LECTURE NOTES
ON

CLINICAL PHARMACOKINETICS
AND
PHARMACOTHERAPEUTIC DRUG MONITORING

(Subject Code: TO850003)

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KRISHNA TEJA PHARMACY COLLEGE (AF)

Chadalawada Nagar, Renigunta Road, Tirupati – 517 506

UNIT 1
INTRODUCTION TO CLINICAL PHARMACOKINETICS

Pharmacokinetics:

Pharmacokinetics is defined as the kinetics of drug absorption, distribution, metabolism, excretion (ADME) and their relationship with the pharmacologic, therapeutic or toxicological response in man and animals.

Clinical Pharmacokinetics:

The applications of pharmacokinetic principles in the safe and effective management of individual patient is called as clinical pharmacokinetics.

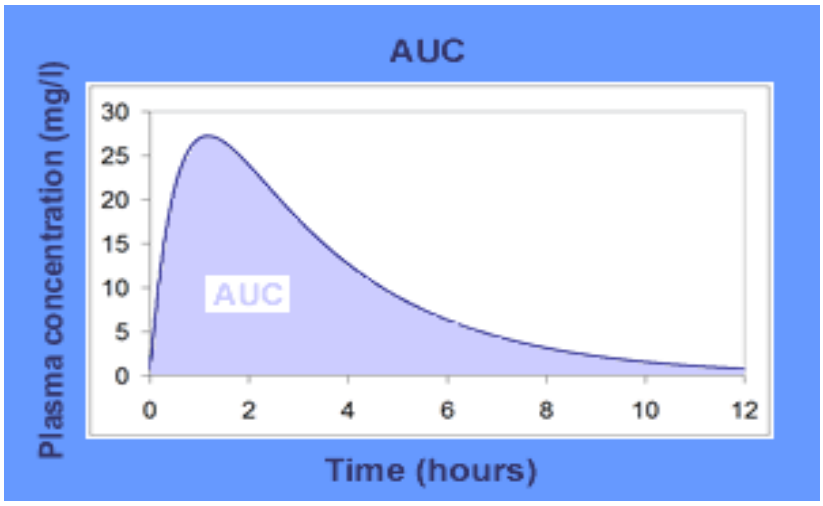
- Clinical pharmacokinetics is the application of pharmacokinetic methods to drug therapy.
- It involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations.
- Pharmacokinetics is also applied to therapeutic drug monitoring (TDM) for very potent drugs such as those with a narrow therapeutic range, in order to optimize efficacy and to prevent any adverse toxicity. For these drugs, it is necessary to monitor the patient, either by monitoring plasma drug concentrations (e.g., theophylline) or by monitoring a specific pharmacodynamic endpoint such as prothrombin clotting time (e.g., warfarin).
- The influence of many diseases on drug disposition is not adequately studied. Age, gender, genetic and ethnic differences can also result in pharmacokinetic differences that may affect the outcome of drug therapy.

Population Pharmacokinetics:

Study of pharmacokinetic differences of drugs in various population groups is termed population pharmacokinetics.

Plasma Drug Concentration-Time Profile:

A direct relationship exists between the concentration of drug at the site of action and the concentration of drug in plasma. A typical plasma drug concentration-time curve is obtained as follows:



The three important pharmacokinetic parameters that describe the plasma level-time curve and useful in assessing the bioavailability of a drug from its formulation are:

Peak Plasma Concentration (Cmax):

The point of maximum concentration of drug in plasma is called as the peak and the concentration of drug at peak is known as peak plasma concentration.

- The peak represents the point of time when absorption rate equals elimination rate of drug.
- It is also called as peak height concentration and maximum drug concentration.
- It is expressed in mcg/ ml .
- Peak concentration is often related to the intensity of pharmacologic response and should ideally be above minimum effective concentration (MEC) but less than the maximum safe concentration (MSC).

Time of Peak Concentration (tmax) :

The time for drug to reach peak concentration in plasma (after extravascular administration) is called as the time of peak concentration. It is expressed in hours.

Area Under the Curve (AUC):

It represents the total integrated area under the plasma level-time profile and expresses the total amount of drug that comes into the systemic circulation after its administration. AUC is expressed in mcg/ml X hours.

The various pharmacodynamic parameters are:

- Minimum Effective Concentration (MEC)

It is defined as the minimum concentration of drug in plasma required to produce the therapeutic effect. In case of antibiotics, the term minimum inhibitory concentration (MIC) is used. It describes the minimum concentration of antibiotic in plasma required to kill or inhibit the growth of microorganisms.

- Maximum Safe Concentration (MSC)

Also called as minimum toxic concentration (MTC), it is the concentration of drug in plasma above which adverse or unwanted effects are precipitated. Concentration of drug above MSC is said to be in the toxic level.

- Sub-therapeutic level

The concentration of drug below MEC is said to be in the sub-therapeutic level.

- Onset of Action

The beginning of pharmacologic response is called as onset of action. It occurs when the plasma dreg concentration just exceeds the required MEC.

- Onset Time

It is the time required for the drug to start producing pharmacologic response. It corresponds to the time for the plasma concentration to reach MEC after administration of drug.

- Duration of Action

The time period for which the plasma concentration of drug remains above the MEC level is called as duration of drug action.

- Intensity of Action

It is the maximum pharmacologic response produced by the peak plasma concentration of drug. It is also called as peak response

- Therapeutic Range

The concentration of drug between MEC and MSC represents the therapeutic range.

- Rate of reaction

The rate of a reaction or process is defined as the velocity at which it proceeds and can be described as either zero-order or first-order or mixed order.

- Zero-order reaction

The reaction proceeds at a constant rate and is independent of the concentration of drug present in the body**.**

Consider the rate of elimination of drug A from the body. If the amount of the drug A is decreasing at a constant rate, then it is written as

$$dA/dt = -K_0$$

Where k_0 is the zero-order rate constant.

- First-order reaction

The reaction proceeds at a rate that is dependent on the concentration of drug present in the body

If the amount of drug A is decreasing at a rate that is proportional to A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

$$dA/dt = -KA$$

Where k is the first-order rate constant.

- Mixed Order reaction:

Reaction that follows both first order and zero order reaction.

COMPARTMENT MODELS :

- Physiologic pharmacokinetic models are frequently used in describing drug distribution in animals, because tissue samples are easily available for assay.

- On the other hand, tissue samples are often not available for human subjects, so most physiological models assume an average set of blood flow for individual subjects.
- In contrast, because of the vast complexity of the body, drug kinetics in the body are frequently simplified to be represented by one or more compartments, that communicate reversibly with each other.
- A compartment is not a real physiologic or anatomic region but is considered as a tissue or group of tissues that have similar blood flow and drug affinity.
- Within each compartment, the drug is considered to be uniformly distributed.

I) One-compartment model :

Following drug administration, the body is depicted as a kinetically homogeneous unit. This assumes that the drug achieves instantaneous distribution throughout the body and that the drug equilibrates instantaneously between tissues.

II) Two-compartment model :

The two-compartment model resolves the body into a central compartment and a peripheral compartment. Although these compartments have no physiological or anatomical meaning, it is assumed that the central compartment comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well- perfused tissues such as muscle, fat and skin.

III) Multicompartment model :

In this model the drug distributes into more than one compartment and the concentration–time profile shows more than one exponential. Each exponential on the concentration–time profile describes a compartment.

Mammillary Model :

- A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment.
- The mammillary model is the most common compartment model used in pharmacokinetics.
- The mammillary model is a strongly connected system, because one can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment.

Catenary Model :

In pharmacokinetics, the mammillary model must be distinguished from another type of compartmental model called the catenary model.

- The catenary model consists of compartments joined to one another like the compartments of a train.
- In contrast, the mammillary model consists of one or more compartments around a central compartment like satellites.
- Because the catenary model does not apply to the way most functional organs in the body are directly connected to the plasma, it is not used as often as the mammillary model.

- Apparent volume of distribution :

It is defined as that volume of plasma in which the total amount of drug in the body would be required to be dissolved in order to reflect the drug concentration attained in plasma.

$$V_d = X/Cp$$

- Half-life :

The time required to reduce the plasma concentration to one half its initial value is defined as the half-life (t1/2).

$$(t_{1/2})=0.693/k$$

- Clearance :

Drug clearance (CL) is defined as the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion.

- Drug can be cleared by renal excretion or by metabolism or both. With respect to the kidney and liver, etc., clearances are additive, that is:

$$Cltotal = Clrenal + Clnon\ renal$$

UNIT 2
DESIGN OF DOSAGE REGIMENS

Dosage Regimen :

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

Dosing of Drug in Obese Patient :

- IBW (men)=50Kg + 1Kg/2.5 cm above or below150 cm in height
- IBW (women)=45Kg +1Kg/2.5 cm above or below 150cm in height
- Any person whose body weight is more than 25% above the IBW is considered as obese.

Dosing of drug in Neonates, Infants & Children :

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

- Mosteller's equation:

$$SA \text{ (in m2)} = \frac{(\text{height X weight})}{60}1/2$$

- Child's maintenance dose can be calculated from adult dose by using the following equation :

$$\text{Child's dose} = \frac{\text{SA of Child in m2 X Adult Dose}}{1.73}$$

$$SA \text{ (in m2)} = \text{Body weight (Kg)}0.7$$

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

$$\text{Child's dose} = \frac{[\text{weight of child in Kg}]\ 0.7}{70} \times \text{Adult dose}$$

Dosing of drug in elderly:

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

$$\text{Patient's dose} = \frac{(\text{weight in Kg})0.7(140 - \text{age in years})}{1660} \times \text{Adult Dose}$$

UNIT 3
PHARMACOKINETICS OF DRUG INTERACTION

INTRODUCTION:

A Drug interaction is an interaction between a drug and some other substance, such as another drug or a certain type of food, which leads to interaction that could manifest as an increase or decrease in the effectiveness or an adverse reaction or a totally new side effect that is not seen with either drug alone that can be severe enough to alter the clinical outcome. Drug interactions are thus:

- Mostly undesirable
- Rarely desirable(beneficial)

  Eg: Enhancement of activity of Penicillines when administered with Probenecid.
- The drug whose activity is effected by such an interaction is called as a "Object drug".
- The agent which precipitates such an interaction is referred to as the "Precipitant".

Pharmacokinetic drug interactions:

Altered concentration, pharmacokinetic drug interactions occur when one drug changes the systemic concentration of another drug, altering 'how much' and for 'how long' it is present at the site of action.

Pharmacodynamic drug interactions:

Altered effect, pharmacodynamic drug interactions occur when interacting drugs have either additive effects, in which case the overall effect is increased, or opposing effects, in which case the overall effect is decreased.

Pharmacokinetic drug interactions:

Pharmacokinetic interactions occur when the absorption, distribution, metabolism or elimination process of the object drug is altered by the precipitant drug and hence such interactions are also called as ADME interactions.

- The resultant effect is altered plasma concentration of the object drug.

TYPES:

- Absorption interactions
- Distribution interactions
- Metabolism interactions
- Excretion interactions

Absorption interactions:

- Absorption interactions are those where the absorption of the object drug is altered.
- Since the oral route is the one, most frequently used to administer drugs, interactions influencing absorption are more likely to occur within the gastrointestinal tract.
- The net effect of such an interaction is:
- Faster or slower drug absorption.
- More or, less drug absorption.
- Most clinically significant interactions occur due to the following factors:

  a) Changes in gastrointestinal pH

  b) Changes induced by chelation

  c) Changes in gastrointestinal motility

Changes in Gastrointestinal P_H:

- Absorption in the gut is governed by the gut pH, lipid solubility and pka of the drug.
- While changes in gastric pH induced by H2 and proton pump blockers and antacids containing Al/Mg formulations have been shown to significantly reduce drug bioavailability.
- However the alteration in pH has certain clinical implications as it can result in a significant reduction in the absorption of Ketoconazole and Itroconazole which are insoluble in water and are only ionized at low pH, hence gastric acidity plays an important part in this interaction.

Changes Induced by Chelation :

- The various possible drug interactions that occur due to alterations in drug absorption the most clinically significant interactions occur due to chelation or formation of insoluble complexes.
- Clinically important interactions relate to use of Tetracyclines as well as ciprofloxacin that can form insoluble chelates with Ca, Al, and iron, resulting in its reduced antibacterial effects.
- This interaction can however be avoided if the interval between the medications is at least 2-3 hours.
- Chelation also seems to play an important part in reducing the bioavailability of Penicillamine caused by some antacids.

Changes in Gastrointestinal Motility:

- Drugs that alter the stomach-emptying rate can affect the rate of absorption of drugs as most of them are absorbed in the small intestine.
- Drugs with anticholinergic properties like Propantheline or those altering bowel motility like Diphenoxylate may affect the absorption of other drugs.
- Eg: Propantheline increases the absorption of slow dissolving Digoxin by 30% as the reduced gut motility allows a slow dissolving Digoxin formulation more time to pass into solution making a greater amount available for absorption but this effect is not seen with fast dissolving tablets.
- Metoclopramide on the other hand produces the opposite effects on motility and digoxin absorption.

DRUG DISTRIBUTION INTERACTIONS:

- Drug distribution interactions are those where the distribution pattern of the object drug is altered.
- The major mechanism for distribution interaction is alteration in protein-drug binding.
- Many drugs interact by displacement of each others binding to plasma proteins.
- Acidic drugs are known to have an affinity to bind to plasma proteins, hence when two or more are given concomitantly, competitive binding for the same site or receptor may displace one drug from the protein binding site increasing the amount of the displaced

free drug in plasma and various tissues setting up an interaction leading to an enhanced potential for toxicity.

- Eg: Concomitant administration of warfarin with Phenylbutazone or other highly protein bound drugs leads to increased levels of warfarin.
- The drugs most likely to lead to clinically significant interactions are those that are: 90% or more protein bound, those bound to tissues or having a small volume of distribution, having a low therapeutic index, low hepatic extraction ratios, or those that are administered I.V.
- Drugs that are more likely to displace other drugs from protein binding sites include NSAID's, Phenylbutazone, salicylic acid, and sulfonamides.

METABOLISM INTERACTIONS:

Stimulation of metabolism

- Certain drugs stimulate the activity of hepatic microsomal enzymes. This effect is referred as enzyme induction.
- The increased activity is due to enhanced enzyme synthesis results in increased amounts of drug metabolizing enzyme.
- Enzyme induction will result in increased metabolism and excretion and reduced effect of agent which is metabolised by the hepatic enzymes.

  Eg :Warfarin and phenobarbital
- Phenobarbital increases the rate of metabolism of warfarin resulting in decrease anticoagulant activity.

Inhibition of metabolism:

- If one drug inhibits metabolism of another drug it result in prolonged action or intensified activity.
- Alcohol- disulfiram inhibit the activity of alcohol dehydrogenase, thus inhibiting oxidation of acetaldehyde, an oxidation product of alcohol. This result in accumulation of acetaldehyde and development of the characteristic unpleasant effect of disulfiram.

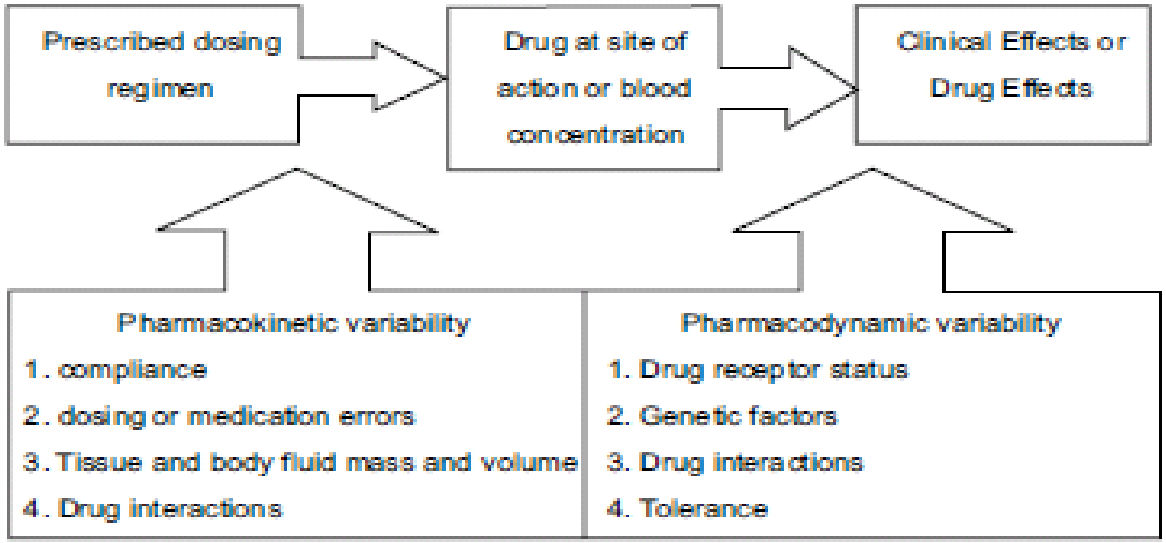
DRUG ELIMINATION REACTIONS:

- Drug elimination reactions are those where the excretion pattern of the object drug is altered.
- The major routes for elimination of drugs remain the kidney and bile, but there are no significant drug - drug interactions through bile elimination, but only drug-disease ones.
- Some drugs are excreted from the body unchanged in the active form, usually in the urine or via the biliary tract in the faeces.
- Drugs that are chiefly excreted by the kidneys can get involved in drug interactions by different mechanisms such as competition at active transport sites, or alterations in glomerular Filtration, passive renal tubular reabsorption or active secretion and urinary pH.
- Changes in renal drug clearance may occur due to effects on renal tubular function or urine pH.
- For example, probenecid reduces the renal clearance of anionic drugs such as methotrexate and penicillin.
- Major mechanisms of excretion interactions are:
    - ✓ Alteration in renal blood flow
    - ✓ Alteration of urine pH
    - ✓ Competition for active secretions
    - ✓ Forced diuresis
- Alteration in renal blood flow- eg: NSAIDs (reduce renal blood flow) with Lithium.
- Alteration of urine pH- eg: Antacids with Amphetamine
- Competition for active secretion- eg: Probenecid and Penicillin

UNIT 4
THERAPEUTIC DRUG MONITORING

Introduction:

- Clinicians routinely monitor drug pharmacodynamics by directly measuring physiological indices of therapeutic response (E.g.: lipid concentration, blood glucose, BP, clotting test)
- For many drugs there is no readily available measure of effect or it is insufficiently sensitive
- Large interindividual variation between dose and response can make individualizing drug dosage difficult
- In other cases it is difficult to distinguish between the progress of the disease and the pharmacological effect of the drug
- In these situations 'Therapeutic Drug Monitoring' becomes an essential part of clinical management



- Therapeutic drug monitoring, or TDM as it is commonly called, is about using drug serum concentrations, pharmacokinetics and pharmacodynamics to individualize and optimize patient response to drug therapy.
- Therapeutic drug monitoring aims to promote optimum drug treatment by maintaining serum drug concentration within a therapeutic range.

- Therapeutic drug monitoring is a practice applied to a small group of drugs in which there is a direct relationship between concentration and response
- Serum concentrations are used as the most practical intermediate endpoint to gauge treatment when there is no clearly observable therapeutic or toxic endpoint
- Therapeutic range represents a range of drug concentrations within which the probability of a desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low
- Some patients have toxic reactions within the therapeutic range
- The most common reasons for using a serum drug level as a guide are to provide additional information to be used in conjunction with other clinical data to assist in determining patient status to provide a basis for individualizing patient dosage regimen
- Therapeutic drug monitoring blends knowledge of therapeutics, pharmacology, pharmacokinetics, laboratory technology, and clinical medicine and applies it to certain drugs that require determination of patient specific dosage regimens to maximize therapeutic effectiveness while minimizing toxicity.

TDM can be used if:

- Drugs have a narrow therapeutic range
- A direct relationship exists between the drug or drug metabolite levels in plasma and the pharmacological or toxic effects
- The therapeutic effect can not be readily assessed by the clinical observation
- Large individual variability in steady state plasma concentration exits at any given dose
- Appropriate analytic techniques are available to determine the drug and metabolite levels

Process of TDM:

I. Reasons for Requesting TDM:

- Low therapeutic index
- Poorly defined clinical end point
- Non compliance
- Therapeutic failure – Sub therapeutic Concentration?

- Drugs with saturable metabolism
- Wide variation in the metabolism of drugs - major organ failure
- Prevention of adverse drug effects
- Toxicity suspected – Toxic Concentration?
- Change in clinical state of the patient
- Assess therapy following a change in dosage regimen
- Potential drug interaction due to change in co-medication

II. Collection of sample:

- Once the decision to monitor the concentration of the therapeutic drug has been made, it is important that the biological sample is collected which will provide a clinically meaningful measurement
- Blood sample should be collected once the drug concentration have attained steady state (at-least 5 half lives at the current dosage regimen)
- Levels approximating steady state may be reached earlier if a loading dose has been administered (drugs with long half lives)
- In general serum or plasma concentrations are comparable but the blood collecting tube used is important as few anticoagulants used are inappropriate to few drugs and analytical procedures
- Whole blood must be sampled for few drugs like, Cyclosporine A, that distributes between plasma and erythrocytes
- In infants, capillary blood may be collected for TDM
- Despite extensive research examined the utility of saliva measurements other biological fluids are not routinely sampled

III. Requesting TDM:

- Patient demographics are critically important so that the contribution of age, disease state, ethnicity, etc to interindividual variation in PK and PD can be considered
- These details must be effectively communicated to the members of TDM team with a drug assay request

- When a drug which is commonly measured for TDM is suspected of causing toxicity, it is very important for requesting clinicians to clearly communicate the expectation of a high concentration and need for a rapid feedback of results

REQUEST FORM:

Address for Results and Correspondence
Results can also be sent to a secure fax

Contact Details
If we have any queries about this request, please give details of a person we may contact.

Name .....
Position .....
Telephone .....
Fax .....
E-mail .....

Patient Information

ID (anonymise) .....
Date of Birth .....
Male ☐ Female ☐

Weight (kg) ..... Height (m) .....
Most recent viral load (& date) .....
Most recent CD4 count (& date) .....

IV. Measurement of TDM:

- Ideally a quality drug assay must be performed within a clinically useful time frame
- The assay procedure should be a validated one (accuracy, precision, sensitivity, specificity, limit of detection, limit of quantification, linear dynamic range, reproducibility, repeatability, robustness)
- Wherever possible assay procedure should be evaluated with an external quality assurance program
- Senior laboratory staff should verify the assay results in light of clinical request
- Ideally the results of the assay should be available to the clinician before the next dose is given

The analytical methodology employed should ideally:

- Distinguish between compounds of similar structure – unchanged drug and metabolites
- Detect small amounts

- Be simple enough to use as a routine assay and
- Be unaffected by other drugs administered simultaneously

Various analytical techniques available for TDM are

- Spectrophotometry and Fluorimetry
- Thin layer chromatography
- HPLC and GLC
- Radio Immunoassay
- Enzyme Immunoassay
- Fluorescence polarization Immunoassay
- Sometimes, the drug's metabolite(s) and or some endogenous compounds or drugs with similar structures can cross react, resulting in either a falsely elevated or decreased assayed drug concentration reading and that should be avoided.

V. Communication of the results by Laboratory:

- The assay results should be communicated as quickly as possible once it is verified by the senior laboratory personnel
- The drug concentrations measured are generally reported in mass or molar units
- But, since most of the assays are done by biochemical methods, results may be in molar units and the laboratory should be able to readily convert mass and molar units from one another
- The result should clearly state the therapeutic concentration range for the drug assayed
- It must be remembered that different indications for therapy, age or ethnic differences in PK or PD could result in different therapeutic ranges being appropriate for different population groups
- Hence, critical assessment of the original literatures and consensus recommendations for therapeutic ranges should be encouraged

VI. Clinical Interpretation:

- Clinical interpretation can 'add value' and convert 'therapeutic measurement service' into 'therapeutic drug monitoring service'
- Just relating a drug concentration to a published therapeutic range is not an adequate interpretation
- The information required to interpret the drug concentration include:
- Time at which blood sample taken
- Time at which dose is given
- Dosage regimen (Dose, Duration, Dosage Form)
- Patient demographic (sex, age, concomitant disease, ethnicity, etc)
- Co medications
- Indications for monitoring
- PK and therapeutic range of the drug
- For drugs with linear kinetics the following formula may be used

New Dose = Old Dose x Desired Concentration / Old Concentration

<u>Pharmacokinetic Evaluation of Serum Drug Concentrations :</u>

I. Serum Concentrations Lower than Anticipated

- Patient compliance
- Error in dosage regimen
- Wrong drug product (controlled-release instead of immediate-release)
- Poor bioavailability
- Rapid elimination (efficient metabolizer)
- Reduced plasma protein binding
- Enlarged apparent volume of distribution

- Steady state not reached
- Timing of blood sample
- Improving renal/hepatic function
- Drug interaction due to stimulation of elimination enzyme autoinduction
- Changing hepatic blood flow

II. Serum Concentrations Higher than Anticipated

- Patient compliance
- Error in dosage regimen
- Wrong drug product (immediate release instead of controlled release)
- Rapid bioavailability
- Smaller than anticipated apparent volume of distribution
    - Slow elimination (poor metabolizer)
    - Increased plasma protein binding
    - Deteriorating renal/hepatic function
    - Drug interaction due to inhibition of elimination

III. Serum Concentration Correct but Patient Does Not Respond to Therapy

- Altered receptor sensitivity (e.g., tolerance)
- Drug interaction at receptor site

VI. <u>Therapeutic Management</u>:

- The clinician caring for a patient will modify a drug dosage regimen in light of all available information
- If the members of the TDM team are well respected, many physicians will accept and implement their recommendations for dosage adjustment, and seek their further advice
- Hence, member of the TDM team with appropriate clinical expertise should be available to conduct a successful TDM

Limitations of TDM Process:

- Scientific accuracy of the drug assays
- Laboratory variability in reporting
- Limited accessibility and infrastructure facilities
- Validity of suggested target ranges
- Lack of training and skills
- Costly

INDIVIDUALIZATION OF DOSAGE REGIMEN

Dosage Regimen:

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

- For some drugs like analgesics single dose is efficient for optimal therapeutic effect however the duration of most illnesses are longer than the therapeutic effect produced by a single dose, In such cases drugs are required to be taken on a repetitive bases over a period of time depending upon the nature of illness.
- An optimal multiple dosage regimen is the one in which the drug is administered in suitable doses with sufficient frequency that ensures maintenance of plasma conc. Within the therapeutic window for entire duration of therapy.
- A proper balance should be obtained between dose frequency and size to attain steady state conc. And with minimum fluctuations to ensure therapeutic efficacy and safety.
- For drugs with wide therapeutic index such as penicillin's, Larger doses may be administered at longer intervals (more than half life of drug) without any toxicity effects.
- For drugs with narrow therapeutic index such as digoxin, small doses with frequent intervals (less than half life of drug) is better to obtain a profile with least fluctuations which is similar to that observed with controlled drug release systems.

Individualization:

- Rational drug therapy requires Individualization of Dosage regimen to fit a particular patient's needs. The application of Pharmacokinetic principles in the dosage regimen design for the safe and effective management of illness in individual patient is called as Clinical Pharmacokinetics.
- Same dose of drug may produce large differences in pharmacologic response in different individuals, this is called as Intersubject variability.
- In other words it means that the dose required to produce a certain response varies from individual to individual.

Advantages of Individualization :

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

Sources of variabiality:

- Pharmacokinetic Variability – Due to difference in drug concentration at the site of action (as reflected from plasma drug concentration) because of individual differences in Drug absorption, Distribution, Metabolism and Excretion.
- Pharmacodynamic Variability – Which is attributed to differences in effect produced by a given drug concentration.
- The Major cause of variability is Pharmacokinetic variability .
- Difference in the plasma conc. levels of given in the same individual when given on different occasions is called as "Intersubject Variability".
- The differences in variability differ for different drugs. Some drugs shows greater variability than others.
- Causes of Intersubject Pharmacokinetics Variability are

- Genetics
- Diseases
- Age
- Body Weight and
- Drug-Drug Interactions.

TDM OF DRUGS USED IN CARDIOVASCULAR DISEASES

CARDIOVASCULAR DISEASES:

- Cardiovascular drugs are primarily used for the treatment of angina, arrhythmias & congestive heart failure.
- Digoxin, used in Congestive heart failure, is widely prescribed and therapeutically monitored.
- Monitoring & use of anti-arrhythmics such as Disopyramide and Lidocaine have been steadily declining.
- Immunoassay are the used currently the most popular methods of measuring cardiac drugs.

DIGOXIN :

Digoxin is a cardiac glycoside indicated in the treatment of atrial fibrillation (AF) and heart failure (HF).

- Its mechanism of action is thought to be mediated through inotropic effects and neurohormonal effects.

INDICATIONS FOR TDM DURING DIGOXIN THERAPY INCLUDES :

- Confirmation of toxicity (in the presence of symptoms of digoxin toxicity)
- Assessing the effect of factors that alter
- Digoxin’s pharmacokinetics (e.g. renal impairment, drug interactions)

- Initiating therapy or dose changes (in patients with renal impairment)
- Therapeutic failure
- Medication adherence

SIGNS AND SYMPTOMS OF TOXICITY

- Common- Nausea, vomiting, anorexia, fatigue, confusion
- Rare or dose dependant – Visual disturbances (blurred vision, green-yellow colour disturbances) and Cardiac arrhythmias.

THERAPEUTIC RANGE:

- **Heart failure**

  – 0.6nmol/L – 1.2nmol/L,

  – Toxicity more likely >2.5nmol/L,

  – Small increase in mortality with con. >1.5nmol/L.

- **Atrial Fibrillation (AF)**

  – 0.6 – 2nmol/L,

  – Toxicity more likely >2.5nmol/L

  – Serum digoxin levels correlate poorly with ventricular rate.

  – In patients who are symptomatic, a low digoxin level may indicate the patient could benefit from a dose increase.

MONITORING REQUIREMENTS DIGOXIN THERAPY:

- Digoxin therapy for HF symptoms has been shown to be effective at lower concentrations (0.6 to 1.2 nmol/L).
- Therapy in lower concentrations was associated with a small but significant reduction in all-cause mortality, worsening heart failure, all-cause hospitalisation and hospitalisation due to heart failure compared with placebo.

- Higher concentrations (>1.5nmol/L) were associated with a small but significant increase in all-cause mortality, cardiovascular mortality and hospitalisation for digoxin-related toxicity.
- The indications for digoxin TDM are relatively few and include confirmation of clinically suspected toxicity, assessing the reasons for therapeutic failure, assessing medication adherence, and assessing the effects of factors that alter the pharmacokinetics of digoxin (predominantly renal dysfunction and drug interactions).
- Samples for digoxin TDM should be taken at least six to eight hours after the last dose, or ideally immediately before the next dose
- This allows for the redistribution of digoxin from plasma into the tissues.
- It is ideal that digoxin levels are taken when concentrations are at steady-state.
- The relatively long half-life of digoxin (30 hours in patients with normal renal function) means that following initiation or dose alterations, it takes at least 7 days for steady-state concentrations to be achieved.
- In the elderly with impaired renal function the half life can be extended to 3.5-5 days, meaning 14-20days may be required before steady state is achieved.

ACTIONS ON THERAPEUTIC LEVEL:

- Serum digoxin levels should be interpreted within the clinical context.
- If the level is above the therapeutic range, the dose should be reduced even if toxicity is not observed.
- This is based on the observation that the patient is at risk of arrhythmia, and no further clinical benefit is likely with higher concentrations.
- Toxicity is observed when digoxin levels are within the normal range, due to other factors which alter tissue sensitivity to digoxin.
- Digoxin TDM may be useful to detect the patients who have a low digoxin concentration and who may benefit from an increase in digoxin dose, as opposed to those with higher concentrations who are likely to develop toxicity symptoms only from an increase in dose.

MEDICATION INTERACTIONS:

- Digoxin is rapidly absorbed with a bioavailability of 70-80% from oral tablets.
- Digoxin is eliminated primarily by renal excretion, via Pglycoprotein (P-gp).
- Interactions with digoxin are mediated through the inhibition or induction of P-gp in the GI tract and renally.
- Inhibition of renally located P-gp results in increased serum digoxin levels.
- Induction of P-gp in the gut reduces digoxin absorption, resulting in lower levels.

MEDICATIONS WHICH INCREASE THE RISK OF TOXICITY :

- Reduce the dose of digoxin prior to initiating therapy:
  - Amiodarone (50% dose reduction when initiating amiodarone)
  - Verapamil (50% dose reduction when initiating verapamil)
- Monitor digoxin level (7 days-21 days depending on renal function after introducing the interacting medicine)
  - Clarithyromycin / erythromycin
  - Spironolactone
  - Cyclosporin
  - Itraconazole
  - Diltiazem
  - Quinine
  - Atorvastatin (high doses only 80mg daily)
  - Trimethoprim (courses >7 days)
- Monitor renal function and potassium level (every 3-6 months or after vomiting, diarrhoea or dehydration)
  - Diuretics (risk of hypokalaemia)
  - ACE-Inhibitors (reduction in renal function – monitor 7 days after starting then 3-6 monthly)

MEDICATIONS WHICH DECREASE DIGOXIN LEVELS

- Decreased absorption (Monitor Levels 7-21 days after introducing the interacting medicine)
  - Rifampicin
- Decreased absorption (separate administration by 2 hours)
  - Antacids (aluminium and magnesium, not calcium based)

UNIT 5
DOSAGE ADJUSTMENT IN RENAL AND HEPATIC DISEASE

Adjustment of Dosage in Renal Impairment:

- 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 of the patient and the fraction of unchanged drug excreted in urine.
- There are two additional method for dose adjustment in renal insuffiency if the Vd change is assumed to be negligible.

General Approach:

- No change in the desired or target plasma concentration.
- Diminished renal clearance but unchanged non-renal clearance.
- Unaltered drug protein binding & volume of distribution in the renally impaired patient.
- Unchanged drug absorption from the GIT.

Three Major Approaches are:

- Dose adjustment based on Total body clearance.
- Dose adjustment based on Elimination rate constant or half life.
- Dose adjustment in renal failure.

Dose adjustment based on Total body clearance:

The average drug conc. at steady-state $C_{ss,av}$ is a function of maintenance dose X_0 , the fraction of dose absorbed F, the dosing interval τ & clearance Cl_T of the drug.

$$C_{ss,av} = Fx_o / ClT\ \tau$$

Dose adjustment based on Elimination rate constant or Half life:

The average drug conc. at steady-state $C_{ss,av}$ is a function of maintenance dose X_0 , the fraction of dose absorbed F, the dosing interval & τ volume of distribution v_d & $t_{1/2}$ of the drug.

$$C_{ss,av} = \frac{1.44\ FX_o\ t_{1/2}\ V_d}{\tau}$$

- Diseases are the major source of variation in drug response.
- Both pharmacokinetic and Pharmacodynamic of many drugs are altered by disease other than the one which is being treated.

Disease state:

- Renal dysfunction - It greatly impair the elimination of drug especially those that are primarily excreted by the kidney. Causes of renal failure are hypertension, diabetes mellitus
- Uremia - It is characterized by impaired glomerular filtration and accumulation of fluid and protein metabolism. In both the cases the half life of the drug are increased as a consequences drug accumulation and toxicity increases.

Adjustment of Dosage in Hepatic Impairment:

- 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

- Impaired Hepatic blood flow leading to an increase in bioavailability caused by a reduction in first pass metabolism (e.g Bioavailabilities of Morphine and Labetalol have been reported to double in patients with Cirrhosis)
- Decreased protein binding and increased toxicity of drugs highly bound to plasma protein (e.g. Phenytoin, Warfarin) due to impaired albumin production, altered volume of distribution of drugs due to increased extracellular fluid (e.g. Rifampicin accumulates in obstruction jaundice).
- Oedema in liver disease may be increased by drugs that cause fluid retention (e.g. Acetylsalicylic acid, Ibuprofen, Prednisolone, Dexamethasone).
- Generally, drug doses should be reduced in patients with hepatic dysfunction since clearance is reduced & bioavailability is increased in such a situation.

Renal function determination :

- Glomerular filtration rate can be determined by following two methods :
  - Insulin clearance
  - Creatinine clearance

UNIT 6
POPULATION PHARMACOKINETICS

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 results of 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 intrasubject 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.
- Bayesian probability is used to improve forecasting in medicine.
- One example is its use in the diagnosis of healed myocardial infarction (HMI) from a 12-lead electrocardiogram (ECG) by artificial neural networks using the Bayesian concept.
- Bayesian results were comparable to those of an experienced electro cardiographer.
- In pharmacokinetics, Bayesian theory is applied to "feed-forward neural networks" for gentamicin concentration predictions .
- A brief literature search of Bayesian applications revealed over 40 therapeutic applications between 1992 to 1996.
- Bayesian parameter estimations were most frequently used for drugs with narrow therapeutic ranges, such as the aminoglycosides, cyclosporin, digoxin, anticonvulsants (especially phenytoin), lithium, and theophylline. The technique has now been extended to cytotoxic drugs, factor VIII, and warfarin. Bayesian methods have also been used to limit the number of samples required in more conventional pharmacokinetic studies with new drugs .

- The main disadvantage of Bayesian methods is the subjective selection of prior probability. Therefore, it is not considered to be unbiased by many statisticians for drug approval purposes.

ADAPTIVE METHOD OR DOSING WITH FEEDBACK

- 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, or Bayesian adaptive method with feedback when a special 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 (see). 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 stimulated 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, OBJOLS.

ANALYSIS OF POPULATION PHARMACOKINETIC DATA

- Traditional pharmacokinetic studies involve taking multiple blood samples periodically over time in a few individual patients, and characterizing basic pharmacokinetic parameters such as k, VD, and Cl; because the studies are generally well designed, there are fewer parameters than data points (ie, that provide sufficient degree of freedom to reflect lack of fit of the model), and the parameters are efficiently estimated from the model with most least-squares programs.
- Traditional pharmacokinetic parameter estimation is very accurate, provided that enough samples can be taken for the individual patient.
- The disadvantage is that only a few relatively homogeneous healthy subjects are included in pharmacokinetic studies, from which dosing in different patients must be projected.

In the clinical setting, patients are usually not very homogeneous; patients vary in sex, age, body weight; they may have concomitant disease and may be receiving multiple drug treatments**.**

- Even the diet, lifestyle, ethnicity, and geographic location can differ from a selected group of "normal" subjects.
- Further, it is often not possible to take multiple samples from the same subject, and, therefore, no data are available to reflect intrasubject difference, so that iterative procedures for finding the maximum likelihood estimate can be complex and unpredictable due to incomplete or missing data.
- However, the vital information needed about the pharmacokinetics of drugs in patients at different stages of their disease with various therapies can only be obtained from the same population, or from a collection of pooled blood samples.
- The advantages of population pharmacokinetic analysis using pooled data were reviewed by and included a summary of population pharmacokinetics for dozens of drugs.

- Pharmacokinetic analysis of pooled data of plasma drug concentration from a large group of subjects may reveal much information about the disposition of a drug in a population.
- Unlike data from an individual subject collected over time, inter- and intrasubject variations must be considered.
- Both pharmacokinetic and nonpharmacokinetic factors, such as age, weight, sex and creatinine concentration, should be examined in the model to determine the relevance to the estimation of pharmacokinetic parameters.
- The nonlinear 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 factors include inter- and intraindividual differences.
- NONMEM is a statistical program written in Fortran that allows Bayesian pharmacokinetic parameters to be estimated using an efficient algorithm called the first-order (FO) method. The parameters 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 parameter 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 factors such as age, weight, and creatinine concentration.
- The model describes the observed plasma drug concentration (Ci) in terms of a model with:
- P k = fixed effect parameters, which include pharmacokinetic parameters or patient factor parameters.

- For example, P 1 is Cl, P 2 is the multiplicative coefficient including creatinine factor, and P 3 is the multiplicative coefficient for weight.
- Random effect parameters, including
- (a) The variance of the structural (kinetic) parameter P k or intersubject variability within the population 2 k and
- (b) The residual intrasubject variance or variance due to measurement errors, fluctuations in individual parameter values, and all other errors not accounted for by the other parameters.
- There are generally two reliable and practical approaches to population pharmacokinetic data analysis.
- One approach is the standard two-stage (STS) method, which 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.
- A second approach, the first-order (FO) 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 utilizeda 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 effects, it is called a mixed-effect statistical model.

UNIT 7
PHARMACOGENETICS

INTRODUCTION :

- The genetic basis underlying variation in drug response among individuals has become evident with the introduction of modern analytical methods for the analysis of gene sequence and expression.
- Pharmacogenetics is the study of how genes affect the way people respond to drug therapy.
- The goal of pharmacogenetics is to individualize drug therapy to a persons unique genetic makeup.
- The environment, diet, age, lifestyle, and state of health can influence a persons response to medicine.
- An understanding of an individuals genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety.
- Pharmacogenetics is an established discipline that studies the genetic basis of interindividual variability in the response to drug therapy, and allows for individualization of drug therapy.
- In contrast, pharmacokinetics provides a means for estimating pharmacokinetic parameters of the drug in various population subgroups and then applying the information to drug therapy for the average patient.
- Pharmacogenetics (PGt), or pharmacogenomics (PGx), a more modern term preferred by some researchers, has been the subject of discussion by industry and regulatory agencies.
- These groups tried to generate a consensus on how and to what extent should PGx or PGt information be applied to improve drug therapy and safety of both old and new drugs.

GENETIC POLYMORPHISM IN DRUG METABOLISM

CYTOCHROME P450 ISOZYMES:

- **CYP2D6** – It is a large isozyme family that affects metabolism of many drugs and is highly polymorphic.
- More than 70 variant alleles of the CYP2D6 locus have been reported.
- The metabolism of the tricyclic antidepressants amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, and the tetracyclic compounds maprotiline and mianserin is influenced by the CYP2D6 polymorphism to various degrees. Genetic polymorphism of CYP2D6 was first investigated with debrisoquine .
- Poor metabolizers often carry two nonfunctional alleles of this gene, resulting in reduced drug clearance.
- Since about 10% of the population are poor CYP2D6 metabolizers, CYP2D6 drug candidates are often dropped fro further development by researchers in favor of others .
- Poor metabolizers have increased plasma concentrations of tricyclic antidepressants when given recommended doses of the drug.
- Adverse effects may occur more frequently in poor metabolizers and may be misinterpreted as symptoms of depression and may further lead to erroneous increases in the dose.
- When determining CYP2D6 metabolic status (slow versus fast metabolizers) in patients on tricyclic antidepressants, co- administration of other CYP2D6 substrates such as serotonin- selective reuptake inhibitors may result in erroneously concluding poor CYP2D6 metabolic status.
- In contrast, ultrarapid metabolizers have relatively fast drug metabolism due to the presence of more enzyme or increased enzyme activity. Patients in this group are prone to therapeutic failure due to the resulting subtherapeutic drug concentrations when & quot ,normal & quot doses are given.

Pharmacogenomic studies have revealed that some fast metabolizers of CYP2D6 are the result of gene duplication among different racial groups.

- Depending on the population studied, 5-20% of patients can be classified as either rapid or poor metabolizers.

CYP1A2

- Another isozyme, CYP1A2, which metabolizes 5% of randomly selected drugs, may also be considered during development, since up to 15% of a patient population can be classified as poor metabolizers, according to .
- Fluvoxamine is a substrate and potent inhibitor of CYP1A2, causing important interactions with drugs such as amitriptyline, clomipramine, imipramine, clozapine and theophylline that are partly metabolized by this cytochrome P-450 enzyme.
- 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.

GENETIC POLYMORPHISM IN DRUG TRANSPORT: P-GLYCOPROTEIN AND MULTIDRUG RESISTANCE

- Transporter pharmacogenetics is a rapidly developing field that is concerned with drug uptake and efflux into or through tissues.
- Significant problems in the clinical application of drugs result from poor or variable oral drug bioavailability, and high intra- and interindividual variation in pharmacokinetics.
- Several membrane transporter proteins are involved in the absorption of drugs from the intestinal tract into the body, into nonintestinal tissues, or into specific target sites of action .
- Drug efflux is an important cause of drug resistance in certain types of cells.
- In cytotoxic chemotherapy for several human cancerous diseases, drugs are generally very effective, but in the case of intrinsic or acquired multidrug resistance, usually highly effective antineoplastic compounds, eg, vincristine, vinblastine, daunorubicin, or doxorubicin, fail to produce cures.
- One of the major causes of such multidrug resistance is the appearance of special integral membrane proteins, the P-glycoprotein multidrug transporter, or MDR1, which is one of the major causes of low drug level in targeted cells. P-glycoprotein is discussed in .
- The multidrug resistance-associated proteins (MRPs) are members of the ATP- binding cassette (ABC) superfamily with six members currently, of which
- MRP1, MRP2, and MRP3 are commonly known to affect drug disposition.
- MRP1 is ubiquitous in the body.
- Substrates for MRP1 include glutathione, glucuronide, and sulfate. MRP1 is expressed basolaterally in the intestine, although its role in extruding drugs out of the enterocytes is still uncertain.

- There is some substrate overlap between MRP1 and apically located P-glycoprotein.
- The aminoacid homology between MDR1 and P-glycoprotein was reported to be 15% in some cell lines.

GENETIC POLYMORPHISM IN DRUG TARGETS

- In the future, proteins involved in disease will become identified as important biomarkers for pharmacodynamic studies. Genomics has led to the development of proteonomics, which involves the study of biologically interesting proteins and their variants.
- Proteins can be used as probes for drug discovery or as biomarkers for drug safety, such as cell surface proteins (eg, COX-2, D-2R), intracellular proteins (eg, troponin I), and secreted proteins (eg, MCP-l).
- The physiologic response of the body to a drug is generally the result of interaction of the drug at a specific target site in the body.
- It is estimated that about 50% of drugs act on membrane receptors, about 30% act on enyzmes, and about 5% act on ion channels .
- Many of the genes encoding these target proteins exhibit polymorphisms that may alter drug response.
- Clinically relevant examples of polymorphism leading to variable responses are listed in .
- For example, the -2-adrenergic receptor, and its common mutation of ArgGly at amino acid 16, greatly reduces the bronchodilator response of albuterol.
- The systematic identification and functional analysis of human genes is changing the study of disease processes and drug development.

- Pharmacogenetics enable clinicians to make reliable assessments of an individuals risk of acquiring a particular disease, be more specific in targeting drugs, and account for individual variation of therapeutic response and toxicity of drugs.

PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) CONSIDERATIONS AND PHARMACOGENETICS/PHARMACOGENOMICS (PGT/PGX)

- The study of drug interactions and PGt/PGx has revealed thatmany unexpected pharmacodynamic responses and pharmacokinetic variations among individuals during drug therapy involve genetic factors.
- These genetic factors contribute to variation at many levels, including drug transport, metabolism, and interaction at the receptor site.
- Applying genetics to study interindividual variations in drug response may greatly improve drug therapy.
- Understanding and monitoring the underlying pharmacogenetic factors will allow physicians to optimize efficacy and minimize side effects.
- The labelling of many new drugs now contains more information on drug interactions and metabolism based on our understanding of PGt / PGx.
- PGt/PGx is influencing the study of pharmacokinetics and pharmacodynamics.
- Population pharmacokinetics has already assimilated some of these changes by enriching what are often simple or even empirical PK/PD models to simulate the quantitative aspect of drug distribution and drug action
- Models that will predict dosing and an individuals drug clearance more

- accurately will require more details concerning the individual patients genetic profile, demographic and pathologic information, as well as the
- Drugs PK profile. If one of the patients parents is homozygous for a specific isoenzyme that metabolizes the drug, how would that information be linked to aclearance prediction for the patient?
- Recognizing the allele that predisposes the patient to a severe adverse reaction or toxic plasma concentration may allow the dose to be reduced or the drug avoided entirely.
- Similarly, if a patient is known to be a non responder due to genetic variation, that information can be used to select an alternate drug a priori.
- In, a mixed-effects model is described that takes into account the effect of enzyme induction due to concomitant administration of a drug that induces enzyme.
- Should new models be developed, or will an extension of some of the mixed-effect models suffice?
- Advances in PGt will no doubt stimulate developments in PK and PD.
- The successful application of genetic screening tests to identify patients with specific risks in drug response or drug toxicity depends on many factors.
- Large amounts of relevant genetic information must be monitored.
- Robust, high-throughput, high-positive and low-negative predictive tests must be developed and implemented.
- Such an endeavour will also involve considerable training, adaptation, and acceptance of the new technology by physicians and other health care personnel.

With genetic diagnostic tests becoming more common and affordable, it is expected that individual drug dosing will become more accurate and ultimately result in vast improvements in therapeutic response and better drug tolerance.