatty acids and urea, which maycompete for the protein-binding sites for the active drug.

Total body clearance of drugs in uremic patients is also reduced by eithera decrease in the glomerular filtration rate and possibly active tubular secretion or reduced hepatic clearance resulting from a decrease in intrinsic hepatic clearance.

In clinical practice, estimation of the appropriate drug dosage regimen inpatients with impaired renal function is based on an estimate of the remaining renal function of the patient and a prediction of the total body clearance. A complete

pharmacokinetic analysis of the drug in the uremicpatient is not possible. Moreover, the patient's uremic condition may not be stable and may be changing too rapidly for pharmacokinetic analysis. Each of the approaches for the calculation of a dosage regimen have certain assumptions and limitations that must be carefully assessed by the clinician before any approach is taken.

## 89. How do you adjust dosage regimen in renal failure patientsbased on total body clearance of drug?

Ans) Dose Adjustment Based on Drug Clearance

Methods based on drug clearance try to maintain the desired $C_{av}^{\infty}$ after multiple oral doses or multiple IV bolus injections as total body clearance, $Cl_t$, changes. The calculation for $C_{av}^{\infty}$ is

$$C_{av}^{\infty} = \frac{FD_0}{Cl_T \tau} \quad (1)$$

For patients with a uremic condition or renal impairment, total body clearance of the uremic patient will change to a new value,$Cl_T$. Therefore, to maintain the same desired $C_{av}^{\infty}$, the dose must be changed to a uremicdose, $D_0^u$ or the dosage interval must be changed to $\tau^u$, as shown in the following equation:

$$C_{av}^{\infty} = \frac{D_0^N}{Cl_T^N \tau^N} = \frac{D_0^u}{Cl_T^u \tau^u} \quad (2)$$

(normal) (uremic)

where the superscripts N and u represent normal and uremic conditions, respectively.

Rearranging Equation 2 and solving for $D^u_0$.

$$D_0^u = \frac{D_0^N Cl_T^u \tau^u}{Cl_T^N \tau^N} \quad (3)$$

If the dosage interval is kept constant, then the uremic dose $D^u_0$ is equal toa fraction ($Cl^u_T/Cl^N_T$) of the normal dose, as shown in the equation

$$D_0^u = \frac{D_0^N Cl_T^u}{Cl_T^N}$$ (4)

For IV infusions the same desired $C_{SS}$ is maintained both for patients with normal renal function and for patients with renal impairment. Therefore, the rate of infusion, R, must be changed to a new value, $R^u$, for the uremic patient, as described by the equation

$$C_{SS} = \frac{R}{Cl_T^N} = \frac{R^u}{Cl_T^u}$$
(normal) (uremic)

**93. Explain the effect of hepatic disease on pharmacokinetics of drugs.**

## Ans) EFFECT OF HEPATIC DISEASE ON PHARMACOKINETICS

Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver. Drugs and metabolites may alsobe excreted by biliary secretion. Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration, and other effects including possible alteration in drug protein binding, and kidney function.

The major difficulty in estimating hepatic clearance in patients with hepatic disease is the complexity and stratification of the liver enzyme systems. In contrast, creatinine clearance has been used successfully to measure kidney function and renal clearance of drugs. Clinical laboratory tests measure only a limited number of liver functions. Some clinical laboratory tests, such as the aspartate aminotransferase (AST) and alanine aminotransferases (ALT), are common serum enzyme tests that detect livercell damage rather than liver function. Other laboratory tests, such as serum bilirubin, are used to measure biliary obstruction or interference with bile flow. Presently, no single test accurately assesses the total liver function. Usually, a series of clinical laboratory tests are used in clinical practice to detect the presence of liver disease, distinguish among different types of liver disorders, gauge the extent of known liver damage, and followthe response to treatment. A few tests have been used to relate the severityof hepatic impairment to predicted changes in the pharmacokinetic profile

of the drug (FDA Guidance for Industry, 2003). Examples of these tests include the ability of the liver to eliminate marker drugs such as antipyrine, indocyanine green, monoethylglycine-xylidide, and galactose. Furthermore, endogenous substrates such as albumin or bilirubin, or a functional measure such as prothrombin time, have been used for the evaluation of liver impairment.

## 90. Give the ideal characteristics of a marker to be used in themeasurement of GFR.

## 107. Give any four ideal characteristics of the marker drugs to beused for GFR measurement.(2 MARKS)

Ans)MEASUREMENT OF GLOMERULAR FILTRATION RATE

Several drugs and endogenous substances have been used as markers to measure GFR. These markers are carried to the kidneyby the blood via the renal artery and are filtered at the glomerulus.

- Several criteria are necessary to use a drug as a marker to measure GFR:

  1.The drug must be freely filtered at the glomerulus.

  2.The drug must neither be reabsorbed nor actively secreted by the renal tubules.

  3.The drug should not be metabolized.

  4.The drug should not bind significantly to plasma proteins.

  5.The drug should neither have an effect on the filtration ratenor alter renal function.

  6.The drug should be nontoxic.

  7.The drug may be infused in a sufficient dose to permit simpleand accurate quantitation in plasma and in urine.

- Therefore, the rate at which these drug markers are filteredfrom the blood into the urine per unit of time reflects the GFR of the kidney.
- Changes in GFR reflect changes in kidney function that maybe diminished in uremic conditions.
- Inulin, a fructose polysaccharide, fulfills most of the criterialisted above and is therefore used as a standard reference for the measurement of GFR.
- Although this procedure gives an accurate value for GFR, inulin clearance is not used frequently in clinical practice because it involves a time consuming procedure.

The clearance of creatinine is used most extensively as a measurement of GFR. However , a small amount of creatinine may be, actively secreted by the renal tubules, and the values of GFR obtained by the creatinine clearancetend to be higher than GFR measured by inulin clearance.

**94) Describe peritoneal dialysis with its advantages and disadvantages.**

- Patients with end-stage renal disease (ESRD) and patients who have become intoxicated with a drug as a result of a drug overdose require supportive treatment to remove the accumulated drug and its metabolites.
- Peritoneal dialysis is one of the extracorporeal method to remove the accumulated drug and its metabolites .
- Peritoneal dialysis uses the peritoneal membrane in the abdomen as the filter.
- The peritoneum consists of visceral and parietal components.
- The peritoneum membrane provides a large natural surface area for diffusion of approximately 1â€“2 m2 in adults; the membrane is permeable to solutes of molecular weights 30,000 Da ().
- Total splanchnic flow is 1200 mL/min at rest, but only a small portion, approximately 70 mL/min, comes into contact with the peritoneum.
- Placement of a peritoneal catheter is surgically simpler than hemodialysis and does not require vascular surgery and heparinization.
- The dialysis fluid is pumped into the peritoneal cavity, where waste metabolites in the body fluid are discharged rapidly.
- The dialysate is drained and fresh dialysate is reinstilled and then drained periodically. Peritoneal dialysis is also more amenable to self-treatment. However, slower drug clearance rates are obtained with peritoneal dialysis compared to hemodialysis, and thus longer dialysis time is required.
- Continuous ambulatory peritoneal dialysis (CAPD) is the most common form of peritoneal dialysis. Many diabetic patients become uremic as a result of lack of control of their diabetes.

- About 2 L of dialysis fluid is instilled into the peritoneal cavity of the patient through a surgically placed resident catheter.
- The objective is to remove accumulated urea and other metabolic waste in the body. The catheter is sealed and the patient is able to continue in an ambulatory mode. Every 4 to 6 hours, the fluid is emptied from the peritoneal cavity and replaced with fresh dialysis fluid. The technique uses about 2 L of dialysis fluid; it does not require a dialysis machine and can be performed at home.

Advantages

- Placement of a peritoneal catheter is surgically simpler than hemodialysis and does not require vascular surgery and heparinization.

Disadvantage

- slower drug clearance rates are obtained with peritoneal dialysis compared to hemodialysis, and thus longer dialysis time is required
-

**95) Explain the Giusti-Hayton method for the dosage adjustment in uremic patients?**

The Giusti-Hayton (1973) method assumes that the effect of reduced kidney function on the renal portion of the elimination constant can be estimated from the ratio of the uremic creatinine clearance, $Cl^{u}_{Cr}$, to the normal creatinine clearance, $Cl^{N}_{Cr}$:

$$\frac{k_r^u}{k^N} = \frac{Cl_{Cr}^u}{Cl_{Cr}^N}$$

where $k^{u}_{r}$ is the uremic renal excretion rate constant and $k^{N}_{r}$ is the normal renal excretion rate constant

$$k_r^u = k_r^N \frac{Cl_{Cr}^u}{Cl_{Cr}^N}$$

Because the overall uremic elimination rate constant, $k^{u}$, is the sum of renal and nonrenal elimination,

$$k_u = k_{nr}^u + k_r^u$$

$$k_u = k_{nr}^u + k_r^N \left( \frac{Cl_{Cr}^u}{Cl_{Cr}^N} \right)$$

Dividing Equation 21.19 by $k_N$ on both sides yields

$$\frac{k_u}{k_N} = \frac{k_{nr}^u}{k_N} + \frac{k_r^N}{k_N} \left( \frac{Cl_{Cr}^u}{Cl_{Cr}^N} \right)$$

Let fe = $k^{N}_{r}/k_N$ = fraction of drug excreted unchanged in the urine and fe = $k^{u}_{nr}/k_N$ = fraction of drug excreted by nonrenal routes. Substitution into Equation 21.20 yields the Giusti -Hayton equation, where G is the Giusti -Hayton factor, which can be calculated from the fe and the ratio of uremic to normal clearance

$$\frac{k_u}{k_N} = (1 - fe) + fe\left(\frac{Cl_{Cr}^u}{Cl_{Cr}^N}\right)$$

or

$$\frac{k_u}{k_N} = 1 - fe\left(1 - \frac{Cl_{Cr}^u}{Cl_{Cr}^N}\right) = G$$

The Giusti-Hayton equation is useful for most drugs for which the fraction of drug excreted by renal routes has been reported in the literature. The ratio $k^u_{nr}/k_N$ can be calculated from the fraction of drug excreted by the kidney, normal creatinine clearance, and the creatinine clearance in the uremic patient.

## 96. Describe the Wagner method for the dose adjustment in uremic patients?

Other method for renal dose adjustments assume that the volume of distribution and the fraction of drug excreted by nonrenal routes are unchanged. These assumptions are convenient and hold true for many drugs. However, in the absence of reliable information assuring the validity of these assumptions, the equations should be demonstrated as statistically reliable in practice.

The Wagner method takes advantage of the fact that the elimination constant for a patient can be obtained from the creatinine clearance, as follows:

$K\% = a + bCl_{cr}$

The values of a and b are determined statistically for each drug from pooled data on uremic patients. The method is simple to use and should provide accurate determination of elimination constants for patients when a good linear relationship exists between elimination constant and creatinine concentration. The theoretical derivation of this approach is as follows;

$k\%$ = total elimination rate constant
$k_{nr}$ = nonrenal elimination rate constant (%)
$k_R$ = renal excretion rate constant
$Cl$ = Total body clearance of drug

$$R = \frac{Cl}{Cl_{Cr}} \qquad (21.29)$$

$$Cl = R\,Cl_{Cr}$$

$$k = k_{nr} + \frac{R}{V_D} Cl_{Cr}$$

$$100k = 100k_{nr} + \frac{100R}{V_D} Cl_{Cr}$$

$$k\% = a + b\,Cl_{Cr} \qquad (21.30)$$

Equation 21.30 can also be used with drugs that follow the two-compartment model. In such cases the terminal half-life is used and b, the terminal slope of elimination curve, is substituted for the elimination rate constant, k. Since the equation assumes a constant nonrenal elimination constant ($k_{nr}$) and volume of distribution, any change in these two

parameters will result in an error in the estimated elimination constant.

**97] The maintanence dose of gentamicin is 80mg every 6 hrs for a patient with normal renal function. Calculate the maintanence dose for a uremic patient with creatinine clearance of 20ml/min .Assume a normal creatinine clearance of 100ml/min.**

From the literature, gentamicin is reported to be 100 % excreted by the kidney (ie ,$f_e$=1)

$$K_u/k_N=1-1\ [1-20/100]=0.2$$

Because ,

$$D_u/D_N=k_u/k_N \qquad \text{or} \qquad D_u=D_N * k_u/k_N$$

Where $D_u$=80 mg *0.2=16mg

The maintanence dose is 16 mg every 6 months .Alternatively ,the dosing interval can be adjusted without changing the dose;

$$t_u/t_N=k_N/k_u \text{ or } t_u=t_N*k_N/k_u$$

$$t_u=6\ h * 1/0.2 =30\ h$$

where $t_u$ and $t_N$ are dosing intervals for uremic and normal patients ,respectively.The patient may be given 80mg every 30 hours.

Other approaches for using fraction of drug excreted unchanged have been developed by Tozer (1974) and Bjornsson (1986). These methods use $f_e$ for dosing regimen design and following eqations.

$$Q=1-f_e(1-k_f)$$

Where Q is the dosage adjustment factor,$k_f$=$Cl^{u}_{cr}$ /$Cl^{N}_{cr}$ and $f_e$ is the fraction of unchanged drug excreted renally.Actually ,Q is exactly the same as G ,as developed by Giusti- Hayton approach in 1973.

The value of Q is multiplied by the normal dose ,$D_N$ ,to give the uremic dose ,$D_u$ is $D_u$=Q * $D_N$

**98] What is the creatinine clearance for 25 year old male patient with serum creatinine of 1mg/dl? The patients is 5ft ,4 inches in height and weighs 103 kg.**

The patient is obese and the $Cl_{cr,}$ calculation should be based on ideal body weight .

LBW(males) = 50 kg + [ 2.3 * 4 ] = 59.2 kg

Using the Cockcroft – Gault method the $Cl_{cr}$ can be calculated.

$Cl_{cr}$ = [140-25] * [59.2 kg ] / 72[ 1 ]

$Cl_{cr}$ = 94.6 mL/min

**99] An adult male patient [52 years old,75kg ] whose serum creatinine is 2.4 mg/dl is to be given gentamicin sulphate .The usual dose of gentamicin in adult patients with normal renal function is 1mg /kg every 8 hours by multiple IV bolus injections. Calculate the appropriate dosage regimen of gentamicin sulfate for this patient.**

The initial dose of gentamicin sulfate in this patient may be estimated using

$$k_u/k_N = 1 - f_e \{1 - Cl^{u}_{cr} / Cl^{N}_{cr} \} = G$$

Normal creatinine clearance is assumed to equal 100 mL/min .The fraction of dose excreted unchanged in the urine ,$f_e$ = 0.98 for gentamicin sulfate.

$$k_u/k_N = Q = 1- 0.98 \{ 1 - 38.19 / 100 \} = 0.39$$

The usual dose of gentamicin sulfate = 1mg/kg every 8 hours. Therefore,for a 75kg adult ,the usual dose is 75mg every 8 hours .The uremic dose may be estimated by,

**A]** <u>Reducing the maintanence dose and keeping the dosing interval constant</u>;

Uremic dose = $k_u/k_N$ * normal dose

Uremic dose = 0.39 * 75 = 29.25 mg

Give 29.95 mg [about 30mg] every 8 hours.Because the concentration of gentamicin sulfate solution is 40 mg/ml ,30 mg gentamicin sulfate is equivalent to 0.75mL.

**B]** <u>Increasing the dosing interval and keeping the maintanence dose constant</u> ;

Dosage interval in uremia , $f_u = k_N /k_u * f_N$

$f_u$ = 2.564 * 8 = 20.5 h [2.564 is the reciprocal of 0.39]

Give 75 mg every 20.5 hours.

**C]** Change both the maintanence dose and dosing interval .Using the dosing rate $D_f$ = 29.25 mg/8 h = 3.66 mg/h, a dose of 23.9 mg every 6 hours or 43.8 mg every 12 hours will produce the same average steady state plasma drug concentration.

Although each estimated dosage regimen shown above produces the same average steady state plasma drug concentration,peak drug concentration,trough drug concentration,the duration of time in which the drug concentration will be above or below the minimum effective plasma drug concentration will be different .The choice of an appropriate dosage regimen requires consideration of these issuses;the patient,the safety, and efficacy of the drug.

## 100. Explain hemodialysis.

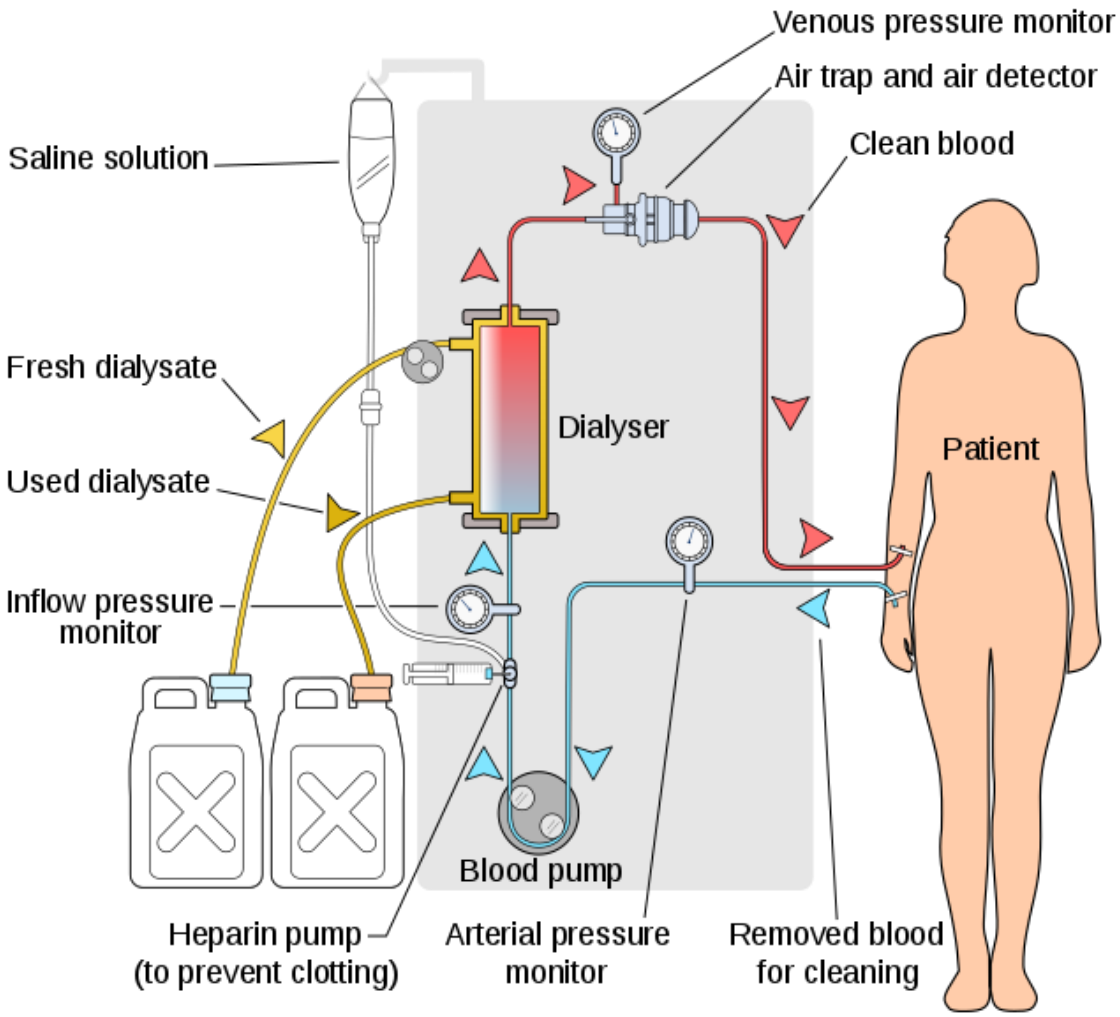
### Ans:

The method for removing waste products such as creatinine and urea, as well as free water from the blood when the kidneys are in renal failure.

Principle: involves diffusion of solutes across a semipermeable membrane.

Procedure:

- A dialysis machine pumps small blood out of the body, mixed with anticoagulant and circulated through a filter called dialyzer.
- Inside the dialyzer, a porous artificial membrane separates blood from the dialysis fluid (dialysate).
- Diffusion of extra fluid and wastes from the blood into the dialysate.
- Purified blood is then pumped back into the body.
- Membrane is permeable to water and small ions but is impermeable to blood cells, lipids or plasma proteins.
- Utilizes counter current flow, ie. Dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit.
- Counter – current flow maintains the conc. Gradient across the membrane at a maximum and increases the efficiency of the dialysis.
- Pressure in the dialysate compartment is lower than blood compartment.




## Types of hemodialsis access:

### For temporary access:

- A shunt is created in the arm, with one tube inserted in an artery and another in a vein.
- Tubes are joined above the skin.

### For permanent access:

- The blood vessels an arteriovenous fistula or graft is created by a surgical procedure to allow access to artery and vein.

### Hemodialysis is preferred in situations:

- Rapid removal of drug from the body is important.
- In overdose or poisoning.
- Dialysis may be required from once every 2 days to 3 times a week with each treatment period lasting 2 to 4 hours.

Factors affecting dialysability of drug: Physiochemical and pharmacokinetic properties of drug

- Water solubility

- Protein binding
- Molecular weight
- Drugs with large volumes of distribution.

Characteristics of dialysis machine:

- Blood flow rate
- Dialysate
- Dialysis membrane
- Transmembrane pressure

Dialysance: It is a clearance term similar in meaning to renal clearance and it describes the amount of blood completely cleared of drugs in ml/min.

$$Clb = \frac{Q\ (Ca-Cv)}{Ca}$$

## Types of hemodialysis:

## Conventional hemodialsis:

- Done 3 times per week, for about 3-4 hrs for each treatment, during which patients' blood is drawn out through a tube at a rate of 3-400 cc/min.
- During treatment, the patient entire blood volume circulates through the machine every 15 minutes.

## Daily hemodiaysis:

- Used by patients who do their dialysis at home.
- Usually done for 2 hours, six days a week.

## Nocturnal hemodialysis:

- Performed six nights a week and six – ten hours per session while the patient sleeps.

**APPLICATIONS:** Mainly used in chronic failure and in poisoning by certain agents such as salicylate, phenobarbitone, methanol, ethylene glycol and lithium.

## 101. Explain methods of determining creatinine clearance.

## Ans:

**Creatinine clearance defined as the rate of urinary excretion of creatine/ serum creatinine.**

- It is used most as measurement of GFR.
- It varies with the age, weight and gender.
- ClCr is the rate of urinary excretion.

## Methods:

1. **A direct method:** For determining creatinine clearance is determining of the amount of creatinine excreted in urine in 24 hours and the mean of serum creatinine from blood samples taken just before and immediately after the urine collection period.

$$Cl_R = \frac{\text{Rate of creatinine excretion}}{\text{Serum creatinine in mg\%}}$$

2. **Using serum creatine and body length:** Using the person body length and serum creatinine value to calculate creatinine clearances.

$$ClCr = \frac{KL}{Ccr}$$

Where,

K: Constant of proportionally that is age specific.

L: Length in cm.

Ccr: serum creatinine concentration.

3. **Estimation of creatinine clearance using serum creatinine and height:**

$$ClCr = \frac{0.48 \times height}{Ccr}$$

4. **Jollife's method:**

This method is generally applicable for adult patients to age of 80 years

- This is based on age and serum creatinine concentration of the patient.
- This method is not intended for patients under 20 years of age.

For males: $$ClCr = \frac{98 - 0.8(Y - 20)}{Ccr}$$

Y: Age in year
Ccr: Serum creatinine concentration.

For females: $$ClCr = (0.9)\ \frac{98 - 0.8(Y - 20)}{Ccr}$$

5. **Cockraft and Gault's method:** this method is based upon the age, weight and serum creatinine concentration of the patients.

For males:

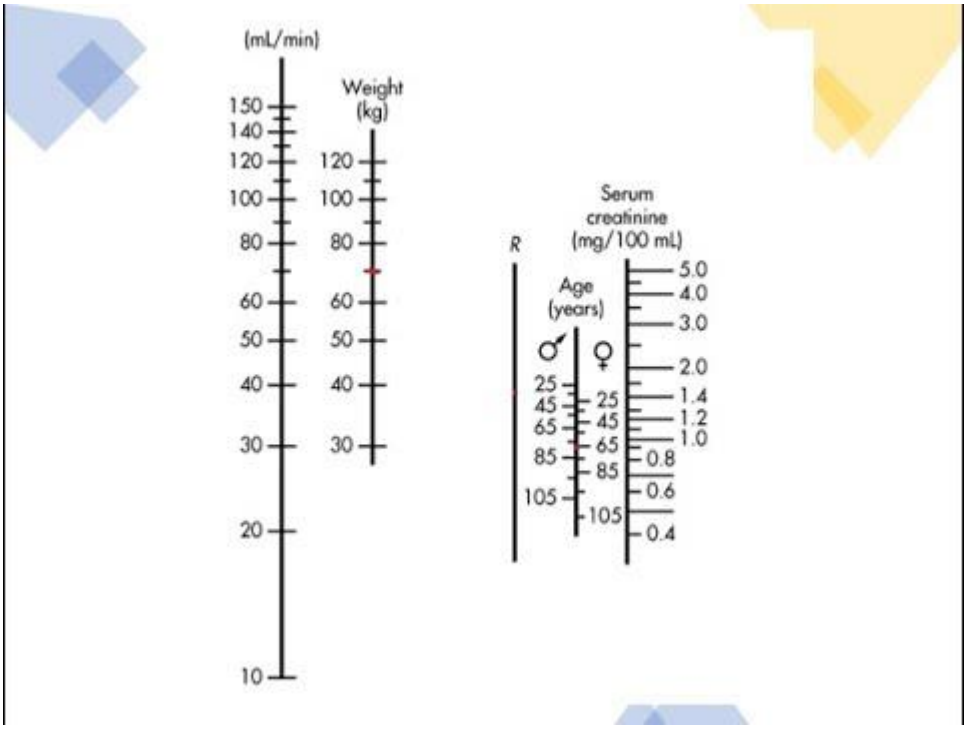
$$ClCr = \frac{[140 - age(year)]\ [body\ weight\ (Kg)]}{72 \times Ccr}$$

For females:

$$ClCr = (0.85)\ \frac{[140 - age(year)][bodyweight\ (Kg)]}{72 \times Ccr}$$

6. **Siersback – Nielsen nomogram method:** Here instead of an equation this method uses a nomogram.

- Draw a straight line to connect patients' weight (on the 2nd line from left) to the patients age (on the 2nd line from right) this gives a point of intersection on the middle line R.
- Draw a straight line to connect the patient's serum creatinine value (in mg / 100 ml) on the first line on right to the point of intersection on line R and extrapolate this straight line to the first line on left to read creatinine clearance.




## Children:

- Based on body length and serum creatinine concentration, developed by Schwartz and associates.
- where Clcr is given in mL/min/1.73 m2.
- The value 0.55 represents a factor used for children aged 1–12 years.

$$ClCr = (0.55) \frac{[\text{body length(cm)}]}{Ccr}$$

- According to this equation creatinine clearance is directly proportional to the height of those children who have similar serum creatinine concentration.

## 102. Describe the methods of measurement of GFR and their significance.

## Ans:

**Glomerular filtration rate:** The amount of fluid from the blood into the glomerular capsule per unit time is known as glomerular filtration rate.

$$GFR = \frac{\text{Excretion rate}}{\text{Plasma concentration}}$$

GFR is usually expressed as ml/min.

Factors influencing glomerular filtration:

- Total surface area available for filtration
- Permeability of the filtration membrane
- Net filtration pressure

Several drugs and endogenous substances have been used as markers to measure GFR. These markers are carried to the kidney by the blood via the renal artery and are filtered at the glomerulus. Several criteria are necessary to use a drug as a marker to measure GFR:

1. The drug must be freely filtered at the glomerulus.
2. The drug must neither be reabsorbed nor actively secreted by the renal tubules.
3. The drug should not be metabolized.
4. The drug should not bind significantly to plasma proteins.
5. The drug should neither have an effect on the filtration rate nor alter renal function.
6. The drug should be nontoxic.
7. The drug may be infused in a sufficient dose to permit simple and accurate quantitation in plasma and in urine.

Therefore, the rate at which these drug markers are filtered from the blood into the urine per unit of time reflects the GFR of the kidney. Changes in GFR reflect changes in kidney function that may be diminished in uremic conditions

## Tests to estimate GFR:

- **Endogenous markers:** 1. Urea

2. creatinine

- **Exogenous markers**: 1. Inulin
  2. Radioactive substance

## 1.Blood urea nitrogen:

- Measurement of blood urea nitrogen (BUN) is a commonly used clinical diagnostic laboratory test for renal disease.
- Urea is the end product of protein catabolism and is excreted through the kidney.
- Normal BUN levels range from 10 to 20 mg/dL.
- Higher BUN levels generally indicate the presence of renal disease.

### Common causes for elevation of BUN:

- Excessive protein intake.
- Reduced renal blood flow.

### Common causes for decreased of BUN:

- Patients who are malnourished.
- Profound liver damage.

## 2. Creatinine: question no 101

## 3. Inulin clearance:

Normal range: male- 127 ml/min/m2

Female – 118 ml/min/m2

- Inulin, a fructose polysaccharide, fulfils most of the criteria listed above and is therefore used as a standard reference for the measurement of GFR.
- In practice, however, the use of inulin involves a timeconsuming procedure in which inulin is given by intravenous infusion until a constant steady-state plasma level is obtained.
- Clearance of inulin may then be measured by the rate of infusion divided by the steady-state plasma inulin concentration.
- Although this procedure gives an accurate value for GFR, inulin clearance is not used frequently in clinical practice.

## 2 MARKS

**103. Enumerate the factors influencing dialyzability of drugs.**

**ANS)**

- **Water solubility**
  – insoluble or fat soluble drugs are not solubilised (eg: glutethimide -a water insoluble drug )

- **Protein binding**
  – tightly bound protein are not dialysed ( eg: propranolol)
- **Molecular weight**

- mol.weight less than 500 are dialyzed.(eg: vancomycin ispoorly dialysed)

- **Drug with large volume of distribution**

- widely distributed drugs are dialysed slowly , drugs concentrated in tissues are difficult to remove by dialysis.

**104. Enumerate the causes for renal failure**

**Ans) CAUSES OF ACUTE RENAL FAILURE**

- Pre-renal
  - vomiting, diarrhea, poor fluid intake, fever, use of diuretics, and heart failure
  - cardiac failure, liver dysfunction, or septic shock
- Intrinsic
  - Interstitial nephritis, acute glomerulonephritis, tubular necrosis, ischemia, toxins
- Post-renal
  - prostatic hypertrophy, cancer of the prostate or cervix, or retroperitoneal disorders
  - neurogenic bladder
  - bilateral renal calculi, papillary necrosis, coagulated blood, bladder carcinoma, and fungus

**CAUSES OF CHRONIC RENAL FAILURE**

- Diabetic Nephropathy
- Hypertension
- Glomerulonephritis
- HIV nephropathy

- Reflux nephropathy in children
- Polycystic kidney disease
- Kidney infections & obstructions

**105. Give any four pharmacokinetic parameter changes observed inthe renal failure patients.**

**Ans)**

- Uremia decreases GI absorption of drugs
- Uremia alters first pass hepatic metabolism
- Uremia slows the rate of phase 1 metabolism(reduction ,oxidation , hydrolysis)
- Renal impairment may alter the distribution of drug as aresultof changes in fluid balance , drug protein binding or other factors that may cause changes in the apparent volume of distribution.

**106. List the markers used in the measurement of GFR.**

**Ans) Various markers used to measure GFR include**

- Exogenous Markers: inulin , iothalamate
- Endogenous Markers: urea , creatinine , beta 2 microglobulin ,cystatin C

**107.Give two advantages and disadvantages of inulin as a markerfor GFR measurement.**

Ans)

**<u>Advantages</u>**

- Freely filtered at glomerulus
- No tubular metabolism
- No tubular reabsorption or secretion

## Disadvantages

- Expensive hard to obtain
- Difficult to assay
- Invasive
- Time consuming

**108. Give the Jellife's equation for the measurement of creatinine clearance.**

**1- Jellife equation:**

*For males:* $CrCl = \frac{98 - 0.8 \times (patient\ 's\ age\ in\ years - 20)}{serum\ creatinine\ in\ mg/dl}$

*For females:* $CrCl = 0.9\ X\ CrCl\ determined\ using\ formula\ for\ males$

**109. Give the Cockraft and Gault's equation for the measurementof creatinine clearance.**

## Ans) Cockraft and Gault's equation

- For male :

CrCl = **(140 – Patient's age in years ) x (Body weight in kg )**
**(Serum creatinine in mg/dl x 72)**

- For Females:

CrCl = **(140 – Patient's age in years) x (Body weight in kg) x 0.85**
**(Serum creatinine in mg/dl x 72)**

**111. Give the formula for the calculation of creatinine clearance in children.**

The Method for calculation of creatinine clearance in children, based on body length and serum creatinine concentration.

$$Clcr = 0.55 \frac{body\ length\ (cm)}{Ccr}$$

where Cl Cr is given in mL/min/1.73 m2.

**112. Give the MDRD equation for the measurement of creatinine clearance.**

$$\text{GFR (mL/min/1.73 m}^2) = 186^{*} \times \text{Creatinine (serum)}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (If Female)} \times 1.210 \text{ (If African-American)}$$

* use 186 for conventional calibration;
* use 175 for calibration traceable to IDMS

**113. Name the methods for the extracorporeal removal of drugs?**

- Dialysis
- Peritoneal dialysis
- Hemodialysis
- Hemoperfusion
- Hemofiltration
- Continuous renal replacement therapy (crrt)

**114. Give any two advantages and disadvantages of peritoneal dialysis ?**

Advantages

- Placement of a peritoneal catheter is surgically simpler than hemodialysis and does not require vascular surgery and heparinization.

Disadvantage

- slower drug clearance rates are obtained with peritoneal dialysis compared to hemodialysis, and thus longer dialysis time is required

**115] Give any two advantages and disadvantages of haemodialysis.**

**Advantages:**

- ❖ Maximum solute clearance
- ❖ Best therapy for hyperkalaemia
- ❖ Limited anti coagulation time.

**Disadvantages:**

- ❖ Haemodynamic instability
- ❖ Rapid fluid and electrolyte shift
- ❖ Complex equipment
- ❖ Specialized personnel
- ❖ Difficult in small infants.

## 116] Define intrinsic clearance of drugs with its clinical significance.

- Intrinsic clearance is the ability of the liver to remove drug in the absence of flow limitations and binding to cells or proteins in the blood.
- Intrinsic drug clearance primiraly occurs because of inherent ability of the biotransformation enzymes (mixed function oxidases) to metabolized the drug as it enters the liver.
- Level of this enzyme are increased by various drugs (Eg: phenobarbital) and environmental agents (Eg: tobaccosmoke).
- These enzymes are inhibited by other drugs and environmental agents (Eg: cimetidine, acutelead poisoning).

## 117] Calculate creatinine clearance for a 30 year old female patient with a serum creatinine value of 0.8 mg/dl .The patient is 5 ft 1 inch tall and weighs 69kgs.

The patient is obese and the $Cl_{cr}$ calculation should be based on ideal body weight.

LBW (females) = 45.5 + [ 2.3 * 1 ] = 47.8 kg

Using the Cockcroft Gault equation method, the $Cl_{cr}$ can be calculated,

$Cl_{cr}$ = 0.85 [140 – age (years) * body weight (Kg) / 72 * $C_{cr}$

$Cl_{cr}$ = 0.85 [140 – 30 ] * 47.8 kg / 72 * 0.8

$Cl_{cr}$= 0.85 [110 * 47.8] / 72 * 0.8

$Cl_{cr}$ =0.85 [5258] / 57.6

$Cl_{cr}$ = 4469.3 /57.6

$Cl_{cr}$ =77.59 mL/min

## 118] Name the metabolic markers used in liver function tests with their normal values.

- Alkaline Phosphate (ALP) = 40 – 125 IU/L
- Gamma Glutamyl Transpeptidase (GGT) = 8 – 17 IU/L
- Albumin = 3.5 – 5.0 g/dl
- Prothrombin Time (PT) = 10 – 14 sec
- Lactate Dehydrogenase (LDH) = 100 – 210 IU/L
- Alkaline Transferase = 3 – 30 IU/L

- Aspartate Transaminase = 8 – 42 IU/L

## 119. Define hepatic clearance.

**Ans:**

- For certain drugs, the non – renal clearance can be assumed as equal to hepatic clearance $Cl_H$. It is given as

$$Cl_H = Cl_T - Cl_R$$

Also, $$Cl_H = Q_H \, ER_H$$

Where,

$Q_H$ = Hepatic blood flow

$ER_H$ = Hepatic extraction ratio

- The hepatic clearance of drugs can be divided into two groups:
  1. Drugs with hepatic blood flow rate – limited clearance.
  2. Drugs with intrinsic capacity – limited clearance.

## 120. Give the importance of extra corporeal removal of drugs.

- Extracorporeal therapy is a medical procedure which is performed outside the body. For patients with end-stage renal disease and drug overdose to remove accumulated drug and its metabolites.
- Objective: To remove rapidly the undesirable drugs and metabolites from the body without disturbing the fluid and electrolyte balance in the body.
- Methods available for drug removal:
  1. Hemodialysis
  2. Peritoneal dialysis
  3. Hemofiltration
  4. Hemodiafiltration
  5. Hemoperfusion

## 121. Calculate creatinine clearance for a 23-year-old male patient with a serum creatinine value of 1.2 mg/dl. The patient is 5 ft 5 inch tall and weighs 98 kgs.

**Ans:**

$$ClCr = \frac{[140 - age(year)]\,[body\ weight\ (Kg)]}{72 \times Ccr}$$

$$ClCr = \frac{[140 - 23]\,[98]}{72 \times 1.2}$$

$$ClCr = \frac{11{,}466}{86.4}$$

$$ClCr = 132.70\ ml/min$$

**122. Using the method of Cockroft and Gault, Calculate creatinine clearance for a 36-year-old female patient with a serum creatinine value of 1.8 mg/dl. The patient is 5 ft 5 inch tall and weighs 58 kgs.**

**Ans:**

$$ClCr = (0.85)\frac{[140 - age(year)][bodyweight\ (Kg)]}{72 \times Ccr}$$

$$ClCr = (0.85)\frac{[140 - 36][58]}{72 \times 1.8}$$

$$ClCr = \frac{5{,}127.2}{129.6}$$

$$ClCr = 39.5617\ ml/min$$

**PHARMACOGENETICS**

10 MARKS 123. Role of genetic polymorphism in drug targets and is clinical significance. And drug transport with suitable examples? And

5 mark- 125) Role of genetic polymorphism in drug targets

**Drug targets**

Genetic polymorphisms occur commonly for drug target proteins, including receptors, enzymes, ion channels, and intracellular signaling proteins.

Drug target genes may work in concert with genes that affect pharmacokinetic properties to contribute to overall drug response.

Receptor genotypes and drug response:

✓β1 - Receptors are located in the heart and kidney, where they are involved in the regulation of heart rate, cardiac contractility, and blood pressure. Two common nonsynonymous SNPs in the β1- receptor gene are located at codons 49 & 389

✓ The influence of the β1-receptor gene on blood pressure response to β1-receptor blockade with metoprolol.

✓ Hypertensive patients who were homozygous for both the Ser49 and Arg389 alleles had greater reductions in diastolic blood pressure with metoprolol monotherapy compared with carriers of the Gly49 and/or Gly389 alleles.
✓β2 - Receptors are located on bronchial smooth muscle cells, where they mediate bronchodilation upon exposure to the β2-receptor agonists.
✓ Inhaled β2-agonists are the most effective agents for acute reversal of bronchospasm; however, the magnitude of their effects varies substantially among asthmatic patients.
✓ More than 11 SNPs have been identified in the β2-receptor gene, three of which occur frequently and result in amino acid changes.
✓ Two common nonsynonymous SNPs are found in the gene's coding block region, at codons 16 and 27, and a third occurs upstream from the coding block in the gene's promoter region.
Enzyme Genes And Drug Response:
➢ Vitamin K epoxide reductase (VKOR) is an example of an enzyme with genetic contributions to drug response.
➢ Warfarin exerts its anticoagulant effects by inhibiting VKOR, thus preventing carboxylation of clotting factors II, VII, IX, and X.
➢ The vitamin K epoxide reductase complex subunit-1 gene (VKORC1) encodes for VKOR.
➢ Mutations in the VKORC1 coding region cause rare cases of warfarin resistance.
➢ Carriers of these mutations either require exceptionally high warfarin doses (>100 mg/wk) to achieve effective anticoagulation or fail to respond to any dose of warfarin.
Genes For Intracellular Signaling Proteins, Ion Channels, And Drug Response: Cellular responses to many drugs are mediated through GTP binding proteins, also called G proteins.
✓ Disturbances in G-protein–mediated signal transduction have been implicated in the response to antidepressant drugs.
✓ A common SNP (C825T) occurs in the gene for the inhibitory G (Gi) protein β3- subunit and has been associated with enhanced intracellular signal transduction.
✓ The TT genotype has been correlated with greater improvement in depression symptoms among patients treated with either a tricyclic antidepressant or serotonin reuptake inhibitor, implying that the Gi protein β3-subunit gene may have a role in therapeutic decisions for depression management.
✓ The epithelial sodium channel (ENaC) is an example of an ion channel with genetic contributions to drug response.
✓ The ENaC is located in the distal renal tubule and collecting duct of the nephron, where it serves as the final site for sodium reabsorption.
✓ The channel is composed of α-, β-, and γ-subunits. Mutations in the β- or γ- subunit cause excessive sodium reabsorption and an inherited form of hypertension called Liddle syndrome.
✓ The more common variant Thr594Met occurs exclusively in blacks and is associated with high blood pressure in this population.
CYP denotes the enzymes present in human cytochrome which is responsible for metabolism of substances.
There are meant for the metabolism of endogenous substance and also will get metabolized by these enzymes.
CYP enzymes are rich in liver and gut cells.
CYP represents human cytochrome enzymes ,while CYP represent Mice cytochome enzymes.
CYP -450
Have a greater role in phase 1 reaction to produce polar molecules in presence of molecules O 2.
NADPH+H++O2O+RH ⟶

All CYP enzymes have an iron core ,when it is combined with carbon monoxide absorption at wave length 450cm.
Cytochrome enzymes thus got “CYP-450” NAME
Many cytochromes CYP 450 enzymes are polymorphic .

Genetic polymorphism:
The genetically determined difference in drug response in individuals is called genetic polymorphism.
A genetic polymorphism is any mutual (or)variant gene that occur with a frequency of more than 1 and a half in normal population.

Genetic polymorphism of CYP:
CYP are major enzymes involved in drug metabolism and bioactive ,accounting for about about 75% of total number of different metabolic reactions.
This super comprises of many enzymes is divided into human into 3 major distinct failies.
1.CYP-450
2.CYP-4502
3.CYP-4503
These are further divide into sub families A-E
Factors affecting CYP activity:
Age,gender,hormones,ifiammation
Pregenancy
Hepatic disease
Drug diet
Life style and environment
Genetic polymorphism

**Drug transport**
MDR1 (P-Glycoprotein) The MDR1 or ABCB1 gene codes for the efflux protein P-glycoprotein (P-gp) that is frequently associated with drug resistance to antineoplastic agents including vincristine and doxorubicin.
In cancers that express PGP, the drug is transported out of the cells, keeping the drug concentrations inside the target cell low.
In addition to this resistance function, expression of PGP also contributes to the efflux of some drugs from various tissues that affect the pharmacokinetics of these compound.
At least 66 SNPs in the ABCB1 gene have been reported, and the three most studied SNPs include two synonymous and one non-synonymous variant.
The synonymous SNPs are reported to result in decreased expression of PGP due to decreased mRNA expression, unstable mRNA, or alterations in protein folding (Sissung et al, 2012).
The effects of these SNPs on drug serum levels have been examined in multiple studies with substrates including digoxin and docetaxel.
The reported results on the pharmacokinetic profile of these two drugs have been inconsistent with studies showing increased blood levels or no change compared to the wild-type gene (Sissung et al, 2012).
These results highlight the dependency on the individual substrate, the complexity, and the effect of specific tissue transporter expression, which contributes to the pharmacokinetic profile of each drug.
Additionally, there are also known inhibitors to PGP that complicate the prediction of the pharmacokinetic profile in patients that are administered multiple drugs.
▪ ABC Transporters.

The multidrug resistance-associated proteins (MRPs) are members of the ATP-binding cassette (ABC) super family with six members currently, of which MRP1 (ABCC1), MRP2 (ABCC2), and MRP3 (ABCC3) are commonly known to effect drug disposition. Like MDR, these transporters can also be expressed in cancer cells, which confer resistance to the chemotherapeutic agent tamoxifen.

It appears that polymorphisms in this family are rare and occur at different frequencies among different populations. Despite numerous studies, the functional importance of these polymorphisms remains unclear Future studies with specific substrates and polymorphisms may ultimately provide additional information on the variable responses or adverse effects of drugs.

▪ Solute Carrier Transporters.

Another important class of drug transporters is the solute carriers (SLCs) such as the organic anion transporter protein (OATP) and organic cation transporter (OCT). These transporters are located throughout the body and have various roles in the transport of many different drugs. OATP1B1 (coded by the SLCO1B1 gene) is a hepatic influx transporter with at least 40 non-synonymous SNPs identified that result in either an altered expression or activity of OATP1B1. While the clinical consequences of all of these SNPs are unknown, one SNP has been associated with an increased risk of simvastatin-induced myopathy. This non-synonymous SNP is associated with a lower plasma clearance of simvastatin and is found in the SLCLO1B1*5, *15, and *17 alleles.

These alleles are present in most populations with a frequency between 5% and 20% and warrant the avoidance of high-dose simvastatin (>40 mg) or treatment with another statin to decrease the risk of simvastatin-induced myopathies.

126. Describe the genetic polymorphism in CYP2D6 and 2C9 isozymes.(5 MARKS) Or 124)Discuss the importance of genetic polymorphism of cytochrome p-450 isozymes on drug metabolism with suitable examples. ( 10 MARKS)

➢CYP2C9 : CYP2C9 has at least 30 different allelic variants with the two most common being CYP2C9*2 and *3. Both of these variants result in reduced CYP2C9 activity and are carried by about 35% of the Caucasian population. CYP2C9 is a major contributor to the metabolism of the narrow therapeutic index blood thinner warfarin. When a patient has one of these two polymorphisms, the dose of warfarin needed for clinically relevant anticoagulation is generally much less since drug clearance is reduced. If the dose of warfarin is not appropriately lowered, then there is an increased risk of bleeding. There are several other drugs affected by the polymorphisms of CYP2C9, including many nonsteroidal anti-inflammatory drugs, sulphonylureas, angiotensin II receptor antagonists, and phenytoin. For each of these, the CYP2C9*2 and *3 polymorphisms result in higher plasma concentrations but, because of their high therapeutic indices (except phenytoin), do not usually result in adverse effects. In the case of phenytoin, the polymorphisms result in drug accumulation and require dose reduction to prevent toxicity.

➢CYP2D6:• CYP2D6 isoenzyme metabolizes 25-30% of all clinically used medications, including

• Dextromethorphan,
• ß-blockers(e.g., metoprolol),
• Antiarrhythmics,
• Anti-depressants (e.g., fluvoxamine, fluoxetine, imipramine, nortriptyline),
• Antipsychotics (e.g., haloperidol, risperidone),
• Morphine derivatives, and many other drugs

Pharmacogenetics:

Drug metabolism via CYP450 enzymes exhibit genetic variability (polymorphism) that influences a patient's response to a particular drug.
For ex 1 out of 15 whites or blacks may have exaggerated response to standard doses of beta-blockers or no response to analgesic-tramadol
The gene encoding CYP2D6 isoenzyme has the most variations of all genes for CYP isoenzymes, with more than 75 allelic variants identified to date, resulting from point mutations, single base-pair deletions or additions, gene rearrangements, and deletion of the entire gene.
These mutations result in either a reduction or complete loss of activity o A specific gene encodes each cyp450 enzyme
Every person inherits one genetic allele from each parent
Alleles are referred to as "wild-type" or "variant" with wild type occuring most commonly in the general population.
An "Extensive" (i.e. normal) metabolizers receives 2 copies of wild- type alleles (i.e.) EMs carry an autosomal dominant wild type gene and may be homozygous or heterozygous for this allele.
Polymorphism occurs when a variant allele replaces 1 or both wild- type alleles. o Persons with 2 copies of variant alleles are "Poor metabolizers" and those with 1 wildtype and 1 variant allele have reduced enzyme activity.
Genotype-phenotype studies have revealed that poor metabolizers possess nonfunctional alleles and that the phenotype is an autosomal recessive trait.
Some persons inherit multiple copies of wild-type alleles, which result in excess enzyme activity. This phenotype is termed as "Ultra-rapid "metabolizers.
An ultra-rapid metabolizer phenotype has been identified and found to result from gene duplication (upto 13 copies of CYP2D6).
Poor metabolizers are more likely to have adverse effects from drugs that are substrates of the isoenzyme and decreased efficacy from drugs requiring CYP2D6-mediated activation (e.g., codeine is converted into morphine by CYP2D6), while extensive and ultra-rapid metabolizers may have therapeutic failure with drugs activated by CYP2D6 o The frequency of the phenotype of poor metabolizers differs among ethnic groups. Less than 1% of Asians, 2-5% of African-Americans, and 6- 10% of Caucasians are poor metabolizers of CYP2D6.
The most common variant alleles in Caucasians areCYP2D6*3, *4, *5, and *6, which account for about 98% of poor metabolizers.
Genotyping CYP2D6 has been shown to successfully predict the clearance of fluoxetine, fluvoxamine, desipramine, and mexiletine.
In some instances, the genotype for CYP2D6 has been useful in predicting adverse effects associated with antidepressants and neuroleptics.

2 mark:

127) and 134) Define pharmacogenetics. With suitable examples?
Pharmacogenetics is the study of how gene affect the way people respond to drug therapy.the goal of pharmacogenetics is to individualize drug therapy to a person's unique genetic makeup.The environment ,diet,age,lifestyle,and state of health can influence a persons response to medicine.An understanding of an individual;s genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety.
Pharmacogentics is an established decipline that studies the genetic basis of inter-individual variability in the response to drug therapy,and allows for individualization of drug therapy.
For example ,a pharmacogenetic study would examine the influence of the beta1 adrenergic receptor gene on blood pressure response to carvedilol.A pharmacogenomic study might

examine the interaction between CYP2D6 and beta1-,beta2-,and alpha1-adrenergic receptor genes on carvedilol effects.

## 128) Describe genetic polymorphism in CYP2D6 isoenzymes

CYP2D6 ia a large sized family that affects metabolism of many drugs .CYP2D6 is highly polymorphic .More than 70 varient allels of the CYP2D6 locus have been reported,The metabolism of the tricyclic antidepressants ,amitriptyline ,tetracyclic compounds is influenced by the CYP2D6 polymorphsm to various degree.Genetic polymorphism of CYP2D6 was first investigated with debrisoquine.Poor metabolizers often carry two non-functional allels of this gene ,resulting in reduced drug clearance.
Pharmacogenetic studies have revealed that some fast metabolizers of CYP2D6 are the result of gene duplication among different racial groups.

## 129) Describe genetic polymorphism in CYP2C9 isozymes

CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds.
Still another example of a clinically important drug metabolism polymorphism is the association of variant alleles of CYP2C9 with the requirement for lower warfarin dose. In a retrospective study of a population from an anticoagulant clinic, the CYP2C9 alleles associated with decreased enzyme activity (*2 and *3) were found to be overrepresented in patients stabilized on low doses of warfarin. These patients had an increase incidence of major and minor hemorrhage.

## 130) How do efflux transporters affect the bioavailability of the drugs.

Transporter pharmacogenetice is concerned with dray uptake and efflux into or through tissus significant problems in the Clinical application of drug result from poor or variable oral drug of bioavailability and high intra and inter individual variation in pharmacokinetic.
Several membrane transporter proteins are innival in the absorption of drugs from the intestinal tract into the body, into non intestinal tissue or into specific target site of action.
Drug efflux is an important cause of drug resistance in certain types of cells in cytotoxic chemother for several cancerons disorder.

131) Give two examples for clinically important polymorphism of drug targets?

**Table 1. Genetic Polymorphisms in Drug Target Genes That Can Influence Drug Response.***

| Gene or Gene Product | Medication | Drug Effect Associated with Polymorphism |
|---|---|---|
| ACE | ACE inhibitors (e.g., enalapril)<br>Fluvastatin | Renoprotective effects, blood-pressure reduction, reduction in left ventricular mass, endothelial function[32-40]<br>Lipid changes (e.g., reductions in low-density lipoprotein cholesterol and apolipoprotein B); progression or regression of coronary atherosclerosis[41] |
| Arachidonate 5-lipoxygenase | Leukotriene inhibitors | Improvement in $FEV_1$[42] |
| $\beta_2$-Adrenergic receptor | $\beta_2$-Agonists (e.g., albuterol) | Bronchodilatation, susceptibility to agonist-induced desensitization, cardiovascular effects[43-50] |
| Bradykinin B2 receptor | ACE inhibitors | ACE-inhibitor–induced cough[51] |
| Dopamine receptors (D2, D3, D4) | Antipsychotics (e.g. haloperidol, clozapine) | Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinesia (D3), antipsychotic-induced acute akathisia (D3)[52-56] |
| Estrogen receptor-$\alpha$ | Conjugated estrogens<br>Hormone-replacement therapy | Increase in bone mineral density[57]<br>Increase in high-density lipoprotein cholesterol[58] |
| Glycoprotein IIIa subunit of glycoprotein IIb/IIIa | Aspirin or glycoprotein IIb/IIIa inhibitors | Antiplatelet effect[59] |
| Serotonin (5-hydroxytryptamine) transporter | Antidepressants (e.g., clomipramine, fluoxetine, paroxetine) | 5-Hydroxytryptamine neurotransmission, antidepressant response[60-62] |

* The examples shown are illustrative and not representative of all published studies, which exceed the scope of this review. ACE denotes angiotensin-converting enzyme, and $FEV_1$ forced expiratory volume in one second.

132) Give two examples for clinically important polymorphism of drug transporters?

Irinotecan is widely used in cancer chemotherapy but has been associated with unpredictable severe toxic reactions such as myelosuppression and delayed-type diarrhea.
Polymorphism of multiple drug transport proteins, such as ABCB1, ABCC1, ABCC2, ABCG2, and SLC01B1 have been suggested to have additive or synergistic effects with UGT1A1.
Polymorphism of the drug-metabolizing enzyme family UGT1A is a known contributor to varied response and toxicity of irinotecan in different individuals.
ATP-binding cassette (ABC) transporters are present in cellular and intracellular membranes and can be responsible for either importing or removing of substances from cells and tissues.
There are at least 49 ABC transporter genes, which are divided into seven different families (AG) based on sequence similarity.
Three of these seven gene families are particularly important for drug transport and multiple drug resistance in tumor cells:
1. the ABCB1 gene, encoding MDR1 (also known as P-glycoprotein);
2. ABCG2 (breast cancer resistance protein);
3. the ABCC family (ABCC1 through ABCC6) or multidrug resistance proteins (MRP).

133) Describe the role of genetic polymorphism in drug transports.

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others.
additionally, genetic variation such as singlenucleotide polymorphisms (SNPs) of the transport proteins can cause differences in the uptake or efflux of drugs.
Genomics has led to the development which involve the study of biological interesting proteins and their variants.
The physiological response of the body to a drug is generally the result of interaction at a specific target site in the body.
It is estimated that about 50% of the drugs act on the membrane receptors and about30% act on enzymes and about 5%act on ion channels.
Many of the genes encoding these target proteins exhibit polymorphism that may alter drug response .

135) with suitable examples, enumerate drug dosing in genetic dependent fast acetylators?
Acetylation is a very common metabolic reaction which occurs with amino, hydroxyl or sulfhydryl groups. The acetyl group is transferred from acetyl-coenzyme A and the reaction is catalysed by acetyltransferases.
The rate of drug acetylation is influenced by genetic factors. Individuals who are phenotypically fast acetylators are either heterozygous or homozygous for a dominant allele of the hepatic acetyltransferase gene.
Isoniazid is metabolized primarily by acetylation by liver N-acetyltransferase. The rate of acetylation is genetically determined.
Slow acetylation may lead to higher blood levels of the drug and thus, to an increase in toxic reactions.and fast acetylation may lead to low blood levels of the drug and there is a need to increase the amount of drug to increase the therapeutic value.
The average concentration of isoniazid in the plasma of rapid acetylators is about one third to one half of that in slow acetylators, and average half-lives are less than 1 hour and 3 hours, respectively.

## **POPULATION PHARMACOKINETICS**:

5 mark:
136 Describe Bayesian theory
Introduction to Bayesian Theory Bayesian theory was originally developed to improve forecast accuracy by combining subjective prediction with improvement from newly collected data in the diagnosis of disease, the physician may make a preliminary diagnosis based on symptoms and physical examination. Later, the rest laboratory tests are received. The clinician then makes a new diagnostic forecast based on both sets of information. Bayesian theory provides a method to weigh the prior information (eg, physical diagnosis) and new information (eg, results from laboratory tests) to estimate a new probability for predicting the disease. In developing a drug dosage regimen, we assess the patient's medical history and then use average or population pharmacokinetic parameters appropriate for the patient's condition to calculate the initial dose, after the initial dose, plasma or serum drug concentrations are obtained from the patient that provide new information to assess the adequacy of the dosage. The dosing approach of combining old information with new involves a "feedback" process and is, to some degree, inherent in many dosing methods involving some parameter readjustment when new serum drug concentrations become known. The advantage of the Bayesian approach is the improvement in estimating the patient's pharmacokinetic parameters based on Bayesian probability versus an ordinary least-squares-based program. An example comparing the Bayesian method with an alternative method for parameter estimation from some simulated theophylline data will be shown in the next section. The method is particularly useful when only a few blood samples are available.
Because of inter- and intra subject variability, the pharmacokinetic parameters of an individual patient must be estimated from limited data in the presence of unknown random error (assays, etc), known covariates and variables such as clearance, weight, and disease factor, etc, and possible structural (kinetic model) error. From knowledge of mean population pharmacokinetic parameters and their variability, Bayesian methods often employ a special weighted least-squares (WLS) approach and allow improved estimation of patient pharmacokinetic parameters when there is a lot of variation in data The methodology is discussed in more detail under the Bayes estimator in the next section and also under pharmacokinetic analysis.

EXAMPLE: After diagnosing a patient, the physician gave the patient a probability of 0.4 of having a disease. The physician then ordered a clinical laboratory test. A positive laboratory test value had a probability of 0.8 of positively identifying the disease in patients with the disease (true positive) and a probability of 0.1 of positive identification of the disease in subjects without the disease (false positive). From the prior information (physician's diagnosis) and current patient-specific data (laboratory test), what is the posterior probability of the patient having the disease using the Bayesian method?

Solution

Prior probability of having the disease (positive) = 0.4

Prior probability of not having the disease (negative) 1 â€" 0.4 =0.6

Ratio of disease positive/disease negative = 0.4/0.6 2/3, or, the physician's evaluation shows a 2/3 chance for the presence of the disease. The probability of the patient actually having the disease can be better evaluated by including the laboratory findings, for this same patient, the probability of a positive laboratory test of 0.8 for the detective of disease in positive patients(with disease)and the probability of 0.1 in negative patients (without disease )are equal to a ratio of 0.8/0.1 or 8/1. This ratio is known as the 2/3, the posterior probability ratio is the likelihood ratio. Combining with the prior probability ratio is:

Posterior probability ratio (2/3) (8/1) = 16/3

Posterior probability = 16/(16 + 3) = 84.2%

Thus, the laboratory test that estimates the likelihood ratio and the preliminary diagnostic evaluation are both used in determining the posterior probability. The results of this calculation show that with a positive diagnosis by the physician and a positive value for the laboratory test, the probability that the patient actually has the disease is 84.2%.

Bayesian probability theory when applied to dosing of a drug involves a given pharmacokinetic parameter (P) and plasma or serum drug concentration (C), as shown in Equation 20â€ 11. The probability of a patient with a given pharmacokinetic parameter P, taking into account the measured concentration, is Prob(P/C):

$$\text{Prob}(P/C) = \frac{\text{Prob}(P) * \text{Prob}(C/P)}{\text{Prob}(C)}$$

where Prob(P) = the probability of the patient's parameter within the assumed population distribution, Prob(C/P) the probability of measured concentration within the population, and Prob(C)= the unconditional probability of the observed concentration.

## 137 Explain dosing with feedback.

In dosing drugs with narrow therapeutic ratios, an initial dose is calculated based on pharmacokinetic parameters. After dosing, plasma drug concentrations are obtained from the patient. As more blood samples are drawn from the patient, the calculated individualized patient pharmacokinetic parameters become increasingly more reliable. This type of approach has been referred to as adaptive, or Bayesian adaptive method with feedback when a spacial extended least-squares algorithm is used many ordinary least-squares computer software packages are available to clinical practice for parameter and dosage calculation.

Some software packages record medical history and provide adjustments for weight, age, and in some cases, disease factors. A common approach is to estimate the clearance and volume of distribution from intermittent infusion. Abbottbase Pharmacokinetic Systems (1986 and 1992) is an example of patient-oriented software that records patient information and dosing history based on 24-hour clock time.

An adaptive-type algorithm is used to estimate pharmacokinetic parameters. The average population clearance and volume of distribution of drugs are used for initial estimates and the program computes patient-specific Cl and VD as serum drug concentrations are entered. The

program accounts for renal dysfunction based on creatinine clearance, which is estimated from serum creatinine concentration using the Cockroft Gault equation. The software package allows specific parameter estimation for digoxin, theophylline, and aminoglycosides, although other drugs can also be analyzed manually.
Many least-squares (LS) and weighted-least-squares (WLS) algorithms are available for estimating patient Pharmacokinetic parameters. Their common objective involves estimating the parameters with minimum bias and good prediction, often as evaluated by mean predictive error. The advantage of the Bayesian method is the ability to input known information into the program, so that the search for the real pharmacokinetic parameter is more efficient and, perhaps, more precise. For example, a drug is administered by intravenous infusion at a rate, R, to a patient. The drug is infused over t hours (t may be 0.5 to 2 hours for a typical infusion). The patient's clearance, Cl T, may be estimated from plasma drug concentration taken at a known time according to a one-compartment-model equation. simulated a set of theophylline data and estimated parameters from the data using one- and two-serum concentrations, assuming different variabilities. These investigators tested the method with a Bayesian approach and with an ordinary least-squares method.

Q138. Discuss Population P.K Analysis using NONMEM method?

Q139. Discuss analysis of population pharmacokinetics data? And 140

141. Describe the two-stage approach in population pharmacokinetic analysis?

Ans. 1: Standard two stage (STS) method:

- Estimates parameters from the plasma drug concentration data for an individual subject during the first stage. The estimates from all subjects are then combined to obtain an estimate of the parameters for the population.
- The method is useful because unknown factors that affect the response in one patient will not carry over and bias parameter estimates of the others. The method works well when sufficient drug concentration-time data are available.

2. First-Order (FO) method:

- This method is also used but is perhaps less well understood. The estimation procedure is based on minimization of an extended least-squares criterion, which was defined through a first-order Taylor series expansion of the response vector about the fixed effects and which utilized a Newton-Raphson-like algorithm.
- This method attempts to fit the data and partition the unpredictable differences between theoretical and observed values into random error terms. When this model includes concomitant effect, it is called a mixed-effect statistical model.
- The advantage of the first-order model is that it is applicable even when the amount of time-concentration data obtained from each individual is small, provided that the total number of individuals is sufficiently large.
- Typically, a computer method is used in the data analysis based on a statistical model using either the weighted least-squares (WLS) or the extended least-squares (ELS) method in estimating the parameters.

142) Explain non-linear mixed effects modeling approach?

Ans: The non-linear mixed effect model (or NONMEM) is so called because the model uses both fixed and random factors to describe data. Fixed factors such as patient weight , age, gender, and creatinine concentration are assumed to have no error. Whereas random factor includes inter and intra individual differences.

- NONMEM is a statistical program that allows Bayesian pharmacokinetic parameters to be estimated using an efficient algorithm called the first-order (FO) method.
- The parameter may now be estimated also with a first-order conditional estimate (FOCE) algorithm.
- In addition, to pharmacokinetic parameters , many examples of population plasma data have been analyzed to determine population factors. Multiplicative coefficients or parameters for patient factors may also be estimated. NONMEM fits plasma drug concentration data for all subjects in the groups simultaneously and estimates the population parameters and its variance. The parameter may be clearance and/or $V_D$ . The model may also test for other fixed effects on the drug due to a factor such as age, weight, and creatinine concentration.
- The model describes the observed plasma drug concentration (Cl) in terms of a model with:

1: $P_k$ = fixed effect parameters , which include pharmacokinetic parameters or patient factor parameters
For ex, $P_1$ is Cl , $P_2$ is the multiplicative coefficient include creatinine factor, and $P_3$ is the multiplicative coefficient for weight.

2: Random effect parameters including,

(a) The variance of the structural (kinetic) parameter $P_k$ or inter subject variability within the population $w^2_k$ and
(b) The residual intrasubject variance or variance due to measurement errors, fluctuations in individual parameter values, and all the other errors not accounted for the other parameters .

143: Give the applications of population pharmacokinetics?

- Ans: Allometric Scaling: PopPK models can be used to predict PK across species (e.g., for selecting doses for First Time in Human studies [FTIH]) or across populations (e.g., from adults to pediatrics).
- Exposure-Response: PopPK models in combination with PD data can support evidence of safety and efficacy.
- Clinical Trial Simulation: Modeling and simulation can drive study design decisions by assessing the impact of variability on sample size, comparing the probability of success with various designs, determining optimum PK sampling, and evaluating long-term study scenarios. Clinical trial simulations are also used to optimize studies with adaptive designs.
- Concentration-QT: Concentration-response analysis across a wide range of doses is used to characterize the potential for a drug to influence the QT interval (a measurement related to the electrical properties of the heart) and can serve as an alternative to a standalone thorough QT study.

- In Vitro In Vivo Correlation (IVIVC): IVIVC models can be used as a surrogate for bioequivalence studies for formulation changes and to set dissolution specifications.
- Model based bioequivalence: In selected scenarios, when dense PK sampling is not feasible (e.g., pediatric and oncology studies), model based bioequivalence can be substituted for the traditional noncompartmental approach to bioequivalence. When this done, attention must be paid to preserving the statistical rigor of the approach.

## 144.Explain sampling design used in population pharmacokinetics.

A pharmacokinetic study of a new drug involves taking some blood samples over a period of time from study participants to determine how the body handles the substance. These studies provide critical information of new drug.

Sampling design used in Pk studies

- Increasing used in drug development
  - estimation of the mean parameters and inter-patient variabilities.
  -Quantification of the influence of covarities.
  -allows sparse data
- Methods
  -NLME nonlinear mixed effects models
  -maximum likelihood estimation; now well known methodology
- Several available software
  -NONMEM , WinNonmix , Monolix
  -SAS
  -Splus(nime)

Design for POP PK Analyses

- Increasing important task for pharmacologist
- FDA Guideline for population PK(1999)
- EMEA Guideline for PK in the paediatric population (2006)
- Estimation of the p parameters of one subject
- Choice of n sampling times with $n \geq p$
- Theory of evaluation /optimization in nonlinear regression
- Tool for helping the design choice

-ADAPT ll

- evaluates and optimizes individual design based on $M_F$
- Estimation of the vector of the population parameters from N subjects
- Choice of N?
- Same number of samples for everybody?
- Same sampling times?
- Different groups of subjects?

## 145. Describe how population pharmacokinetic data analysis is carried out.

Analysis of population pharmacokinetic data

- Pharmacokinetic data -intended to define the time course of drug and major metabolite concentration in plasma and other biological fluids in order to obtain information on absorption, distribution, metabolism and elimination.

**Importance**

-Pharmacologicaly guided dose escalation (PGDE)studies

-dose fixing in phase 2 and subsequent studies
-to adopt drug dosage to individual patient (therapeutic drug monitoring)

Relevant pharmacokinetic parameters
- total clearance
- fraction of dose excreted unchanged in urine
- volume of distribution at steady state
- volume of distribution during the termina phase
- blood /plasma concentration ratio
- termina half fife
- fraction of unbound drug in plasma
- BioavaiIabIe fraction of dose ,if appIicable and
- absorption rate constant

Designing a Dosing Regimen FoIIowing parameters shouId be known:
-area under the pIasma concentration time curve
- Maximum concentration
- minimum concentration after repeated dosing and time of $C_{max}$
- In addition , the effective and toxic concentration shouId be assessed.

**Population pharmacokinetic analysis** :Refers to a set of stasticaI techniques that can be used to Iearn about the average response in the population as weII as the variabiIity in response that rises from different sources.
Population analysis is the application of a modeI to describe that arise from more than one individuaI.
Pharmacokinetic analysis is the of pooIed data of pIasma drug concentration from a Iarge group of subjects may reveaI much information about the disposition of drug in a population .
Inter and Intra subjects must be considered.
Both pharmacokinetic and non-pharmacokinetic factors such as age ,sex , weight and creatinine concentration , shouId be examined in the modeI to determine the reIeavance to the estimation of pharmacokinetic parameters.

Non Linear Mixed Effect Model (NONMEM)
NONMEM is called because the model uses both fixed and random factors to describe data fixed factor such as patient weight,age, sex and creatinine concentration are assumed to have no error, where as random factors include inter and intra-individual differences.
NONMEM is a statistical program that allows Bayesian pharmacokinetic parameters to be estimated using an efficient algorithm called the first order method.

146.Give the reasons for conducting population pharmacokinetic study.

Population PK analyses are a crucial aspect of almost all NDAs and BLAs. They provide an integrated assessment of PK and explain variability in PK due to covariates. Understanding variability in PK is important to guide optimal dosing in subpopulations and to support critical drug development decisions.

Pharmacokinetic modeling is useful in

- Prediction of drug concentration in plasma/tissue/urine at any point of optimum dosage regimen for each patient.
- Estimation of the possible accumulation of drugs /metabolities .
- Quantitative assessment of the effect of disease on drugs ADME

147) what are the Limitationsof population pharmackokinetic approach?

Advantages

- pharmacokinetic analysis is usually conducted in patients taking the drug
- can accommodate flexible study designs which occur during treatment • only a few samples are needed from each patient
- opportunistic sampling has the potential to be cost-effective
- screening and quantification of covariates for explaining variability can distinguish between interindividual and intra individual variability modelling software is widely available (e.g. NONMEM)

Disadvantages

- relatively large numbers of patients are required (typically >40)
- complex pharmacostatistical analyses
- requires collection, compilation and verification of large amounts of data • model building may be tedious, labour intensive and time-consuming
- model diagnostics are often complex and time-consuming
- difficulties with handling missing data (eg. all covarlates in all patients)

148) explain the difference between traditional pharmacokinetics and population pharmacokinetics

| | Traditional | Population |
|---|---|---|
| Population | Healthy volounteers<br><br>Highly selected patients | Target patient population (Pediatrics, elderly, AIDS) |
| Study size | Small | Large or integrated (observational or experimental) |
| Sampling data | Dense (typically 1 to 6 time points) following drug administration. | Sparse, few samples for many patients |
| Inter-individual Variability | Minimized through restrictive criteria | Demographics<br>Pathophysiological<br>Concomitant medications |
| Relationships of concentration, PK/PD | Limited | Extensive, make predictions about future events -steady state concentrations and efficacy, guide dosage adjustments, determine therapeutic window. guide dosage for safety |

Q. 149 Define adaptive method in population pharmacokinetics study.

A. In dosing drugs with narrow therapeutics ratios, an initial dose is calculated based on mean population pharmacokinetics parameters. After dosing, plasma drug concentrations are obtained from the patient. As more blood samples are drawn from the patient, the calculated individualized patient

Pharmacokinetics parameters become increasingly more reliable. This type of approach has been referred to as adaptive.

The adaptive model for dosage regimen calculation uses patient variables such as weight, age, sex, body surface area and known patient pathophysiology, such as renal disease, as well as the known population average pharmacokinetic parameters of the drug.

In this case, calculation of the dosage regimen takes into consideration any changing pathophysiology of the patient and attempts to adapt or modify the dosage regimen according to the needs of the patient.

Q. 150. And 152. Define population pharmacokinetics.

A. Population pharmacokinetics is the study of the source and correlates of variability in drug concentration among individuals who are the target patient population receiving clinically relevant doses of a drug of interest.

Certain patient demographical, pathophysiological and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships.

Q.151. Define adaptive method in population pharmacokinetics study.

In dosing drugs with narrow therapeutic ratios, an initial dose is calculated based on mean population pharmacokinetic parameters. After dosing, plasma drug concentrations are obtained from the patient. As more blood samples are drawn from the patient, the calculated individualized patient pharmacokinetic parameters become increasingly more reliable. This type of approach has been referred to as adaptive

The adaptive model for dosage regimen calculation s patient variables such as weight, age,sex, body surface area, and known patient pathophysiology, such as renal disease, as well as the known population average pharmacokinetic parameters of the drug.

In this case, calculation of the dosage regimen takes into consideration any changing pathophysiology of the patient and attempts to adapt or modify the dosage regimen according to the needs of the patient.

Q. 153. What are the advantages of population pharmacokinetics study over traditional pharmacokinetics study?

A. Population pharmacokinetics analysis is usually conducted in patients taking the drug but traditional pharmacokinetic study in which subjects are sampled intensively

Population pharmacokinetics study can accommodate flexible study designs which occur during treatment but traditional pharmacokinetics study cannot accommodate flexible study designs.

Population pharmacokinetics study only a few samples are needed from each patient but traditional pharmacokinetic study large amount of samples are needed from each patient.

## Q. 154. Define inter individual variation

A. The inter individual variation in the response to any drug can be defined as "an effect of varying intensity occurring in different individuals at a specified dose of a drug", Or as "a requirement of arrange of concentrations (doses) in order to produce an effect of specified intensity in all of the patients"

## 155. Define within subject variation

- Within-subject variation is the random variation in an individual over trials.
- Within-subject variation may occur because: the individual does not always respond in the same way (e.g. blood pressure) of measurement error.

- E.g. readings of systolic blood pressure on a man may range between 135-145 mm Hg when repeated 10 times
- Usually less variation than between-subjects

## 156. What is random error?

A random error, as the name suggests, is random in nature and very difficult to predict. It occurs because there are a very large number of parameters beyond the control of the experimenter that may interfere with the results of the experiment.

Random error is also called as statistical error because it can be gotten rid of in a measurement by statistical means because it is random in nature.

## 157. What is residual error?

The difference between observed concentration and model predicted concentration \

Residuals are usually assumed to be independent, normally distributed with mean zero and variance of $\sigma^2$ & = N(0, $\sigma$)

## 158. What do you understand by typical value?

Ans :A **typical value** is a specified **value** for a technical characteristic that: Lies within the range of **values** specified by the operating behavior. Given the **typical** manufacturing process, is representative of that characteristic during operation when you meet the **typical value** conditions or other specified conditions.

## 159. Define theta, omega, sigma in NONMEM method of analysis

THETA: Initial estimates of the parameters of the structural model. NONMEM typically tries to optimize these, but they can also have fixed values.

OMEGA: Initial estimates of the variance of the interindividual random effects (ETAS). NONMEM typically tries to optimize these, but they can be fixed in value. If they are all fixed at "0", that is called "naïve pooled data", and is often useful for testing other parts of the model.

SIGMA: Initial estimates of the variance of the intraindividual random effects (i.e.. residual noise). NONMEM virtually always estimates this.

## 160. List the methods used for the population pharmacokinetic model evaluation.

Ans; Population pharmacokinetic (PK) modeling methods can be statistically classified as either parametric or nonparametric. Each classification can be divided into maximum likelihood or Bayesian approaches.

## 161. Difference between observed and predicted concentrations.

Observation lead to inferences …..it is a possible explanation for the observation .

Prediction can be made from inferences. A scientific prediction is an educated guess about a future event.

## 162. What do you understand by over-estimation?

Ans: To estimate (something) as being greater than the actual size, quantity, or number. to think of (someone or something) as being greater in ability, influence, or value than that person or thing actually is.

## 163. List various softwares used for conducting population pharmacokinetic analysis

- PCNonlin
- WinNonlin
- SAS
- RSTRIP
- NONMEM
- MKMODEL ADAOT II
- DIFFEQ and DIFFEQ pharmacokinetics library
- scientist for windows

## 164. Give Bayesian equation.

Bayesian probability theory when applied to dosing of a drug involves a given pharmacokinetic parameter (P) and plasma or serum drug concentra tion (C), as shown in Equation 20.11. The probabil ity of a patient with a given pharmacokinetic parameter P, taking into account the measured con centration, is Prob(PIC):

$$\text{Prob(PIC)} = \frac{\text{Prob (P) Prob (CIP)}}{\text{Prob (C)}}$$

where Prob(P) = the probability of the patient's parameter within the assumed population distribu tion, Prob(C/P) = the probability of measured concentration within the population, and Prob (C)= the unconditional probability of the observed concentration.

## 165. What do you understand by Goodness of Fit plot

‣ Goodness of fit is a statistical term referring to how far apart the expected values of a financial model are from the actual values.

➢ Goodness of fit is a component of regression analysis, which is a statistical method used in finance and a variety of other fields to make predictions based on observed values. In other words, it is a measure of how correlated a group of actual observations are to a model's predictions

➢ Such measures can be used in statistical hypothesis testing, e.g. to test for normality of residuals, to whether two samples are drawn from identical distributions or whether outcome frequencies follow a specified distribution. In the analysis of variance, one of the components into which the variance is partitioned may be a lack-of-fit sum of squares

## 166. Define FO AND FOCE:

The first-order conditional estimation (FOCE) method is more complex than the first-order (FO) approximation method because it estimates the empirical Bayes estimate (EBE) for each iteration. By contrast, it is a further approximation of the Laplacian (LAPL) method, which uses second-order expansion terms.

## 167. What do you understand by nested models?

It means that one model is a subset of another. example, take a model for pregnancy outcomes that includes four categorical independent variables: Age.Weight, Pre-existing conditions, Hereditary factors.

Nested models are used for several statistical tests and analyses, including multiple regression, likelihood-ratio tests, conjoint analysis, and independent of irrelevant alternatives (IIA).

## 168. What is naïve pool data?

- It was proposed by Sheiner and Beal.
- Method involves pooling all the data from all individuals as if they were from a single individual to obtain population parameter estimates.
- Generally, the naive pooled approach performs well in estimating population pharmacokinetic parameters from balanced pharmacokinetic data with small between subject variations.

## 169. Give the advantages of Bayesian method in population pharmacokinetic study

Bayesian method involves estimation of the joint posterior distribution of all unobserved stochastic quantities conditional on observed data.

Advantages:

• Generating random samples from the joint posterior distribution of the parameters.

• Marginal distribution of each parameter is completely characterized (numerical integration)

## 170. What is interoccasion variation?

- Its define as random variability in individual pharmacokinetic parameters between study occasions.

- The variance of the pharmacokinetic observations of an individual about the individual specific pharmacokinetic model on a given occasion (i.e., the intra individual variability) can be factored conceptually into two components: (1) variability of pharmacokinetic observations due to variability of the pharmacokinetic model from occasion to occasion (interoccasion variability) and (2) variability of pharmacokinetic observations about the individual pharmacokinetic model appropriate for the particular occasion (noise; pharmacokinetic model misspecification)

## Q138. Discuss Population P.K Analysis using NONMEM method?

**A**: INTRO: Population P.K Analysis is pharmacokinetics analysis of pooled data of plasma drug concentration from a large group of subjects which may reveal much information about disposition of a drug in a population.

- Non-linear mixed effective model [NONMEM]
- A NONMEM is a pharmacometrics software
    - ♦ A platform program as a Dos application
    - ♦ Requires the user to write a "control stream"

⬇

Identifies, How to read in the data

- ♦ How model id defined
- ♦ What postprocessor activities should be called

- Uses both fixed and random factors to describe the data:
    1. Fixed factor: Patient weight, age, gender.
    2. Random factor: inter-intra individual differences.
- To obtain quality scatter plots require input into another statistical program such as SAS, R, S-Plus, Xpose.

- Allow Bayesian pharmacokinetic parameters to be estimated using an efficient algorithm called the
  - ♦ The first order [FO] method.

Parameters are also estimated :

- ♦ The first order conditional estimate [FOCE] algorithm.

- Multiplicative coefficients or parameters for patient factors is also estimated
- Fits plasma drug concentration data for all subjects in the group simultaneously
- Estimate population parameters and its variances.
- Parameters: 1. $\frac{\text{Clearance}}{V_d}$

## *Advantages:*

- Combine all data in one Model.
- The difference between the individuals are described with random effects.
- Possible to use data that would not be adequate for individual PK modelling [eg: spare sampling]
- More data per model yield more power.
- Easier to locate source of between subjects variability.
- It estimate basic PK and random effects parameters.
- Population PK parameters is used to calculate the initial dose or to adjust the dose.
- Allows the evaluation and quantification of potential sources of variability in PK and pharmacodynamics in target population.
- Useful in design of dosing regimen and the therapeutic drug monitoring.

COMPONENTS

Explained:

- NM-TRAN:
  - Convert the data file and control stream into FORTAN code files.

- PREDPP:
  - Prediction for population PK
  - Computes the predictions of observations arising from one of several specialized PK models in a library of PK subroutine

***Objective function of NONMEM is***

Proportional to the sum of squared differences of the observation from the model prediction smaller value represent a better fit.

## Q139. Discuss analysis of population pharmacokinetics data?

**A:** Population PK is the study of variability in plasma drug concentration between & within the target population receiving clinically relevant therapeutic doses of a drug.

- Population PK seeks to identify the measurable pathophysiological factors that cause changes in dose concentration relationship.
- Population PK analysis provide Qualitative estimates of both interindividual and intraindividual variability of a population.
- Has a potential to provide high quality, relevant info on a drugs PK from sparely sampled data if study is conducted in appropriate manner.
- The application of population analysis methods to therapeutic problems has led to on going methodological & software developments as following:

***COMMON SOFTWARES:***

- NONMEM [non linear mixed effect of modeling]
- MK MODEL >SAS
- NPEM-2 [non parametric expectation maximization] >S-PLUS
- NPML [non parametric maximum likelihood] > semi non parametric approach
- Bayesian approach using Gibbs sampling.

- Each methods of applying pop PK has its own assumptions and limitations.

A

B

Two stage approach

Estimate individual parameters of
In this theory drug administration + sampling schedules.

Each patient data [1st stage]
considered identical for all subjects.

Merits: Easy to obtain estimates.

Compares them generally
Used in bioequivalence studies.

[2nd stage]
Demerits: Misleading results.

Risk of confounding.

Population parameters estimation.

C

Methode

Non-linear me

POPULATION MODEL ELEMENTS
POPULATION MODEL ELEMENTS

A

Model for typical response

Estimation of
interindividual kinetics variations

C

Taking
into concentration:

- Structural model *
  Data variations # Describes why
  1st and 2nd models do not match
- Like a compartmental model that *
  Individual dosing history etc. the
  observations exact.

describes plasma drug concentration
# Uncertainty is also called residual errors.
over time
force method # Uncertainty arises from 4 sources.
-First order
NONMEM approach *
Process error
POPULATION MODEL ELEMENTS
loplace method * Measurement error

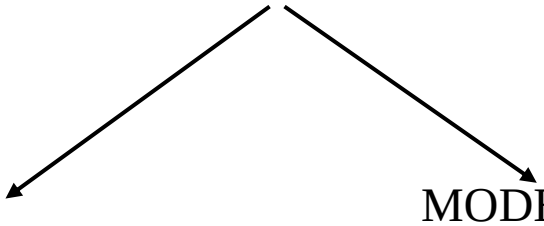
Model of heterogeneity

-
Alter
nate
first
order
*
Mode
l
missp
ecific
ation

B - Condition
first order approach *
Moment to moment variability within a patient.

-
Non parametric maximum likelihood (NPML)
To describe the variability between individuals. –
Semi parametric maximum likelihood (SNP)

MODELS



MODEL1

To describe predictable remaining
Reason why individuals variability
Are different.

MODEL2

To quantify the

source of random