

CLINICAL PHARMACOKINETICS & PHARMACOTHERAPEUTIC DRUG MONITORING

5TH YEAR

PHARM D

5 MARKS

A

Age & body weight in individual action > 63
Adaptive method > 131
Analysis of population pharmacokinetics data > 133

B

biliary excretion > 99
Bayesian theory > 129

C

Conversion from IV to PO > 41
Cytochrome P-450 enzyme in drug interaction > 93
Creatinine clearance > 115
CYP2D6 & CYP2C9 > 127

D

Dosing in elderly > 45
Dosing in children > 49
Dosing in obese patient > 51
Determination of dose & dosing interval > 53
Design of dosage regimens > 57
Disease condition & drug interaction in individualization > 67
Drug absorption > 87
Dose adjustment
 Elimination half-life > 105
 Total body clearance > 106
Drug target > 125
Dosing with feedback > 131

E

Elimination half-life & duration of activity > 78
E max model > 79
Enzyme inhibition & enzyme induction > 95
Elimination half-life in dose adjustment > 105
estimates of fixed effects and variability > 143

F

Fixed effect & variability > 143

G

Genetic and disease condition in individualization > 65
Giusti-hayton method > 119
GFR
 various formulae > 101
 ideal characteristics > 107
 advantages & disadvantages > 111

H

Hemodialysis > 123

I

inhibition of biliary excretion > 99

N

Nomograms > 33
Nomogram & tabulation > 39
Nonlinear mixed effect modeling approach (NONMEM) > 137

P

Pharmacokinetics of drug interactions > 83
pharmacokinetic considerations in the renal failure > 103
pharmacokinetic considerations in the hepatic disease > 114
peritoneal dialysis > 117
Population Pharmacokinetics
 Sampling design > 138
 Application > 145
 Limitation > 146
population pharmacokinetic VS
 traditional pharmacokinetic > 147

S

Sigmoidal E max model > 81

T

TDM
 Protocol > 69
 Definition & indication > 71
 Role of pharmacist > 73
Two-stage approach > 148
total body clearance in dose adjustment > 106
traditional pharmacokinetic VS
 population pharmacokinetic > 147

W

Wagner method > 121

Q. what are nomogram, Application, advantage and disadvantage

Nomograms:

- Nomograms are charts available for use in estimating dosage regimens in uremic patients
- The nomograms may be based on serum creatinine concentrations, patient data (height, weight, age, gender), and the pharmacokinetics of the drug.
- A nomogram is a graphical calculating device, a two-dimensional diagram designed to allow the approximate graphical computation of a function.
- The word Nomogram is derived from Greek, (nomos=law & gramme=line).
- A nomogram typically has 3 scale:
 - ❖ 2 scales represent known values and 1 scale is the where the result read off.
 - ❖ These scale may be linear, logarithmic or have some more complex relationship.
 - ❖ The nomogram method provides an estimate of the ratio of the uremic elimination rate constant (k_u) to the normal elimination rate constant (k_n) on the basis of creatinine clearance

★
$$k_u = k_{nr} + \alpha cl_{cr}$$

APPLICATIONS:

1. For case of calculation of dosage regimens, many clinicians rely on nomogram to calculate the proper dosage regimen for their patients.
2. The use of a nomogram may give a quick dosage regimen adjustment for patients with characteristics requiring adjustments, such as age, body weight, and physiologic state.
3. In general, the nomogram of a drug is based on population pharmacokinetic data collected and analyzed using a specific pharmacokinetic model.
4. In order to keep the dosage regimen calculation simple, complicated equations are often solved and the results displayed diagrammatically on special scaled axes to produce a simple dose recommendation based on patient information.)
5. Some nomogram make use of certain physiologic parameters, such as serum creatinine concentration, to help modify the dosage regimen according to renal function.
6. Nomograms are charts available for use in estimating dosage regimens in uremic patients
7. The nomograms may be based on serum creatinine concentrations, ⁽¹⁾ patient data ⁽²⁾ (height, weight, age, gender), and the pharmacokinetics of the drug. ⁽³⁾

Advantages:

- The advantage of the Nomograms is that it can be easily mass-produced (distributed and evaluated), while providing the same information as the logistic regression it represent. بسته بندی
- Nomograms are typically used in applications where the level of accuracy they offer is sufficient and useful.

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

Q. explain role of nomograms and tabulations in the design of dosage regimen

DESIGN OF DOSAGE REGIMENS

NOMOGRAMS AND TABULATIONS IN DESIGNING DOSAGE REGIMENS

- For ease of calculation of dosage regimens, many clinicians rely on nomograms to calculate the proper dosage regimen for their patients. The use of a nomogram may give a quick dosage regimen adjustment for patients with characteristics requiring adjustments, such as age, body weight, and physiologic 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 results displayed diagrammatically on special scaled axes to produce a simple dose recommendation based on patient information. Some nomograms make use of certain physiologic parameters, such as serum creatinine concentration, to help modify the dosage regimen according to renal function
- For many marketed drugs, the manufacturer provides tabulated general guidelines for use in establishing a dosage regimen for patients, including loading and maintenance doses.
- For drugs with a narrow therapeutic range, such as theophylline, a guide for monitoring serum drug concentrations is given.
- Another example is the aminoglycoside antibiotic, tobramycin sulfate USP (Nebcin, Eli Lilly), which is eliminated primarily by renal clearance. Thus, the dosage of tobramycin sulfate should be reduced in direct proportion to a reduction in creatinine clearance (~~clearance~~). The manufacturer provides a nomogram for estimating the

Q₁. Explain process of conversion from IV to oral dosing.

Q₂. different method of conversion of intravenous to oral dosing?

CI Pharmacokinetics

Design of Dosage Forms

percent of the normal dose of tobramycin sulfate assuming the serum creatinine level (mg/100 mL) has been obtained.)

CONVERSION FROM INTRAVENOUS INFUSION TO ORAL DOSING

(After the patient's dosing is controlled by intravenous infusion, it is often desirable to continue to medicate the patient with the same drug using the oral route of administration. When intravenous infusion is stopped, the serum drug concentration decreases according to first-order elimination kinetics. For most oral drug products, the time to reach steady state depends on the first-order elimination rate constant for the drug. Therefore, if the patient starts the dosage regimen with the oral drug product at the same time as the intravenous infusion is stopped, then the exponential decline of serum levels from the intravenous infusion should be matched by the exponential increase in serum drug levels from the oral drug product.)

The conversion from intravenous infusion to a controlled-release oral medication given once or twice daily has become more common with the availability of more controlled-release drug products, such as theophylline () and quinidine. Computer simulation for the conversion of intravenous theophylline (aminophylline) therapy to oral controlled-release theophylline demonstrated that oral therapy should be started at the same time as intravenous infusion is stopped (). With this method, minimal fluctuations are observed between the peak and trough serum theophylline levels. Moreover, giving the first oral dose when IV infusion is stopped may make it easier for the nursing staff or patient to comply with the dosage regimen.

Methods :

i) Iv infusions usually follow zero order

Kinetics → based on that the oral preparations are done to release the drug at a constant zero order rate.

This is called as oral osmotic pumps popularly called as oros. A core

comprising a drug such as potassium chloride or sodium chloride is

surrounded by a rigid semi-permeable coating or membrane such as cellulose

ester or cellulose ~~or~~ ether, having

an orifice of 0.4 mm diameter

produced by laser beam for drug exist. when exposed to GIT fluids

water flows through the membrane into

the ~~table~~ tablet due to osmotic

pressure difference the drugs come

out through an orifice maintaining

the zero order kinetics. The oros (41)

principle can be used to design multunit dosage forms

ii) Hydrodynamic pressure controlled system

→ The hydrodynamic pressure is generated by swelling of a hydrophilic gum. It can also be used as an active delivery of drugs. The capsule is made up of a rigid shaped having in which the electrolyte substance is present. The outer semi-permeable membrane is made up of a hydrophilic gum such as polyhydroxyalkylmethacrylate.

→ in GI the gum imbibes and it opens the orifice and squeezes out the drug at zero-order rate, It's also called as push pull osmotic pump.

iii) Step down therapy:

→ Conversion of IV to oral agent in another class or to different / same class where frequency, dose, spectrum may not be same

→ eg: Ampicillin / Salbactam

→ eg: converting from Ampicillin Salbactam
3g IV every 6hr to Ampicillin ~~salbactam~~
clavulanate 875 mg po every 12hr

iv) Conversion method:

→ If assumed that C_{ss} after IV infusion is identical to desired C_{avg}^{∞} (after multiple oral doses of drug)

$$C_{av}^{\infty} = \frac{SF D_o}{kV_D}$$

$$\frac{D_o}{t} = \frac{C_{av}^{\infty} kV_D}{SF}$$

where: S = salt form of drug

$\frac{D_o}{t}$ = dosing rate

f = bioavailability

V.) Sequential therapy :

→ refers to replacing parenteral version of therapy to its oral type

→ eg: Conversion of Famotidine 20mg (IV) to Famotidine 20mg (PO)

VI.) Switch therapy :

→ conversion from IV to oral equivalent that may be in same class & and have same level of potency but it's different compounds

eg: Conversion of IV to oral agent in frequency

dose & spectrum may not be same

eg - Ampicillin ~~salbactam~~ salbactam

eg: Conversion from Ampicillin Salbactam 3g IV

every 6 hr to Amoxicillin clavulanate 875

mg PO every 12 hr

eg: Conversion of IV Pantoprazole to rapidly dissolving lansoprazole Tab or omeprazole Capsule

DOSING OF DRUGS IN THE ELDERLY

Defining "elderly" is difficult. 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 physiologic changes during aging rather than purely chronological age. Chronologically, the elderly have been classified as the *young old* (ages 65-75 years), the *old* (ages 75-85 years), and the *old old* (age > 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 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 in some geriatric patients, complicated drug dosage schedules, and/or the high cost of drug therapy may result in poor drug compliance, resulting in lack of drug efficacy, possible drug interactions, and/or drug intoxication.

→ 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. ~~For some drugs, 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/or 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, whereas qualitatively, a change in the affinity for the drug may occur. ~~Alternatively, the pharmacokinetic hypothesis assumes that age-dependent increases in adverse drug reactions are due to physiologic~~

changes in drug absorption, distribution, and elimination, including renal excretion and hepatic clearance.

→ In the elderly, age-dependent alterations in drug absorption may include a decline in the splanchnic blood flow, altered gastrointestinal motility, increase in gastric pH, and alteration in the gastrointestinal absorptive surface. The incidence of achlorhydria in the elderly may have an effect on the dissolution of certain drugs such as weak bases and certain dosage forms that require an acid environment for disintegration and release. ~~From a distribution consideration, drug-protein binding in the plasma may decrease as a result of decrease in the albumin concentration, and the apparent volume of distribution may change due to a decrease in muscle mass and an increase in body fat. Renal drug excretion generally declines with age as a result of decrease in the glomerular filtration rate and/or active tubular secretion. Moreover, the activity of the enzymes responsible for drug biotransformation may decrease with age, leading to a decline in hepatic drug clearance.~~

→ Elderly patients may have several different pathophysiologic conditions that require multiple drug therapy that increases the likelihood for a drug interaction. Moreover, increased adverse drug reactions and toxicity may result from poor patient compliance. Both penicillin and kanamycin show prolonged $t_{1/2}$ in the aged patient, as a consequence of an age-related gradual reduction in the kidney size and function.

$$\text{Patient dose} = \frac{(\text{weight in kg})^{0.7} (140 - \text{Age in year})}{1660} \times \text{adult dose}$$

Q. DOSING OF DRUGS IN INFANTS AND CHILDREN

→ Infants and children have different dosing requirements than adults. Dosing of drugs in this population requires a thorough consideration of the differences in the pharmacokinetics and pharmacology of a specific drug in the preterm newborn infant, newborn infant (birth to 28 days), infant (28 days to 23 months), young child (2 to 5 years), older child (6 to 11 years), adolescent (12 to 18 years), and the adult (*FDA Guidance for Industry*, 2000). Unfortunately, the pharmacokinetics and pharmacodynamics 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 pharmacokinetics with respect to age. For convenience, "infants" are here arbitrarily defined as children 0 to 2 years of age. ~~However, within this group, special consideration 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 for 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 a calibrated dropper or a premeasured teaspoon (5 mL) for accurate dosing and have a cherry flavor for pediatric patient compliance. Pediatric drug formulations may also contain different

~~drug concentrations compared to the adult drug formulation.~~

→ Furthermore, (alternative drug delivery such as an intramuscular antibiotic drug injection into the gluteus medius may be considered for a pediatric patient, as opposed to the deltoid muscle for an adult patient.)

→ In general, complete hepatic function is not attained until the third week of life. Oxidative processes 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 show only 30-50% of the renal activity of adults on the basis of activity per unit of body weight. Drugs that are heavily dependent on renal excretion will have a sharply decreased elimination half-life.

Formula for calculation of child dose:

① Mosteller's equation:

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

② Young's Rule:

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

③ Dilling Rule:

$$\text{child dose} = \frac{\text{Age in year}}{20} \times \text{adult dose}$$

④ Clark's formula: child dose = $\frac{\text{weight in kg}}{70} \times \text{adult}$

DOSING OF DRUGS IN THE OBESE PATIENT

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 increases in the incidence of hypertension, atherosclerosis, coronary artery disease, diabetes, and other conditions compared to nonobese patients.)

A patient is considered obese if actual body weight exceeds ideal or desirable body weight by 20%, according to Metropolitan Life Insurance Company data (latest published tables). Ideal or desirable body weights are based on average body weights and heights for males and for females considering age. Athletes who have a greater body weight due to greater muscle mass are not considered obese. Obesity often is 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 is calculated according to the following two equations:

$$\text{BMI} = \left[\frac{\text{weight} \cdot (\text{lb})}{\text{height} \cdot (\text{in})^2} \right] \times 703$$

$$\text{BMI} = \left[\frac{\text{weight (kg)}}{\text{height (cm)}^2} \right] \times 10,000$$

The obese patient (BMI > 30) has a 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 to total body weight compared to the patient of ideal body weight, which could affect the apparent volume of distribution of the drug.) For example, showed a significant difference in the apparent volume of distribution of antipyrine in obese patients (0.46 L/kg) compared to ideal body weight patients (0.62 L/kg) based on actual total body weight. Ideal body weight (IBW) refers to the appropriate or normal weight for a male or female based on age, height, weight, and frame size; ideal body weights are generally obtained from the latest table of desirable weights for men and women compiled by the Metropolitan Life Insurance Company.)

In addition to differences in total body water per kilogram body weight in the obese patient, the greatest proportion of body fat in these patients could lead to distributional changes in the drug's pharmacokinetics.

Q. Explain the determination of dose and dosing interval

Determination of dose and dosing interval

- The magnitude of both therapeutic and toxic responses depends upon dose size
- Dose size calculation also requires the knowledge of amount of drug absorbed after administration of each dose
- greater the dose size, greater the fluctuations between $C_{ss \max}$ and $C_{ss \min}$ during each dosing interval and greater the chances of toxicity
- for drug administration chronically, dose size calculation is based on average steady state blood levels and is computed from equation:

$$X_{ss,av} = \frac{1.44 f X_0 t_{1/2}}{\tau}$$

where:

f = fraction of dose absorbed

τ = dosing interval

X_0 = maintenance dose

→ Dose interval or dosing frequency is calculated on the basis of half life of the drug, If the interval is increased and the dose is unchanged C_{max} , C_{min} and C_{av} decreased but the ratio C_{max} / C_{min} increase

→ opposite is observed when dosing interval is reduced or dosing frequency increased

→ It also results in greater drug accumulation in the body and toxicity

→ A proper balance between both dose size and dosing frequency is often desired to attain C_{ss} with minimum fluctuations and to ensure therapeutic efficacy and safety the same can not be obtained by giving longer doses less frequency, However administering smaller doses more frequently results in smaller fluctuations

→ generally every subsequent dose should be administered at an interval equal to $t_{1/2}$ of drug, A rule of thumb is that

- for drugs with wide therapeutic index such as penicillin, larger doses may be administered at relatively longer intervals without any toxicity problem
- for drugs with narrow therapeutic index such as digoxin, small doses at frequent intervals is better to obtain a profile with least fluctuation which is similar to that observed with constant rate infusion

→ Both dose and dosage interval should be considered in the dosage regimen calculations, ideally the calculated dosage regimen should maintain the serum drug concentration between $C_{\max}^{\infty}$ and $C_{\min}^{\infty}$.

→ for intravenous multiple-dosage regimen the ratio of $C_{\max}^{\infty} / C_{\min}^{\infty}$ expressed by:

$$\frac{C_{\max}^{\infty}}{C_{\min}^{\infty}} = \frac{C_p^0 / (1 - e^{-k\tau})}{C_p^0 e^{-k\tau} / (1 - e^{-k\tau})}$$

→ which can be simplified to :

$$\frac{C_{\max}^{\infty}}{C_{\min}^{\infty}} = \frac{1}{e^{-k\tau}}$$

Q. Factors to be considered during the design of dosage regimen

DESIGN OF DOSAGE REGIMENS

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

For some drugs like analgesics, hypnotics, antiemetics, etc., a single dose may provide effective treatment. However, the duration of most illnesses is longer than the therapeutic effect produced by a single dose. In such cases, ~~drugs are required to be taken on a repetitive basis over a period of time depending upon the nature of illness.~~ Thus, for successful therapy, ~~design of an optimal multiple dosage regimen is necessary.~~ An *optimal multiple dosage regimen* is the one in which the drug is administered in suitable doses (by a suitable route), with sufficient frequency that ensures maintenance of plasma concentration within the therapeutic window (~~without excessive fluctuations and drug accumulation~~) for the entire duration of therapy. For some drugs like antibiotics, a minimum effective concentration should be maintained at all times and for drugs with narrow therapeutic indices like phenytoin, attempt should be made not to exceed toxic concentration.

Approaches to Design of Dosage Regimen 2

~~The various approaches employed in designing a dosage regimen are~~

1. *Empirical Dosage Regimen* : is designed by the physician based on empirical clinical data, personal experience and clinical observations. This approach is, however, not very accurate.

2. **Individualized Dosage Regimen** : is the most accurate approach and is based on the pharmacokinetics of drug in the individual patient. The approach is suitable for hospitalised patients but is quite expensive.

3. **Dosage Regimen on Population Averages** : This is the most often used approach. The method is based on one of the two models –

(a) **Fixed model** : Here, population average pharmacokinetic parameters are used directly to calculate the dosage regimen.

(b) **Adaptive model** : It is based on both population average pharmacokinetic parameters of the drug as well as patient variables such as weight, age, sex, body surface area and known patient pathophysiology such as renal disease.

→ In designing a dosage regimen based on population averages —

1. It is assumed that all pharmacokinetic parameters of the drug remain constant during the course of therapy once a dosage regimen is established. The same becomes invalid if any change is observed.
2. The calculations are based on open one-compartment model which can also be applied to two compartment model if β is used instead of K_E , and $V_{d,ss}$ instead of V_d while calculating the regimen.

→ Irrespective of the route of administration and complexity of pharmacokinetic equations, the two major parameters that can be adjusted in developing a dosage regimen are —

1. The dose size — *the quantity of drug administered each time.*
2. The dosing frequency — *the time interval between doses.*

→ Both parameters govern the amount of drug in the body at any given time.

Q. explain effect of age and body weight 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

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 function are 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 (70 kg)
- 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 if the patient is grossly obese
- Thus, though many drug doses are based on the body weight of the patient (expressed as mg/kg), the influence of obesity or malnourishments is not always considered

Q. explain role of genetic and disease conditions in the individualization of drug regimen

Genetics:

- Genetic polymorphism that lead to the production of isoenzyme with reduced or no activity or 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 – glycoproteins 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 CYP2D6)

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, cardio vascular 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 (e.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 of the patient and the fraction of unchanged drug excreted in urine.
- There are two additional method for dose adjustment in renal insufficiency if the V_d change is assumed to be negligible.
- The adjustment of drug dosage in case of renal disease are carried out by mainly three approaches :
 - Dose adjustment based on Total body clearance.
 - Dose adjustment based on Elimination rate constant or Half life.
 - Dose adjustment in renal failure

Q. explain role of Coexisting disease and interacting drug in the individualization of drug regimen

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
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 - Dose adjustment in renal failure

Drug Interactions:

- Many of the clinically significant interactions between drugs are pharmacokinetic in origin, often due to induction and inhibition of metabolizing enzymes or transporter proteins
- ~~However, interactions can also occur between drugs and food supplements or herbal remedies~~

- Interactions involving competitive inhibition often occur within two to three days whereas induction may take anything from hours to weeks
- If the interacting drug has a long elimination half life, the interaction may persist for some time 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~~
- Absorption can also be altered by drug interactions within the gut that result from binding to other drugs, such as cholestyramine or antacids, or to enteral feeds, as in the case of Phenytoin

Distribution:

- Drug distribution can be altered by interactions that cause displacement from plasma protein binding
- But, these do not 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 timescale of the offset and onset of the effect depends not only on the PK 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
- Changes in biliary secretion and entero-hepatic circulation can also play a role
- For example, Penicillins can impair the recirculation of oral contraceptives by altering the bacterial flora of the gut

8. protocol 4 TDM

→ TDM is a multidisciplinary function and requires collaboration and good communication between scientists, clinicians, nurses and pharmacologists.

Step1: Request drug level

- ❖ The target concentration is depended on the clinical outcome to be achieved eg- phenytoin used as prophylaxis
- ❖ Drug selected based indication and need
- ❖ Procedures have been implemented where proper justifications is now required to carry out a TDM study.

Step2: collection of biological sample

- Blood sample- collect when drug concentrations reaches steady state (~~its half lives at current dosing regimen~~)
- Monitor to prevent toxicity
 - ~~Drug with long half lives~~
 - ~~Patient with renal failure/liver failure~~
- If toxicity suspected – drug levels to be monitored- ~~do not wait for 5 half lives, steady state etc..~~
- If poor therapeutic control-
- ~~Time of collection of blood sample is vital relative to the time of administration of drug since blood/plasma conc. change with time.~~
- ~~Absorption after oral administration- variable hence sample to be collected in elimination phases rather than absorption/distribution phase~~
- ~~Drug levels usually collected at end of dosage interval through level~~
- ❖ IV Antibiotics – peak conc., also measured (30 minutes after stopping infusion)
- ❖ Antibiotics therapeutic ranges- based on peak and through levels
- ❖ ~~If short $T_{1/2}$ of the drugs measure more frequently~~
- ❖ Usually drug levels are monitored from venous blood- samples easier to collect
- ❖ ~~Sometimes whole blood may be required cyclosporin A- distributes between RBC and plasma~~
- ❖ Infants- capillary blood samples
- ❖ Saliva and other fluids not usually used erratic drug levels

Step3: requesting the drug information

- ❖ Patient demographic information is important to:
- ❖ Include the effect of race, genetics, environment etc
- ❖ If a drug is suspected to cause toxicity-rapid reporting of results is required and should be conveyed to the staff concerned

Step4: measurement of drug concentration

- ❖ Drug concentrations usually analysed in accredited laboratories
- ❖ Laboratories should ensure the following
 - Procedure are in place to procure missing drug info

Accuracy, precision, sensitivity and specificity of each assay is documented regularly
 Assay procedure is evaluated by external audit- wherever possible
~~Each assay is performed with appropriate number of standard and controls.~~
~~Assay results should be verified by senior staff~~
~~Results should be available in a short interval of time ideally before the next dose is administered~~

- ❖ Major concern for TDM monitoring was cost effectiveness of measurement methods
- ❖ ~~Cost effective strategies, commercial kits, automated analysers~~
- ❖ However kits are not available for all drugs and certain conditions (pregnancy) require specialized techniques and highly trained staff
- ❖ Multiple databases also are being used to coordinate results of tests
- ❖ Technique to measure drug levels
 - HPLC(~~High performance liquid chromatography~~)
 - ~~GC/MS~~
 - ~~LC/MS~~
 - RIA(~~Radio immunological assay not used today~~)
 - ~~PETINA(particle enhanced turbidimetric inhibition immune assay)~~
 - EIA(~~Enzyme Immunoassay~~)
 - ~~Chemiluminisence~~

Step5: Communication of results by labs

- ❖ Labs should communicate results immediately after verification
- ❖ All required details and also the analysis method should be mentioned along with clinical implications of the method
- ❖ Usually concentrations are reported in molar units- conversion to dosage units(~~mg, grams etc..~~) should also be done.
- ❖ ~~The original therapeutic ranges should be mentioned on the report~~
- ❖ ~~Facilities should be made to encourage expedited reporting if required~~

Step6: Interpretation of results

- ❖ Vital step in the TDM
- ❖ Converts a drug measurement service to a drug monitoring service
- ❖ Just relating drug level to therapeutic service is not enough – ~~have to relate to current disease state of the patient (PFTs, presence/absence of acidosis)~~
- ❖ Concentration of the drug must be measured relative to:
 - Patient demographic (~~race, gender etc..~~)
 - Current dosage regimen
 - ~~Clinical response of the patient~~
- ❖ Should be done by TDM team-pharmacologist ,pharmacist,analytical ,scientist
- ❖ ~~Dosage predictions can be made using softwares~~

Q. Define TDM, indication & TDM of drugs

Therapeutic drug monitoring (TDM)

- Therapeutic drug monitoring (TDM) is the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens.
- it's defined as the clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures.

INDICATIONS:

1. Pharmacokinetic variability e.g. aspirin, digoxin.
2. Concentration related therapeutic and adverse effects e.g. phenytoin: ataxia, vertigo, drowsiness
3. Narrow Therapeutic Index: digoxin
4. Effect difficult to monitor.
5. Inter individual variations in metabolism.
6. Saturation kinetics: omeprazole: P450 2C19
7. Difficult to recognize toxicity clinically: cyclosporine, Seizures
8. Hepatic and renal diseases: aminoglycoside
9. Multiple drug therapy and drug interaction, Probenicid increases level of penicillin
10. Doubtful patients compliance.
11. to monitor drug interaction. eg. Rifampicin
12. for drugs which exhibit poor and erratic absorption

Q. Role of clinical pharmacist in TDM

→ TDM is a multidisciplinary task and requires a good collaboration among patients and the medical staff including physician, pharmacist, nurses. A clinical pharmacist may assist the other medical professionals by advising them about the correct use of TDM -sampling techniques and interpretation of results. Additionally clinical pharmacist may be engaged in:

- ① selecting initial drug regimen-dose, dosing interval, route of administration, dosage form. before selecting the drug regimen various patient factors like age, sex, body weight, race, renal and hepatic function etc., should be considered.
- ② Depending upon the TDM results and patients response revision and adjustment of dosage regimen should be done.
- ③ assessing various other possible reasons for unexpected results like patients non-compliance medication or laboratory errors, drug interactions, pharmacogenetic variations etc..
- ④ Evaluating and adjusting dosage for patients on hemodialysis
- ⑤ Managing acute drug intoxication
- ⑥ Involving in research activities like determining possible drug interaction, estimation of cost-benefit ratio

Q. explain with suitable examples how elimination ~~half~~ half life of drug influence the duration of activity

Elimination half life and duration of activity

→ There's ~~some~~ a correlation between the half-life of a drug & the duration of its effects. The longer the half-life, 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 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. (Ex: ~~PCW~~ 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:

- o 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 $K = 0.693 / t_{1/2}$

$$t_{eff} = 1.44 t_{1/2} \ln \left(\frac{D_0}{V_D C_{eff.}} \right)$$

- o Pathophysiologic changes in (hepatic) and (renal) function (decrease elimination) thus (prolonging $t_{1/2}$). This in turn will lead to (retention) of drug in body, thereby (increasing) duration of activity of drug as well as (increasing) possibility of drug toxicity.

- o To improve the (antibiotic therapy) with the penicillin 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. (cephalosporins)

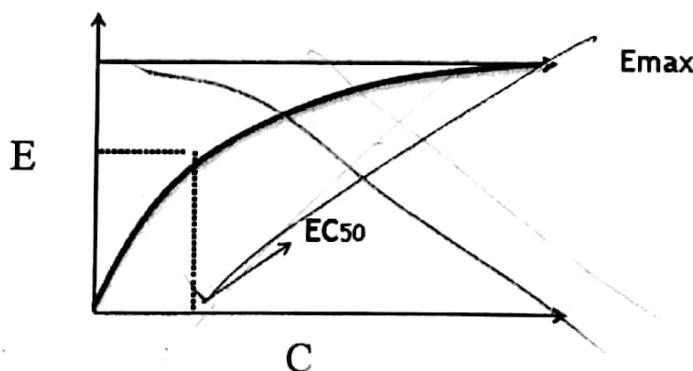
Q. write about $E_{\max}$ model

$E_{\max}$ MODEL

- ⊙ This model incorporates the observation known as the law of diminishing returns.
- ⊙ This law shows that an increase in drug concentration near the maximum pharmacological response produces a disproportionately smaller increase in the pharmacological response.
- ⊙ This model describes the drug action in the terms of :
 - $E_{\max}$ (maximum effect)
 - EC_{50} (the drug concentration that produces 50% maximum pharmacological effect)

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

- ⊙ It mimics the hyperbolic shape of pharmacologic response vs. drug concentration curve.
- ⊙ After maximum response ($E_{\max}$) has reached, no further increase in pharmacologic response is seen on increase in concentration of the drug.
- ⊙ EC_{50} is useful for determining drug concentration that lies within the therapeutic range.



In case, there is a baseline effect i.e. the measured pharmacologic effect has some value in absence of drug (e.g. blood pressure, heart rate, respiratory rate) then the equation becomes:

$$E = E_0 + \frac{E_{\max} C}{EC_{50} + C}$$

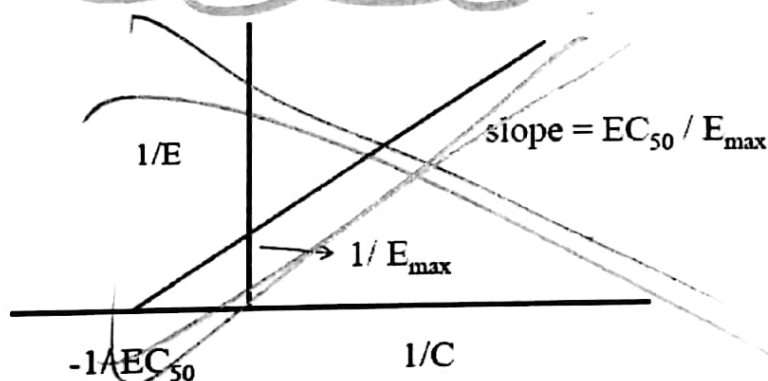
where,

E_0 = Pharmacologic effect (baseline activity) at zero drug concentration in the body

It is a saturable process and resembles the Michaelis-Menton equation.

- ⊙ A double-reciprocal plot of equation is used to linearize the relation, similar to Lineweaver-Burke equation.

$$\frac{1}{E} = \frac{EC_{50}}{E_{\max} C} + \frac{1}{E_{\max}}$$



Advantages

- ⊙ Maximum pharmacological response can be found out.
- ⊙ EC_{50} can be calculated (i.e., concentration needed to produce half maximum response).

Limitations

- ⊙ In case of highly potent drugs it is not possible to find the maximum effect because test organisms die long before the maximum effect is attained.
- ⊙ The method can be time consuming if maximum effect is obtained at a very high concentration.

Q. Explain sigmoidal $E_{\max}$ model in PK/PD correlation

SIGMOIDAL $E_{\max}$ MODEL

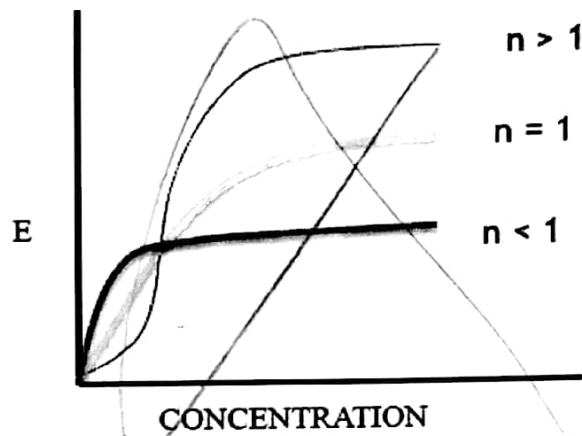
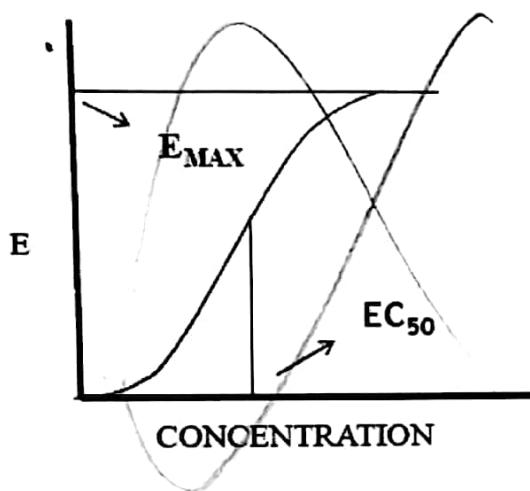
- ⊙ Given by Hill.
- ⊙ It describes the pharmacologic response versus drug concentration curve for many drugs that appear to be S-shaped (i.e. Sigmoidal) rather than hyperbolic as described by more simple $E_{\max}$ model.
- ⊙ The equation for the sigmoid $E_{\max}$ Model is an extension of the $E_{\max}$ Model:

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

→ n is an exponent describing the number of drug molecules that combine with each receptor molecule.

When $n=1$, the Sigmoid $E_{\max}$ Model reduces to the $E_{\max}$ Model

- ⊙ A value of $n>1$ influences the slope of the curve and the model fit.
- ⊙ In the Sigmoid $E_{\max}$ Model, the slope is influenced by the number of drug molecules bound to the receptor.
- ⊙ A very large n value may indicate allosteric or cooperative effects in the interaction of the drug molecules with the receptor.
- ⊙ Cooperativity is the case when binding of substrate at one binding site affects the affinity of other sites to their substrates.



Advantages :

- ⊙ Maximum pharmacological response can be found out.
- ⊙ EC_{50} can be calculated (i.e., concentration needed to produce half maximum response).

Limitations :

- ⊙ In case of highly potent drugs it is not possible to find the maximum effect because test organisms die long before the maximum effect is attained.
- ⊙ The method can be time consuming if maximum effect is obtained at a very high concentration.

Q. explain various pharmacokinetic drug interactions with suitable examples

Pharmacokinetic Drug Interactions

Drug interactions are said to occur when the pharmacological activity of a drug is altered by the concomitant use of another drug or by the presence of some other substance. *The drug whose activity is affected by such an interaction is called as the **object drug** and the agent which precipitates such an interaction is referred to as the **precipitant**.*

Drug interactions include—

1. *Drug-drug interactions.*
2. *Food-drug interactions, ~~for example, inhibition of metabolism of several drugs by grapefruit juice.~~*
3. *Chemical-drug interactions, ~~for example, interaction of a drug with alcohol, tobacco or environmental chemicals.~~*
4. *Drug-laboratory test interaction, ~~for example, alteration of diagnostic laboratory test results by the presence of drug.~~*
5. *Drug-disease interactions, ~~for example, worsening of disease condition by the drug.~~*

Pharmacokinetic Interactions : These interactions are those in which the absorption, distribution, metabolism and/or excretion of the object drug are altered by the precipitant and hence such interactions are also called as **ADME interactions**. The resultant effect is altered plasma concentration of the object drug. Pharmacokinetic interactions can thus be classified as—

(i) **Absorption interactions :** are those where the absorption of the object drug is altered. The net effect of such an interaction is:

- Faster or slower drug absorption
- More, or, less complete drug absorption.

Major mechanisms of absorption interactions are—

- Complexation and adsorption.
- Alteration in GI pH.
- Alteration in gut motility.
- Inhibition of GI enzymes.
- Alteration of GI microflora.
- Malabsorption syndrome.

example :

tetracycline,
fluoroquinolones
like ciprofloxacin
(object drug)

+ Antacids, food
and mineral
supplements
containing Al, Mg,
Fe, Zn

(precipitant
drug)

formation of poorly soluble
and unabsorbable complex
with such heavy metal ions

(ii) **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*.

Example:

phenytoin + valproic acid → phenytoin
(displaced drug) (displacer) toxicity

(iii) **Metabolism interactions** : are those where the metabolism of the object drug is altered. Mechanisms of metabolism interactions include—

- **Enzyme induction** : increased rate of metabolism
- **Enzyme inhibition** : decreased rate of metabolism. It is the most significant interaction in comparison to other interactions and can be fatal.

Example:

corticosteroids, oral
contraceptives, phenytoin + Barbiturates
(object drug) (precipitant drug)

Decreased plasma levels
decreased efficacy of
object drugs

(iv) **Excretion interactions** : are those where the excretion pattern of the object drug is altered. Major mechanisms of excretion interactions are—

- Alteration in renal blood flow : ~~e.g. NSAIDs (reduce renal blood flow) with lithium.~~
- Alteration of urine pH : ~~e.g. antacids with amphetamine.~~
- Competition for active secretion : ~~e.g. probenecid and penicillin.~~
- Forced diuresis.

example :

Ranitidine (object drug) + Cimetidine (precipitant drug) → Increased plasma level at basic object drug, risk of toxicity

Q. explain influence of drug interaction on drug absorption with examples

Drug absorption

Interactions Affecting Absorption of Drugs

→ Altered absorption after oral administration is very common. The interaction may result in a change in the rate of absorption (an increase or a decrease), a change in the amount of drug absorbed (an increase or a decrease) or both. Several mechanisms may be involved in the alteration of drug absorption from the GIT. In general, drugs that are not absorbed completely/rapidly are more susceptible to changes in GI absorption. A decrease in the rate of absorption is clinically significant in acute conditions such as pain where the drug is administered in a single dose but is of little importance for drugs used in chronic therapy.

An alteration in parenteral drug absorption is rare but can occur when an adrenergic agent such as adrenaline or a cholinergic drug such as methacholine is extravascularly injected concomitantly with another drug. These agents alter the systemic absorption of the latter due to vasoconstriction or vasodilation.

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Major mechanisms of absorption interactions are—

- *Complexation and adsorption.*
- *Alteration in GI pH.*
- *Alteration in gut motility.*
- *Inhibition of GI enzymes.*
- *Alteration of GI microflora.*
- *Malabsorption syndrome.*

Example:

Object Drug(s)	Precipitant Drug(s)	Influence on Object Drug(s)
----------------	---------------------	-----------------------------

1. Complexation and Adsorption

Tetracycline, fluoroquinolones like ciprofloxacin, penicillamine	Antacids, food and mineral supplements containing Al, Mg, Fe, Zn, Bi and Ca ions	Formation of poorly soluble and unabsorbable complex with such heavy metal ions
Cephalexin, sulphamethoxazole, trimethoprim, warfarin and thyroxine	Cholestyramine	Reduced absorption due to adsorption and binding

2. Alteration of GI pH

Sulphonamides, aspirin	Antacids	Enhanced dissolution and absorption rate
Ferrous sulphate	Sodium bicarbonate, calcium carbonate	Decreased dissolution and hence absorption
Ketoconazole, tetracycline, atenolol	Antacids	Decreased dissolution and bioavailability

3. Alteration of Gut Motility

Aspirin, diazepam, levodopa, lithium carbonate, paracetamol, mexiletine	Metoclopramide	Rapid gastric emptying; increased rate of absorption
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5. Alteration of GI Microflora

Digoxin

Antibiotics (erythromycin, tetracycline)

Increased bioavailability due to destruction of bacterial flora that inactivates digoxin in lower intestine

~~Oral contraceptives~~

~~Antibiotics (ampicillin)~~

Decreased reabsorption of drugs secreted as conjugates via bile in the intestine

6. Malabsorption Syndrome

Vitamin A, B₁₂,
digoxin

Neomycin
(and colicinins)

Inhibition of absorption due to malabsorption/steatorrhoea caused by neomycin

Q. role of cytochrome P-450 enzymes in drug interaction with example

CI. Pharmacokinetics

Pharmacokinetics of Drug Interactions

coadministration 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 800 mg of cimetidine daily for 1 week increased the steady-state plasma diazepam and nordiazepam concentrations due to a cimetidine-induced impairment in microsomal oxidation of diazepam and nordiazepam. The concurrent administration of cimetidine caused a decrease in total metabolic clearance of diazepam and its metabolite, nordiazepam

INDUCTION OF DRUG METABOLISM

5^m 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

Cl. Pharmacokinetics

Pharmacokinetics of Drug Interactions

other 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.

Q. explain the influence of drug interaction on drug metabolism with respect to enzyme induction and enzyme inhibition

CI. Pharmacokinetics

Pharmacokinetics of Drug Interactions

need to be considered carefully if there is a potential for a drug interaction.

Drug Interaction	Examples (Precipitant Drugs)	Effect (Object Drugs)
Glomerular filtration rate (GFR) and renal blood flow	Methylxanthines (eg, caffeine, theobromine)	Increased renal blood flow and GFR will decrease time for reabsorption of various drugs, leading to more rapid urinary drug excretion
Active tubular secretion	Probenecid	Probenecid blocks the active tubular secretion of penicillin and some cephalosporin antibiotics
Tubular reabsorption and urine pH	Antacids, sodium bicarbonate	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
Diet		
Charcoal hamburgers	Theophylline	Elimination half-life of theophylline decreases due to increased metabolism
Grapefruit	Terfenadine, cyclosporin	Blood levels of terfenadine and cyclosporine increase due to decreased metabolism
Virus drug interactions		
Reye's syndrome	Aspirin	Aspirin in children exposed to certain viral infections such as influenza B virus leads to Reye's syndrome

INHIBITION OF DRUG METABOLISM

→ 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 with injury or severe cardiovascular disease, blood flow may be 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 fentanyl 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-desmethyldiazepam 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-blocking agents:** Quinidine

coadministration 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

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Q. Explain effect of inhibition of biliary excretion,
list out drug interaction

Inhibition of Biliary Excretion

➤ Drug interaction in the process of biliary excretion may effect the residence time and AUC of unchanged drug in plasma.

• Drug interactions in biliary excretion:

- ○ Drugs or often conjugated and excreted in bile. Some drugs are excreted in bile biotransformation.
Eg: In humans most water soluble drugs and metabolites of relatively high molecular weight (more than 450) are excreted largely in the bile.
- ○ This excretion is mainly via transporters and possibility exists for drug interaction with concomitant administration.
- ○ Conjugates such as glucuronides are often excreted in bile and deconjugated in the intestinal tract and reabsorbed enterohepatic circulation.
- ○ Drug interaction in the process of biliary excretion may affect the residence time and AUC of unchanged drug plasma.

Hepatobiliary drug interaction:

- The co-administration of drugs which inhibit the transporter involved in biliary excretion can reduce the biliary excretion of drug which are substrates of the transporter, leading to elevated plasma concentration of drug, Eg; biliary and urinary excretion of digoxin, both mediated by P-gp, are inhibited by quinidine which is a inhibitor of P-gp
- 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 glucuronide transferase 1 A 1 to the SN-38 glucuronide. PROBENECID inhibitor MRI*2 transporter resulting in decreased biliary excretion and increased plasma drug concentration
- Decrease clearance of drug through inhibition of P-gp translates clinically into increased AUC and increase in toxicity.

Examples:

1. Decrease in vincristine clearance in presence of verapamil
2. Decrease in paclitaxel or etoposide clearance in presence of chromophore
3. Decrease in etoposide or doxorubicin clearance in presence of cyclosporine.

Q. list various formula for measurement of GFR

MEASUREMENT OF GLOMERULAR FILTRATION RATE (GFR)

➤ 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.

- Inulin, a fructose polysaccharide, 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.
- 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.

For Children (between 1 to 20 years),

$$Cl_{cr} = \frac{0.48 H}{S_{cr}} \left[\frac{W}{70} \right]^{0.7}$$

For Adults (above 20 years),

Males,

$$Cl_{cr} = \frac{(140 - \text{Age}) W}{72 S_{cr}}$$

Females,

$$Cl_{cr} = \frac{(140 - \text{Age}) W}{85 S_{cr}}$$

= 0.9 . Cl_{cr} of Male

where, Cl_{cr} = creatinine clearance in ml/min,
 S_{cr} = serum creatinine in mg%,
H = height in cms, and
W = weight in Kg.

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

- 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.

Q. Various pharmacokinetic changes in renally impaired patient

PHARMACOKINETIC CONSIDERATIONS

- Uremic patients may exhibit pharmacokinetic changes in bioavailability, volume of distribution, and clearance. The oral bioavailability of a drug in severe uremia may be decreased as a result of disease-related changes in gastrointestinal 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 may alter 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 binding of weak basic drugs is less affected. The decrease in drug protein binding results 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 may compete for the protein-binding sites for the active drug.

→ Total body clearance of drugs in uremic patients is also reduced by either a 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 in patients 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 uremic patient 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. Dosing guidelines for Individual drugs in patients with renal

of drug

Dosing of Drugs in Renal Disease

Excretion of Drugs.

regimen and normal renal function.

life : renal insufficiency are:

to be kept normal	assumed constant	decreased due to disease	needs adjustment
$\frac{1}{2} \frac{dC}{dt} = \frac{1}{2} \frac{dC}{dt} + \frac{1}{2} \frac{dC}{dt}$	$\frac{1}{2} \frac{dC}{dt} = \frac{1}{2} \frac{dC}{dt} + \frac{1}{2} \frac{dC}{dt}$	$\frac{1}{2} \frac{dC}{dt} = \frac{1}{2} \frac{dC}{dt} + \frac{1}{2} \frac{dC}{dt}$	$\frac{1}{2} \frac{dC}{dt} = \frac{1}{2} \frac{dC}{dt} + \frac{1}{2} \frac{dC}{dt}$

then:

$$C_{ss,av} = \frac{t_{1/2} X_0}{\tau} = \frac{t_{1/2} \bar{X}_0}{\tau}$$

be adjusted, we get:

$$\frac{X_0}{\tau} = \frac{t_{1/2} X_0}{t_{1/2} \tau}$$

loading dose.

Q. How do you adjust dosage regimen in renal failure based on total body clearance of drugs

~~Dosing of Drugs in Renal Disease~~

→ In patients with renal failure, the half-life of a drug is increased and its clearance drastically decreased 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. One such method was discussed in chapter 6 on *Excretion of Drugs*.

→ There are two additional methods for dose adjustment in renal insufficiency if the V_d change is assumed to be negligible. These methods are based on maintaining the same average steady-state concentration during renal dysfunction as that achieved with the usual multiple dosage regimen and normal renal function.

★ Dose adjustment based on total body clearance : ~~Rearranging equation 12.6~~, the parameters to be adjusted in renal insufficiency are ~~shown below~~:

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

$\uparrow$ $\uparrow$ $\uparrow$ $\uparrow$
 to be assumed decreased needs
 kept constant due to adjustment
 normal disease

If Cl_T' , X_0' and τ' represent the values for the renal failure patient, then the equation for dose adjustment is given as:

$$C_{ss,av} = \frac{X_0}{Cl_T \tau} = \frac{X_0'}{Cl_T' \tau'}$$

Rearranging in terms of dose and dose interval to be adjusted, the equation is:

$$\frac{X_0'}{\tau'} = \frac{Cl_T' X_0}{Cl_T \tau}$$

From above equation, the regimen may be adjusted by reduction in dosage or increase in dosing interval or a combination of both.

Q. Give the ideal characteristics of a markers to be used in the measurement of GFR

Cl. Pharmacokinetics

Dosage Adjustment in Renal and Hepatic

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.

MEASUREMENT OF GLOMERULAR FILTRATION RATE

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.

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

→ *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.~~

→ 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.

- **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. »

SERUM CREATININE CONCENTRATION AND CREATININE CLEARANCE

Under normal circumstances, creatinine production is roughly equal to creatinine excretion, so the serum creatinine level remains constant. In a patient with reduced glomerular filtration, serum creatinine will accumulate in accordance with the degree of loss of glomerular filtration in the kidney. The serum creatinine concentration alone is frequently used to determine creatinine

Q. markers used in measurement of GFR with advantage and disadvantage

MEASUREMENT OF GLOMERULAR FILTRATION RATE (GFR)

➤ 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.

- Inulin, a fructose polysaccharide, 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:

- - Most accurate
- - Represents the standard to measure GFR¹
- - used in processed foods because it has unusually adaptable characteristics

Disadvantages:

- - Intestinal discomfort, including flatulence, bloating, stomach noises, belching, and cramping,
- - Diarrhea
- - Anaphylactic allergic reaction (rare) - inulin is used for GFR testing, and in some isolated cases has resulted in an allergic reaction, possibly linked to a food allergy response
- ~~Clinically impractical for serial assessment~~

- 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:

- - A) It is a normal metabolite of the body
- - B) It does not require I.V. administration
- - C) Estimation of creatinine is simple
- ~~D) In early stages it has got advantage over S.Creatinine~~

Disadvantages:

- • Estimate of GFR
- • 10% is secreted by renal tubules
- • Secretion increases as kidney function decreases.

→ - Secretion of creatinine is dependent on renal function

- ~~Not corrected for body surface area~~

- 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:

- Imperfect marker of $\downarrow$ GFR
- Marker for adequacy of protein intake
- Marker for presence of uremic toxins in chronic renal failure

Disadvantages:

- bleeding at the puncture site
- bruising at the puncture site
- accumulation of blood under the skin

Q. effect of hepatic disease on pharmacokinetics of drug

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 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, 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 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. 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 follow the response to treatment. A few tests have been used to relate the severity of 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.

Q. Define creatinine clearance, write the formula

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 the serum creatinine concentration is known:

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

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

Where, C_{Cr} = creatinine concentration (mg/dL) ~~of the serum 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

For Children (between 1 to 20 years),

$$Cl_{Cr} = \frac{0.48 H}{S_{Cr}} \left[\frac{W}{70} \right]^{0.7}$$

For Adults (above 20 years),

Males,

$$Cl_{Cr} = \frac{(140 - \text{Age}) W}{72 S_{Cr}}$$

Females,

$$Cl_{Cr} = \frac{(140 - \text{Age}) W}{85 S_{Cr}}$$

= 0.9 . Cl_{Cr} of Male

where, Cl_{Cr} = creatinine clearance in ml/min,
S_{Cr} = serum creatinine in mg%,
H = height in cms, and
W = weight in Kg.

Age is measured in years.

Jelliffe's method

→ This is based on age and serum creatinine concentration of the patient

→ This method is not intended for patient under 20 years of age and should be used to calculate creatinine clearance in mature male adult only (upto age 80 years)

male

$$CL_{cr} = \frac{98 - 0.8(Y - 20)}{C_{cr}}$$

female

$$CL_{cr} = \frac{0.9 \times 98 - 0.8(Y - 20)}{C_{cr}}$$

where: Y = age in years

C_{cr} = serum creatinine in $mg/100ml$

COCKCRAFT and GAULT's method

→ This method is based on the age, weight and serum creatinine concentration of the patient

males

$$CL_{cr} = \frac{(140 - Y)(W)}{72 \times C_{cr}}$$

female

$$CL_{cr} = \frac{(0.85)(140 - Y)(W)}{72 \times C_{cr}}$$

where:

Y = age in year

C_{cr} = serum creatinine concentration in $mg/100ml$

W = weight in kg

Q. Describe peritoneal dialysis with its advantages and disadvantages

PERITONEAL DIALYSIS

- Introducing dialyzing fluid into the peritoneal cavity via a catheter and 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) are exchanged from the blood.
- Membrane restricts the movement of formed elements (eg. erythrocytes) and large molecules (eg. protein) but allows the movement of smaller molecules according to the conc. gradient.

↓
Concentration

Techniques used for peritoneal dialysis:

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

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

Advantage:

- regular visits to a dialysis unit aren't required and it can be carried out at home without needing any bulky haemodialysis equipment.
- There are also fewer restrictions on diet and fluid intake for people having peritoneal dialysis, compared to those having haemodialysis.
- Simple to set up & perform
- Easy to use in infants
- Hemodynamic stability
- No anti coagulation
- Bedside access
- Treat severe hypo/hyperthermia

Disadvantage:

- it needs to be carried out every day, which you may find very disruptive.
- the dialysis fluid used can cause a reduction in protein levels, which can lead to a lack of energy and, in some cases, malnutrition.
- Unreliable ultrafiltration
- Slow fluid & solute removal
- Drainage failure & leakage
- Respiratory compromise
- Hyperglycaemia
- Peritonitis
- Not good for intoxication

Q. explain Giusti-Hayton method for the dosage adjustment in uremic patient

The Giusti-Hayton (1973) method

- 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} :

$$k^u_r / k^N_r = Cl^u_{cr} / Cl^N_{cr}$$

- where
- k^u_r is the uremic renal excretion rate constant,
- k^N_r is the normal renal excretion rate constant.

$$k^u_r = k^N_r \cdot Cl^u_{cr} / Cl^N_{cr}$$

- Because the overall uremic elimination rate constant, k_u , is the sum of renal and non-renal elimination,

$$K_u = k^u_{nr} + k^u_r$$

$$K_u = k^u_{nr} + k^N_r (Cl^u_{cr} / Cl^N_{cr})$$

- Dividing Equation by k_N on both sides yields

$$K_u / K_N = k^u_{nr} / K_N + k^N_r / K_N (Cl^u_{cr} / Cl^N_{cr})$$

- Let $fe = k^N_r / k_N$ - fraction of drug excreted (unchanged) in the urine and $1 - fe = k^u_{nr} / k_N$ - fraction of drug excreted by nonrenal routes.

- **Substitution** into Equation 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:

$$K_u / K_N = (1 - fe) + fe (Cl^u_{cr} / Cl^N_{cr})$$

Or

$$K_u / K_N = 1 - fe (1 - Cl^u_{cr} / Cl^N_{cr}) = G$$

Q. Describe wagner method for the dose adjustment in uremic patient

creatinine clearance in this patient has decreased to a stable level of 50 mL/min. Calculate the appropriate dose of tobramycin for this patient.

Solution

Obtain $f_e = 0.9$ from the literature (see Appendix D) and apply Equation 21.27:

$$\frac{Cl_u}{Cl} = (1 - f_e) + f_e \frac{Cl_u^u}{Cl_{Cr}^u}$$

$$\frac{Cl_u}{Cl} = 1 - 0.9 + 0.9 \left(\frac{50}{100} \right) = 0.55$$

Therefore, the dose for the uremic patient = $150 \text{ mg} \times 0.55 = 82.5 \text{ mg}$ (given twice a day).

k_R = renal excretion rate constant

Cl = total body clearance of drug

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

$$Cl = R Cl_{Cr}$$

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

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

$$k\% = a + b Cl_{Cr}$$

→ this Equation ~~21.27~~ 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.

The Wagner Method

The methods for renal dose adjustment discussed in the previous sections 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. A statistical approach was used by Wagner (1975), who established a linear relationship between creatinine concentration and the first-order elimination constant of the drug in patients. The Wagner method is described in greater detail in the third edition of this book.

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

$$k\% = a + b Cl_{cr}$$

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 (%)

Q. Explain hemodialysis

HEMODIALYSIS

- 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

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:

- conventional hemodialysis
- daily hemodialysis
- nocturnal hemodialysis

How is blood removed and replaced?

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

Applications:

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

Q. Role of genetic polymorphism in drug target

Cl. Pharmacokinetics

Pharmacogenetics

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 amino acid 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-I).
- 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 enzymes, 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 β -adrenergic receptor, and its common mutation of ArgGly at amino acid 16, greatly reduces the bronchodilator response of albuterol

Clinically Important Genetic Polymorphisms of Drug Targets and Drug Transporters			
Gene	Frequency	Drug	Drug Effect
Multidrug resistance gene (<i>MDR1</i>)	24%	Digoxin	Increased concentrations of digoxin in plasma
Beta-2 adrenergic receptor gene (<i>2AR</i>)	37%	Albuterol	Decreased response to Beta-2 adrenergic agonists
Sulphonylurea receptor gene (<i>SUR1</i>)	2-3%	Tolbutamide	Decreased insulin response
Five genes coding for cardiac ion channels	1-2%	Antiarrhythmics, terfenadine, many other drugs	Sudden cardiac death due to long-QT syndrome

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 individual's 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 that many 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.

Q. Describe polymorphism in CYP2D6 and 2C9 isozymes

CL Pharmacokinetics

Pharmacogenetics

GENETIC POLYMORPHISM IN DRUG METABOLISM: CYTOCHROME P450 ISOZYMES:

(a) CYP2D6

→ CYP2D6 () is a large isozyme family that affects metabolism of many drugs. CYP2D6 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 from 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 "normal" 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.~~

⑥ **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.

⑥ **CYP2C9**

→ 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.

Q. Describe Bayesian theory

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 intraindividual 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 (1). A brief literature search of Bayesian applications revealed over 400 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),~~

Q. Explain dosing with feed back

CL. Pharmacokinetics

Population Pharmacokinetics

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 (SPSS). 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 V_D 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 Cockcroft 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 (~~it 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*, OBJols.

Q. Discuss analysis of population pharmacokinetic data

CL Pharmacokinetics

Population Pharmacokinetics

$$C_i = f(P, t_i) + \epsilon_i$$

$$OBJ_{OLS} = \sum_{i=1}^n \frac{(C_i - \hat{C}_i)^2}{\sigma_i^2}$$

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 , V_D , 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** (~~see~~) 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 (C_i) in terms of a model with:

1. 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.

2. Random effect parameters, including (a) the variance of the structural (fixed) 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 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 effects, it is called a **mixed-effect statistical model**.

Q. Discuss population pharmacokinetic analysis using NONMEM method
Q. explain NONMEM

The Nonlinear Mixed-Effects Modeling Approach

(NONEM)

→ It was developed by S.L. Beal and L.B. Sheiner is a statistical program used for fitting parameters in population pharmacokinetics

- When properly performed, population PK studies in patients combined with suitable mathematical/statistical analysis, for example, using nonlinear mixed-effects modeling, is a valid, and on some occasions, preferred alternative to extensive studies. In sparse data situations, where the traditional two-stage approach is not applicable because estimates of individual parameters are, a priori, out of reach, a single-stage approach, such as nonlinear mixed-effects modeling, should be used.

→ The NONMEM is so called because the model uses both fixed and random factors to describe data

- In the context of drug evaluation, the nonlinear mixed-effects modeling approach developed from the recognition that, if pharmacokinetics and pharmacodynamics are to be investigated in patients, pragmatic considerations dictate that data should be collected under less stringent and restrictive design conditions. This approach considers the population study sample, rather than the individual, as a unit of analysis for the estimation of the distribution of parameters and their relationships with covariates within the population. The approach uses individual pharmacokinetic data of the observational (experimental) type, which may be sparse, unbalanced, and fragmentary, in addition to, or instead of, conventional pharmacokinetic data from traditional pharmacokinetic studies characterized by rigid and extensive sampling design (dense data situation). Analysis according to the nonlinear mixed-effects model provides estimates of population characteristics that define the population distribution of the pharmacokinetic (and/or pharmacodynamic) parameter
- In the mixed-effects modeling context, the collection of population characteristics is composed of population mean values (derived from fixed-effects parameters) and their variability within the population (generally the variance-covariance values derived from random-effects parameters). A nonlinear mixed-effects modeling approach to the population analysis of pharmacokinetic data, therefore, consists of estimating directly the parameters of the population from the full set of individual concentration values. The individuality of each subject is maintained and accounted for, even when data are sparse. The mixed-effects modeling approach is discussed in more detail and is referred to below as the population PK approach.

Sampling Designs used in population pharmacokinetics

In the population pharmacokinetics context, three broad approaches exist for obtaining information about pharmacokinetic variability:

1. Single-Trough Sampling Design:

- In the single-trough sampling design, a single blood sample is obtained from each patient at, or close to, the trough of drug concentrations, shortly before the next dose, and a frequency distribution of plasma or serum levels in the sample of patients is calculated. Assuming that the sample size is large, the assay and sampling errors are small, and the dosing regimen and sampling times are identical for all patients, a histogram of the trough screen will give a fairly accurate picture of the variability in trough concentrations in the target population. If the three conditions are not met, a histogram will not represent strict pharmacokinetic variability because the data will include other sources of random fluctuation that significantly contribute to the observed spread. When related to therapeutic outcome and occurrence of side effects, such histograms can provide information about the optimal concentration range of a given drug.
- The relationship between patient characteristics and trough levels can be explored using simple statistical procedures, such as multiple linear regression. Although simple, the trough (pharmacokinetic) screen can yield information about apparent clearance, but not about other parameters of interest. Components of variability — interindividual and residual variability — cannot be separated. ~~This method will identify, qualitatively, pharmacokinetically relevant covariates and their differences among subpopulations.~~
- ~~With the single-trough sampling design, it is not advisable to measure peak observations unless the drug is given intravenously or is a certain type of sustained-release formulation. The time for achieving maximum concentration depends on rates of all processes of drug disposition and may vary among subjects.~~

2) *Multiple-Trough Sampling Design:*

- In the multiple-trough sampling design, two or more blood samples are obtained near the trough of steady-state concentrations from most or all patients. In addition to relating blood concentration to patient characteristics, it is possible now to separate interindividual and residual variabilities. Since patients are studied in greater detail in this design, the design requires fewer subjects, and the relationship of trough levels to patient characteristics can be evaluated with greater precision. To estimate interindividual variability in clearance, nonlinear mixed-effects modeling should be used.) ~~When using pharmacokinetic models for parameter estimation, a sensitivity analysis (24) should be done by fixing a parameter, such as absorption rate constant, to estimate other parameters and to determine the fixed parameter value that has the least effect on the estimation of the remaining parameters.~~

3) *Full Population PK Sampling Design:*

- The full population PK sampling design is sometimes called experimental population pharmacokinetic design or full pharmacokinetic screen. When using this design, blood samples should be drawn from subjects at various times (typically 1 to 6 time points) following drug administration. The objective is to obtain, where feasible, multiple drug levels per patient at different times to describe the population PK profile. This approach permits an estimation of pharmacokinetic parameters of the drug in the study population and an explanation of variability using the nonlinear mixed-effects modeling approach.) ~~The full population PK sampling design should be planned to explore the relationship between the pharmacokinetics of a drug and demographic and pathophysiological features of the target population (with its subgroups) for which the drug is being developed.~~

9. methods used to obtain the estimates of fixed effect and variability

There are two common methods for obtaining estimates of the fixed-effect (mean) and of the variability: the two-stage approach and the nonlinear mixed-effects modeling approach. The two-stage approach involves multiple measurements on each subject (the data-rich situation), which will be described briefly below. The nonlinear mixed-effects modeling approach, which can be used in situations where extensive measurements will not be made on all or any of the subjects (data-sparse situation), will be the main focus of this guidance.⁴

A. The Two-Stage Approach

→ The traditional method of pharmacokinetic data analysis uses a two-stage approach. The first stage of this approach involves the estimation of pharmacokinetic parameters through nonlinear regression using an individual's dense concentration-time data (data-rich situation). Individual parameter estimates obtained during the first stage serve as input data for the second-stage calculation of descriptive summary statistics on the sample, typically, mean parameter estimates, variance, and covariance of the individual parameter estimates. Analysis of dependencies between parameters and covariates using classical statistical approaches (linear stepwise regression, covariance analysis, cluster analysis) can be included in the second stage. The two-stage approach, when applicable, can yield adequate estimates of population characteristics. Mean estimates of parameters are usually unbiased, but the random effects (variance and covariance) are likely to be overestimated in all realistic situations (5,6). Refinements have been proposed (e.g., global two-stage approach) to improve the two-stage approach through bias correction for the random effects covariance and differential weighting of individual data according to the data's quality and quantity (7,8).

→ The two-stage approach has been applied in the new drug development and evaluation process for more than 20 years, and because it is described elsewhere, it will not be comprehensively discussed in this document.

B. The Nonlinear Mixed-Effects Modeling Approach

→ When properly performed, population PK studies in patients combined with suitable mathematical/statistical analysis, for example, using nonlinear mixed-effects modeling, is a valid, and on some occasions, preferred alternative to extensive studies. In sparse data situations, where the traditional two-stage approach is not applicable because estimates of individual parameters are, a priori, out of reach, a single-stage approach, such as nonlinear mixed-effects modeling, should be used.

In the context of drug evaluation, the nonlinear mixed-effects modeling approach developed from the recognition that, if pharmacokinetics and pharmacodynamics are to be investigated in patients, pragmatic considerations dictate that data should be collected under less stringent and restrictive design conditions. This approach considers the

⁴ Other approaches, such as the naive averaged-data approach, which provides mean population pharmacokinetic parameter estimates without variability estimates, are available for use, but will not be discussed.

population study sample, rather than the individual, as a unit of analysis for the estimation of the distribution of parameters and their relationships with covariates within the population. The approach uses individual pharmacokinetic data of the observational (~~experimental~~) type, which may be sparse, unbalanced, and fragmentary, in addition to, or instead of, conventional pharmacokinetic data from traditional pharmacokinetic studies characterized by rigid and extensive sampling design (~~dense data situation~~). ~~Analysis according to the nonlinear mixed-effects model (11) provides estimates of population characteristics that define the population distribution of the pharmacokinetic (and/or pharmacodynamic) parameter (12).~~

→ In the mixed-effects modeling context, the collection of population characteristics is composed of population mean values (~~derived from fixed effects parameters~~) and their variability within the population (~~generally the variance-covariance values derived from random effects parameters~~). A nonlinear mixed-effects modeling approach to the population analysis of pharmacokinetic data, therefore, consists of estimating directly the parameters of the population from the full set of individual concentration values. The individuality of each subject is maintained and accounted for, even when data are sparse. ~~The mixed-effects modeling approach is discussed in more detail and is referred to below as the population PK approach.~~

IV. ~~WHEN TO USE THE POPULATION PK APPROACH~~

In drug development, use of the population PK approach can help increase understanding of the quantitative relationships among drug input patterns, patient characteristics, and drug disposition (12). This approach is helpful when wishing to identify factors that affect drug behavior, or explain variability in a target population. The nonlinear mixed-effects modeling approach is especially helpful in certain adaptive study designs, such as dose-ranging studies (e.g., so called titration, or effect controlled designs).

Population modeling is most likely to add value when a reasonable a priori expectation exists that intersubject kinetic variation may warrant altered dosing for some subgroups in the target population. Likely circumstances would include (1) when the population for which the drug is intended is quite heterogeneous and (2) when the target concentration window is believed to be relatively narrow.

The population PK approach can be used to estimate population parameters of a response surface model in phase 1 and late phase 2b of clinical drug development, where information is gathered on how the drug will be used in subsequent stages of drug development (12). The population PK approach can increase the efficiency and specificity of drug development by suggesting more informative designs and analyses of experiments. In phase 1 and, perhaps, much of phase 2b, where patients are sampled extensively, complex methods of data analysis may not be needed. Two-stage methods can be used to analyze the data, and standard regression methods can be used to model dependence of parameters on covariates. Alternatively, data from individual studies in phases 1 and 2b can also be pooled and analyzed using the nonlinear mixed-effects modeling approach.

Population pharmacokinetics

Application:

- Population pharmacokinetic modelling is a complex activity. It is also labour intensive and time consuming.
- Like all mathematical models, a population pharmacokinetic model only provides estimates of the true (but unknown) pharmacokinetic parameter values. Fitting a model to the data results in some uncertainty in the true value of the estimated parameter, therefore plasma concentrations predicted by a model also have a degree of uncertainty attached to them. There is an oft-quoted adage that 'all models are wrong, but some are useful'. Population analyses have numerous useful clinical applications, especially in patients who otherwise may be difficult to recruit for a traditional pharmacokinetic study, for example young children or patients in intensive care.
- Population pharmacokinetics is a much underused resource in Australia which could potentially improve clinical outcomes by informing individualised prescribing. One example is the use of population pharmacokinetics to develop a dosage nomogram for caffeine in the treatment of infants with apnoea of prematurity.
- Another example is safely prescribing metformin for patients with impaired renal function. Using data from patients with various stages of renal dysfunction, a model was developed to identify and quantify the covariates, such as weight, which influence the pharmacokinetics of metformin. It then simulated dosage scenarios that could be used at various levels of renal dysfunction without the plasma concentration of metformin reaching a level which would result in adverse effects. This work is valuable because it provided guidelines for using metformin in patients with renal impairment in whom the drug was previously contraindicated.
- Population pharmacokinetic methods are an emerging and important part of drug development including preclinical studies, clinical trials and postmarketing surveillance. There are excellent reviews from the pharmaceutical industry and regulatory perspectives, and web-based guidelines from regulatory agencies.
- Studies have involved research and clinical applications in a wide variety of patients and conditions including diabetes, clotting disorders, malignancy, serious infection, apnoea of prematurity, pregnancy, organ transplantation, self-poisoning and arthritis.

Q. limitation of population pharmacokinetics

Limitation:

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 intraindividual 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 (e.g. all covariates in all patients)

Difference b/w traditional pharmacokinetics and population pharmacokinetics

Parameters	Traditional	Population
Population	Healthy volunteers 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 Pathophysiological 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. Describe two stage approach in population pharmacokinetic analysis

The Two-Stage Approach

→ The traditional method of pharmacokinetic data analysis uses a two-stage approach. The first stage of this approach involves the estimation of pharmacokinetic parameters through nonlinear regression using an individual's dense concentration-time data (data-rich situation). Individual parameter estimates obtained during the first stage serve as input data for the second-stage calculation of descriptive summary statistics on the sample, typically, mean parameter estimates, variance, and covariance of the individual parameter estimates. Analysis of dependencies between parameters and covariates using classical statistical approaches (linear stepwise regression, covariance analysis, cluster analysis) can be included in the second stage. The two-stage approach, when applicable, can yield adequate estimates of population characteristics. Mean estimates of parameters are usually unbiased, but the random effects (variance and covariance) are likely to be overestimated in all realistic situations (~~and~~). Refinements have been proposed (e.g., global two-stage approach) to improve the two-stage approach through bias correction for the random effects covariance and differential *weighting* of individual data according to the data's quality and quantity (~~and~~). The two-stage approach has been applied in the new drug development and evaluation process for more than 20 years, and because it is described elsewhere, it will not be comprehensively discussed in this document.

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

$$\frac{k_u}{k_N} = 1 - 1 \left(1 - \frac{20}{100} \right) = 0.2$$

Because :

$$\frac{D_u}{D_N} = \frac{k_u}{k_N} \quad \text{or} \quad D_u = D_N \times \frac{k_u}{k_N}$$

where D_u = uremic dose and D_N = normal dose,

$$D_u = 80 \text{ mg} \times 0.2 = 16 \text{ mg}$$

The maintenance dose is 16 mg every 6 hours. Alternatively, the dosing interval can be adjusted without changing the dose:

$$\frac{\tau_u}{\tau_N} = \frac{k_N}{k_u} \quad \text{or} \quad \tau_u = \tau_N \times \frac{k_N}{k_u}$$

$$\tau_u = 6 \text{ hr} \times \frac{1}{0.2} = 30 \text{ hr}$$

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

99. An adult male patient (52 years old, 75 kg) 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 1 mg/kg every 8 hours by multiple IV bolus injections. Calculate the appropriate dosage regimen of gentamicin sulfate for this patient.

$$Cl_{cr}^U = \frac{(140-A) \times LBW}{72 Ccr}$$

$$= \frac{(140-52) \times 75}{72 \times 2.4}$$

$$= 38.19 \text{ ml/min.}$$

$$G = 1 - f_e \left(1 - \frac{Cl_{cr}^U}{Cl_{cr}^N} \right)$$

$$= 1 - 0.98 \left(1 - \frac{38.19}{100} \right)$$

$$= 0.39$$

→ Then for,

$$D_o^u = D_o^N \times G$$

$$= 75 \times 0.39$$

$$= 29.57$$

→ 80 mg Gentamicin Sulfate Present in 2 ml Vials

→ 1 mg ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ $\frac{2}{80}$ ml

→ 29.57 mg ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ $\frac{2 \times 29.57}{80}$ ml

= 0.75 ml

So, 0.75 ml in every 8hr.

Now,

$$\tau^u = \tau^N \times \frac{1}{G}$$

$$= 8 \times \frac{1}{0.39} = 20.5 \text{ hr.}$$

→ 80 mg Gentamicin Sulfate Present in 2 ml Vials

→ 1 mg ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ $\frac{2}{80}$ ml

→ 75 mg ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ ~~1~~ $\frac{2 \times 75}{80}$ ml

= 1.88 ml

→ So, 75 mg, or, 1.88 ml in every 20.5 hr.

98. What is the creatinine clearance for a 25 year old male patient with a serum creatinine of 1mg/dL? The patient is 5 ft, 4 inches in height and weighs 103 Kg.

$$Cl_{cr} = \frac{(140 - Y) (W)}{72 \times C_{cr}}$$

$$Cl_{cr} = \frac{(140 - 25) \times 103}{72 \times 1}$$

$$Cl_{cr} = \frac{11845}{72}$$

$$Cl_{cr} = 164.5 \text{ ml/min}$$