CLINICAL PHARMACOKINETICS & PHARMACOTHERAPEUTIC DRUG MONITORING

5TH YEAR

PHARM D

10 MARKS

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Q. explain factor considered in design of dosage regimen for geriatric and obese patients

Dosing of Drugs in Elderly

Drug dose should be reduced in elderly patients because of a general decline in body function with age. The lean body mass decreases and body fat increases by almost 100% in elderly persons as compared to adults. Because of smaller volume of body water, higher peak alcohol levels are observed in elderly subjects than in young adults. V_d of a water-soluble drug may decrease and that of a lipid-soluble drug like diazepam increases with age. Age-related changes in hepatic and renal function greatly alters the clearance of drugs. Because of progressive decrease in renal function, the dosage regimen of drugs that are predominantly excreted unchanged in urine should be reduced in elderly patients.

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

$$\text{Patient's Dose} = \frac{(\text{Weight in Kg})^{0.7}(140 - \text{Age in years})}{1660} \times \text{AdultDose}$$

Dosing of Drugs in Obese Patients

The apparent volume of distribution of a drug is greatly affected by changes in body weight since the latter is directly related to the volume of various body fluids. The *ideal body weight* (IBW) for men and women can be calculated from following formulae:

IBW (men) = 50 Kg ± 1 Kg/2.5 cm above or below 150 cm in height

IBW (women) = 45 Kg ± 1 Kg/2.5 cm above or below 150 cm in height

Any person whose body weight is more than 25% above the IBW is considered obese. In such patients, the lean-to-adipose tissue ratio is small because of greater proportion of body fat which alters the V_d of drugs. The ECF of adipose tissue is small in comparison to lean tissue in obese patients.

→ Following *generalizations* can be made regarding drug distribution and dose adjustment in obese patients:

1. For drugs such as digoxin that do not significantly distribute in the excess body space, V_d do not change and hence dose to be administered should be calculated on IBW basis.
2. For polar drugs such as antibiotics (gentamicin) which distribute in excess body space of obese patients to an extent less than that in lean tissues, the dose should be lesser on per Kg total body weight basis but more than that on IBW basis.
3. In case of drugs such as caffeine, theophylline, lidocaine and lorazepam which distribute to the same extent in both lean and adipose tissues, the V_d is larger in obese patients but same on per Kg total body weight basis; hence, dose should be administered on total body weight basis.
4. For drugs such a phenytoin, diazepam and thiopental which are lipid-soluble and distribute more in adipose tissues, the V_d is larger per Kg body weight in obese patients and hence they require larger doses, more than that on total body weight basis.

→ Changes in dose based on alteration of V_d is also attributed to modification of clearance and half-life of the drug.

Q. process of TDM in patient receiving cyclosporine and carbamazepine

Cyclosporine

→ It's a potent immunosuppresant agent

→ The drug finds application in organ transplanted patient to prevent organ rejection by suppressing immune System

monitoring of pharmacokinetic Parameter and TDM information

→ pharmacokinetic parameters vary from person to person, A mild variation is observed with cyclosporine in pharmacokinetic parameter

→ when cyclosporine is administered orally

(i) Bioavailability varies from 20-50%

(ii) Peak plasma level (T_{max}) are achieved within 2-6 hours

(iii) $T_{1/2}$ is 5.6 ± 2 hours

(iv) It's metabolized in liver, elimination though bile to the faeces and also eliminated through renal (less than 1%)

(v) therapeutic range of cyclosporine is 50-300 ng per ml in plasma.

Dosing of Cyclosporine

→ 15 mg/kg once daily dose, this dose is initiated for 4-24hrs prior to transplantation and continued for 1-2 weeks

Sampling & TDM

→ plasma drug concentration of cyclosporine is most useful information for TDM several blood sample between 2-6 hrs after oral dosing can be obtained to minimize variation in bioavailability

→ cyclosporine level should be monitored 2-3 times a week and more frequent monitoring is required if the patient has clinical problems that can change cyclosporine pharmacokinetics

Toxicity (Adverse effect)

→ severe headache
→ hirsutism
→ visual disturbance
→ hypertension
→ tremor
→ convulsions
→ neurological toxicity
→ nephrotoxicity

• The above Adverse effect may vary with the dosage of cyclosporine and it's concentration should be estimated in blood

factor affecting plasma level

→ food : High fat meals may increase plasma level
→ Age : children below 10 years may decrease the level of plasma because they have a large volume of distribution of faster body clearance
→ Drugs : drugs which decrease cyclosporine level are carbamazepine, phenobarbital, phenytoin
→ physiological disorders : fever and DM increase fraction of unbound cyclosporine

Carbamazepine

→ It's an anticonvulsant and mood stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder as well as trigeminal neuralgia

pharmacokinetic parameters and TDM information

parameters	values
(1) Elimination half life ($T_{1/2}$)	1> 25-40 hrs (single dose in normal)
	4> 15-24 hrs (monotherapy in chronic condition)

iii) 6-14 hrs (polytherapy
in chronic condition

iv) 2.5 - 15 hrs (in chil

② total body clearance (TBC) (ml/kg/hr)

i) 21 ± 5 (single close in normal)

ii) 25 ± 15 (monotherapy in chronic condition)

iii) 108 ± 39 (polytherapy in chronic condition)

③ volume of distribution (Vd)

i) 1-2 litres/kg

④ plasma drug binding

i) ~~2 litres~~ 40-90 %.

⑤ therapeutic range

i) ~~40-90 %~~ 4-12 µg/ml

⑥ loading close

i) ~~4-12 mg/ml~~ 3.5-10.4 mg/kg (for adult)

⑦ maintainance close (As thrice a day therapy)

i) 7-15 mg/kg (for adu

ii) 11-40 mg/kg (for children

→ The absorption of cbz is very slow and irregul maximum activity (t_{max}) is observed in 4-8 hrs but may be prolonged to as much as 24 hrs

→ The plasma protein binding is 40-90% and i

Converted to clinically important metabolites, 10-11 episode which is also active in various animals, later its metabolized to inactive compound and excreted as glucuronoides these drug can induce hepatic enzymes hence half life ($t_{1/2}$) varies with repeated administration

→ bioavailability of Cbz is more than 75%.

→ clearance and plasma $t_{1/2}$ of Cbz are changed by Co-administration with other anti-epileptic drugs & therapy

monitoring of Cbz toxicity

→ generally ADR includes nausea, vomiting, dizziness skin rashes, impaired vision and confusion

→ Serious toxicity includes obstructive Jaundice aplastic anemia, respiratory depression

available dosage

i) Tablets 100-200mg

ii) chewable tablets - 100mg

iii) suspension 100mg per 5ml

factor affecting plasma level

→ food : decreased plasma level when cbz is given as a form of suspension.

→ Drugs : like phenytoin, warfarin, valporate haloperidol, isoniazid

Q. list out the indication for TDM, process of TDM for patient receiving digoxin and phenytoin

INDICATIONS for TDM:

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 recognized toxicity clinically: cyclosporine , Seizures
8. Hepatic and renal diseases: aminoglycoside
9. Multiple drug therapy and drug interaction, Probenicid increases level of penicillir
10. Doubtful patients compliance.
11. to monitor drug interaction. eg . Rifampicin
12. for drugs which exhibit poor and erratic absorption

Digoxin

-> Digoxin is a drug belonging to a class of glycoside (digitalis / cardiac glycosides) which is used in the treatment of severe left ventricular Systolic dysfunction, after initiation of diuretics and vasodilation therapy

pharmacokinetic parameters and TDM information of digoxin

parameters	values
① $T_{1/2}$ elimination half life (biological half life)	I> 36 hrs (for adults) II> 18 - 37 hrs (for children)
② Total body clearance (TBC)	I> 2.7
③ volume of distribution (Vd)	I> 6 - 7 Ltr/kg
④ plasma protein binding	I> 20 - 30%
⑤ Therapeutic range	I> 0.9 - 2 ng/ml (for atrial fibrillation) II> 0.5 - 1.2 ng/ml (for congestive heart failure)

⑥ Time to steady State Concentration — i) 6 - 10 days

⑦ Loading dose

i) Two 0.5 mg oral tablet doses

ii) Two 0.375 mg IV doses separated by 6 hrs

iii) 0.2 mg per day (Creatinine clearance more than 20 ml/min)

⑧ maintainance dose

i) 0.1 - 5 mg per day (Creatinine clearance less than 20 ml/min or body weight less than ~~the~~ 40 ~~kg~~

→ Volume of distribution values is for ~~normal~~ normal renal ~~of~~ function in CHf and renal failure it is decreased

→ Sample for TDM should be collected at least 6hrs and ~~peak~~ preferably 12 hrs from the last dose

→ maintainance dose may be started without a loading dose

Assesment of appropriate Digoxin dose

→ It's started that at between plasma concentration of 0.9 - 2 ng/ml, a therapentic effect is most likely to be achieved However So many evidance suggested that there is a relationship between the effect of digoxin and plasma digoxin concentration within the therapeutic range is conflicting studies design to illustrate.

→ This relationship has been two types:

1> Comparision of plasma and tissue digoxin Concentration

11> Comparision between plasma digoxin concentration and its clinical effect

phenytoin

PHENYTOIN:

- It s used in all types of seizure except absence seizure, n seizure caused by theophylline overdose.
- It s also useful for digitalis induced ventricular arrhythmias.
- NEED FOR TDM: Monitoring is imperative as a guide to dosage adjustment, since phenytoin has a low therapeutic index and exhibits nonlinear kinetics. The relative rate of elimination is slower at higher concs than at lower concs of the drug.

PHARMACOKINETIC PROPERTIES:

- Bioavailability – 70-100%
- Ka = 50mg/hr saturable kinetics of absorption (zero order)
- tmax = 3-12 hr (increases with dose)

- Vd = 0.6-0.8 l/kg
- Albumin bound fraction = 0.9
- Biotransformation = 70-90%
- Renal excretion = 1-5%

Patients	Vmax	Km
Adults	6mg/kg/day	5.7mg/l
6month-6 yrs	12mg/kg/day	4mg/l
7-16 yrs	9mg/kg/day	

THERAPEUTIC RANGE:

~~Patients~~	~~Therapeutic Range~~
Adult n children	10-20 mg/l
Newborns n children under 3 years	6-14 mg/l
ESRD or hypoalbuminaemia	5-10 mg/l
ESRD with hypoalbuminaemia	3-7 mg/l
Liver disease	7-14 mg/l
Acute hepatitis	8-16 mg/l

ADR:

- They are related to plasma concentrations:

Plasma levels	Symptoms
20-30 mg/l	Nystagmus
30-40 mg/l	Ataxia
>40 mg/l	Mental changes

LONG TERM EFFECTS OF PHENYTOIN:

- Gingival hyperplasia
- Acne
- Hirsutism
- Folate n Vit.D deficiency

INDICATIONS FOR TDM:

- At the initiation of therapy, in order to achieve a plasma conc. within the therapeutic range.
- When there is intercurrent illness (AIDS, hypoalbuminaemia, renal impairment) or a change in physiological state exists (age, pregnancy).
- When drug toxicity is suspected.
- When the therapy is about to be withdrawn.
- Intervals during the course of therapy.

SAMPLE TIMING:

- The time required to attain a Css after initiation of therapy is difficult to predict due to non linear kinetics.
- Css might not b attained for as long as 3 wks.
- Thus samples r obtained prior to steady state (after 3-4 days) n at the end of dosage interval.
- In case of oral phenytoin, the sample can b drawn anytime during the dosage interval as it is slowly absorbed.

SPECIMENS:

- Serum or plasma are generally recommended for total phenytoin measurements..
- Use of anti coagulants r not recommended.
- Saliva is proposed for children.
- Saliva is a useful specimen for monitoring unbound phenytoin conc.

COLLECTION METHODS AND ASSAYS:

- Immunoassays are most common methods of measurement.
- Immunoassays that use monoclonal antibodies or HPLC can b used in samples from patients with renal impairment.

DOSAGE RECOMMENDATIONS:

- Phenytoin exhibits nonlinear behavior following therapeutic doses.
- Thus increase in dose rate will produce greater than proportional increase in the average serum conc. during the dosing interval.
- Normograms can b used to estimate individual dosage requirements.

Population	Maintenance dose	Dosage interval
Adults	5-7 mg/kg/day	12 hrs
Children<3months	3-5mg/kg/day	8 hrs
6month-6year	5-15 mg/kg/day	12 hrs
Pregnancy	5-15 mg/kg/day	12 hrs

FACTORS AFFECTING PHENYTOIN PLASMA CONCENTRATION:

- Liver disease
- Hypoalbuminaemia
- Displacement from protein binding
  eg. Aspirin, sodium valproate
- Drug interactions

Inhibition of metabolism	Stimulation of metabolism
Amidarone	Carbamazepine
Allopurinol	Chlordiazipoxide
Anti TB drugs	Diazepam
Cimitidine	Dexamethazone
Chlorpromazine	Rifampin
Disulfiram	Phenobarbitol
H2-antagonists	Lamotrigine
Sulfonamides	Nagabine
Anticoagulants	Topiramate

Q. write TDM for methotrexate and lithium

Methotrexate

→ It's an antimetabolite, antifolate drug which is mainly used for the treatment of cancer, autoimmune disease like rheumatoid arthritis, immunosuppresent

pharmacokinetics parameters and TDM information

Parameters	Values
I) Normal elimination	I) 10 μmol (24 hrs post dose) II) 1 μmol (42 hrs post dose) III) 0.2 μmol (72 hrs post dose)
II) plasma protein binding	I) 35 %
III) platelete count	I) 140 - 400 $X 10^3 mm^3$
IV) Serum creatinine	I) 0.6 - 1.3 mg/dl
V) volume of distribution	I) 6-7 litr/kg
VI) Therapeutic range	I) 50 - 300 ng/ml in plasma
VII) Bioavailability	I) 20-50 %
VIII) Complete blood Count with differentiate	

(A) Complete blood count

i> Haemoglobin	i> 12 - 16 g/dL (female) ii> 14-18 g/dL (male)
ii> Haematocrite	i> 37 - 48%. (female) ii> 40 - 52%. (male)
iii> RBC	i> $4 - 5.6 \times 10^6 mm^3$
iv> WBC	i> $5 - 10 \times 10^3 mm^3$

(B) Differentials

i> neutrophils	i> 45 - 75%.
ii> leucocytes	i) 16 - 45%.
iii> monocytes	i) 4 - 10%
iv> Eosinophils	i> 0 - 7%.
v) Basophils	i> 0 - 2%.

Toxicity :

→ general ADR effect includes Nausea, vomiting, anorexia, megaloblastic anemia, depression

→ The drug is also toxic to bone marrow, epithelium of intestine and cause heamorrhage, decrease in blood

count , Risk of infection

Monitoring guidelines for mtx

-> monitor MTX level according to ~~dem~~si dosing protocol , complete blood count with differentials and ~~complete~~ platelets , liver, renal function tests should be monitored more frequently during initial period or on changing the dosage

factors affecting plasma level of MTX

① Food : High fatty meal ↑ plasma level of MTX
low " " ↓ " "

② Age : plasma level in children below 10 years may be decreased because they have increased volume of distribution and faster body clearance

③ Drugs :-> mainly anticonvulsant ↓ mTx level (eg: Carbamazepine , Phenytoin)
-> other drugs also decrease MTX level
eg: Rifampicin , sulfonamide

LITHIUM

Absorption : Lithium is well absorbed orally

Distribution:

- Distribution is slightly less in patient > 65 years, leading to smaller daily dose requirements than in younger patients.
- is not bound to plasma proteins.
- Lithium crosses the placenta.

Elimination: Lithium exhibits first-order kinetics.

Half-life: In euthymic psychiatric patients, it is estimated to range from 15-55 hrs.

In manic patients with normal renal function, the half-life ranges from 8 to 64 hrs.

Prophylaxis:

- 0.45 to 0.59 meq/L based on single daily dosing, this level is preferred because lower adverse effects at this level enhance compliance.
- A level of 0.8 to 1.0 meq/L is indicated for patients > 65 yrs old.

Lithium prospective dosing –P kinetic method:

- A linear relationship exists between concentration in serum or plasma at steady state and a single lithium concentration at some time after a dose of lithium carbonate.
- Equation can be utilized to dose lithium prospectively for which C is the steady state lithium concentration at the 12 hrs post-dosing period for an 1800 mg/day dose and C 24 hr serum lithium concentration following an initial 1200mg dose. The dosing nomogram can be utilized in place of equations.

  $C_{ss}12h = 0.13+3.3(Cx24)$

Sampling:

- Therapeutic lithium levels are based on the serum sample obtained in the morning 12 hrs after the last dose.
- Acutely manic patients require and tolerate higher lithium doses due to an increased lithium clearance.
- Frequently lithium levels, normally drawn twice weekly are required in the treatment of an acute manic episode because of the

Therapeutic levels:

→ *Acute mania*: 0.9 to 1.4 meq/L

- Patients with concentration > 1.4 meq/L experience no greater improvement in their manic symptoms than patients with Lower serum lithium concentration.
- Patients with serum lithium concentration < 0.9 meq/L generally do not experience complete remissions.

Specimens, collection methods and assays of lithium:

- Serum sample should be rejected if there is any evidence of hemolysis since release of high concentration of lithium from the red blood cells will artifactually raise the serum concentration.
- To minimize the chance of hemolysis, serum should be separated from the red blood cells within 1 hr of collection.
- Lithium in serum or plasma is stable at room temperature or refrigeration temperature for extended periods of time.
- Lithium erythrocyte concentration has been proposed to correlate better with response and toxicity since it represents intracellular lithium.
- Saliva concentration of lithium have been proposed as noninvasive substitutes for serum or plasma lithium concentration.
- Flame emission photometry and atomic absorption spectroscopy are still the most commonly used methods for lithium quantization, accuracy and low interferences.
- ~~Ion-Selective Electrode (ISE) methods are more rapid and less costly but may have problems with interference.~~

Q. explain various factors in individualization of dosage regimen

INDIVIDUALIZATION OF DOSAGE REGIMEN

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

Factors:

1. Age:

- The factors that affect drug absorption, including gastric pH, gastric emptying, intestinal motility , and blood flow change with age
- Thus, in the neonate a condition of achlorhydria persists for the first week of life, and only after 3 years of age gastric acid secretion approaches the adult value
- Gastric emptying is also prolonged and peristalsis is irregular during the early months of life
- Skeletal muscle mass is also much reduced, and muscle contractions, which tend to promote both blood flow and spreading of an intramuscularly administered drug, are relatively feeble
- An elevated gastric pH, a delay in gastric emptying, and both diminished intestinal motility and blood flow are also seen in the elderly
- Differences in drug absorption among adults, the very young and the elderly, are therefore expected
- Generally, changes in rate rather than in extent of absorption are found
- These changes tend to be less apparent in the elderly than in the very young
- Children often appear to absorb drugs as completely and, if anything, more rapidly than adults

- Accordingly, in subsequent calculations of dosage, extent of absorption is assumed not to vary with age
- A major exception is for some first-pass drugs given to the elderly, where oral bioavailability increase with age
- The half life is shortest around 1 year of age; it is longest in both newborn and elderly patients
- In premature newborns, the urinary excretion is even more depressed per kilogram of body weight than in full-term neonates
- Metabolic activity may take months to mature, the time required for full maturation varies with the enzyme system
- A decrease in unbound metabolic clearance in the elderly patient has been demonstrated for an increasing number of drugs, especially, those principally by oxidation
- These changes may be associated in part, with the decrease in the size of the liver, as a proportion of body weight, from 2.5 % in the young adult to 1.6 % at 90 years of age

2. 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

3. Gender:

- Genetic and physiological differences between men and women can influence both PK and PD
- For example, many genes on the Y chromosome, which are expressed only in males, have no counterpart on the X chromosome
- The Y chromosome has genes involved in basic cellular function and some genes on the X chromosome are expressed at higher levels in females
- Gene expression and regulation are likely to be influenced by hormonal differences between males and females
- Genomic imprinting, body size, organ size, body fat, ADME can also affect pharmacological outcome
- Other factors such as gastrointestinal transit time, liver enzyme function and urinary creatinine clearance are influenced by both age and sex
- Across the path of a woman's life it is necessary to consider the stages of ovarian function to appreciate the potential for drug, sex, and age interactions as they influence rational drug therapy Use of oral contraceptives and hormonal changes which occur throughout the menstrual cycle influence pharmacological results.
- Necessary considerations during pregnancy are alterations in body composition, cardiac output, pulmonary and renal function as well as changes in immune and gastrointestinal systems
- In menopause, the ovaries, uterus, urinary tract, hypothalamus, cardiovascular systems, and liver are some of the tissues, organs or systems which are altered by the loss of estrogens, androgens, and progestagens
- These hormonal changes are also associated with the expression of different diseases after menopause

4. Genetics:

- Genetic polymorphism that lead to the production of isoenzyme with reduced or no activity of to multiple copies of an enzyme with high activity make a major contribution to the variability in the dose requirements of drugs that eliminated by hepatic metabolism
- Cytochrome P450 (CYP 450) enzymes, P – 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)

5. 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 Vd 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

6. 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 form 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. Dosage adjustment in Renal Failure (general approach)

Dose Adjustment in Renal Failure

Generally speaking, drugs in patients with renal impairment have altered pharmacokinetic profile. Their renal clearance and elimination rate are reduced, the elimination half-life is increased and the apparent volume of distribution is altered. Thus, dose must be altered depending upon the renal function in such patients. However, except for drugs having low therapeutic indices, the therapeutic range of others is sufficiently large and dosage adjustment is not essential.

→ *Dosage regimen need not be changed* when

- The fraction of drug excreted unchanged, f_u is ≤ 0.3,
- The renal function RF is ≥ 0.7 of normal.

→ The above generalization is based on the assumption that the metabolites are inactive and binding characteristics and drug availability are unaltered and so is the renal function in kidney failure conditions.

→ When the f_u value approaches unity and RF approaches zero, elimination is extremely slowed down and dosing should be reduced drastically. The significance of nonrenal clearance increases in such conditions.

→ The required dose in patients with renal impairment can be calculated by the simple formula:

$$\text{Drug dose in renal impairment} = \text{Normal dose} \times \text{RF} \qquad (6.20)$$

→ The dosing interval in hours can be computed from the following equation:

$$\text{Dosing interval} = \frac{\text{Normal interval in hours}}{\text{RF}} \qquad (6.21)$$

→ When the drug is eliminated both by renal and nonrenal mechanisms, the dose to be administered in patients with renal failure is obtained from equation .

$$\text{Drug dose} = \text{Normal dose} \left[\begin{array}{l} \text{RF} \times \text{Fraction excreted in urine} + \\ \text{Fraction eliminated nonrenally} \end{array} \right] \qquad (6.22)$$

→ There are two additional methods for dose adjustment in renal insufficiency if the Vd 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 renal function normal

→ The adjustment are based on:

1. **Dose adjustment based on total body clearance :** Rewriting equation 12.6, the parameters to be adjusted in renal insufficiency are shown below:

$$C_{ss,av} = F \times \frac{1}{Cl_T} \times \frac{X_0}{\tau} \qquad (12.6)$$

↑	↑	↑	↑
to be kept normal	assumed constant	decreased due to disease	needs adjustment

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

$$C_{ss,av} = \frac{X_0}{Cl_T \tau} = \frac{X_0'}{Cl_T' \tau'} \qquad (12.24)$$

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

$$\frac{X_0'}{\tau'} = \frac{Cl_T' X_0}{Cl_T \tau} \qquad (12.25)$$

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

2. **Dose adjustment based on elimination rate constant or half-life :** Rewriting equation 12.7, the parameters to be adjusted in renal insufficiency are:

$$C_{ss,av} = \frac{1.44\,F}{V_d} \times t_{1/2} \times \frac{X_0}{\tau} \qquad (12.7)$$

↑ to be kept normal; ↑ assumed constant; ↑ decreased due to disease; ↑ needs adjustment

If $t_{1/2}'$, X_0' and τ' represent the values for the renal failure patient, then:

$$C_{ss,av} = \frac{t_{1/2}\,X_0}{\tau} = \frac{t_{1/2}'\,X_0'}{\tau'} \qquad (12.26)$$

Rearranging the above equation in terms of dose and dose interval to be adjusted, we get:

$$\frac{X_0'}{\tau'} = \frac{t_{1/2}\,X_0}{t_{1/2}'\,\tau} \qquad (12.27)$$

Because of prolongation of half-life of a drug due to reduction in renal function, the time taken to achieve the desired plateau takes longer, the more severe the dysfunction. Hence, such patients sometimes need loading dose.

Q. different methods of extracorporeal removal of drugs

EXTRACORPOREAL METHODS OF DRUG REMOVAL

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

Objective:

To remove rapidly the undesirable drugs and metabolites from the body without disturbing the fluid and electrolyte balance in the body

Methods ~~available for drug removal~~

1. Hemodialysis
2. Peritoneal dialysis
3. Hemofiltration
4. Hemodiafiltration
5. Hemoperfusion

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

Concentration

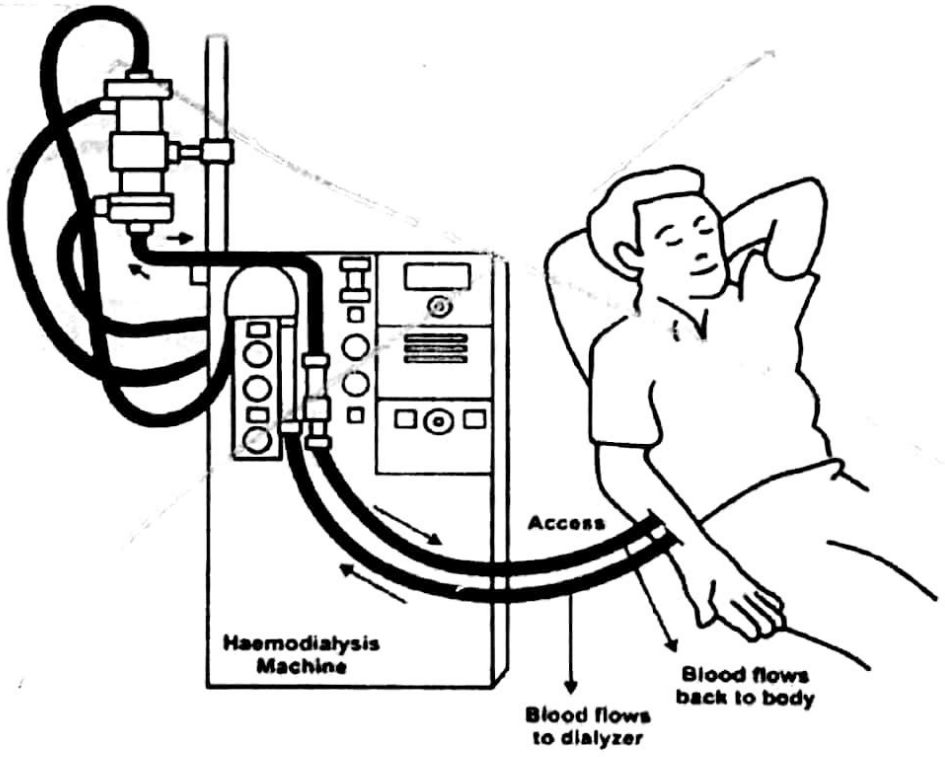
1. HEMODIALYSIS:

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

Principle: involves diffusion of soiutes across a semipermeable membrane

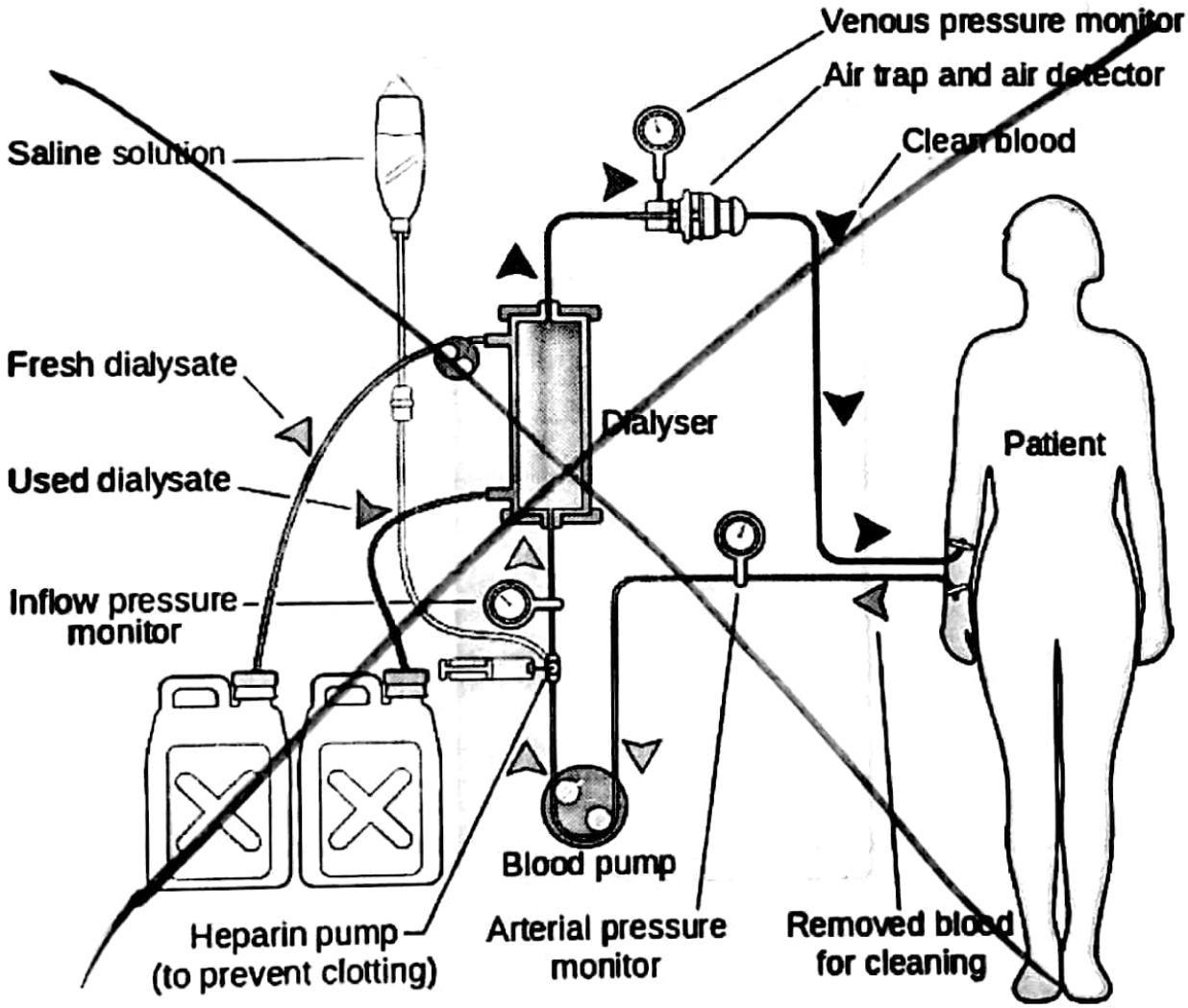
How Does Hemodialysis Work?

- A dialysis machine pumps small blood out of the body, mixed with anticoagulant and circulated through a filter called dialyzer.
- inside the dialyzer, a porous artificial membrane separates blood from the dialysis fluid (dialysate)
- diffusion of extra fluid and wastes from the blood into the dialysate
- purified blood is then pumped back into the body.



- Membrane is permeable to water and small ions but is impermeable to blood cells,lipids, or plasma proteins
- utilizes counter current flow,ie. dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit.

- Counter-current flow maintains the conc. gradient across the membrane at a maximum and increases the efficiency of the dialysis.
- Pressure in the dialysate compartment is lower than blood compartment



TYPES OF HEMODIALYSIS ACCESS

For temporary access

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

For permanent access

- An arterio-venous fistula or graft is created by a surgical procedure

How is blood removed and replaced?

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

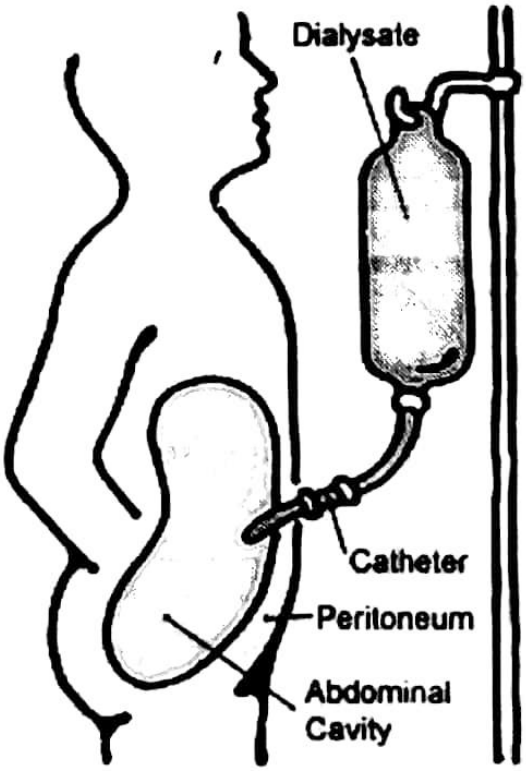
Types of hemodialysis

- conventional hemodialysis
- daily hemodialysis
- nocturnal hemodialysis

2. 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.

Techniques used for peritoneal dialysis

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

Manual intermittent peri.dialysis

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

Automated cycler intermittent peri.dialysis

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

Continuous ambulatory peritoneal dialysis

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

Peritoneal Dialysis solution

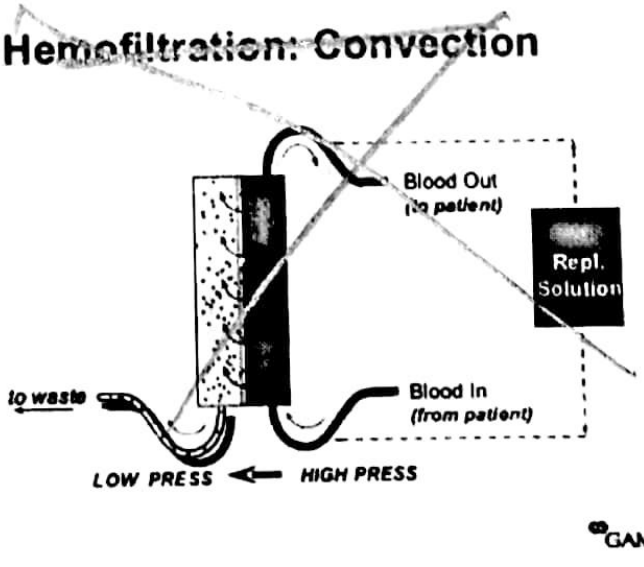
- Sodium chloride 5.6g
- Calcium chloride 0.26g
- Magnesium chloride 0.15g

- Sodium lactate 5.0g
- Anhydrous glucose 13.60g
- Water for inj. To 1000ml

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

3. HEMOFILTRATION

- Convective solute transport ie. Movement of dissolved substances with fluid flow through filtering membrane
- blood is passed through a set of tubing
- (a *filtration circuit*) via a machine to a semipermeable membrane (the *filter*) where waste products and water are removed.
- Replacement fluid is administered to the patient for volume replacement
- purified blood is returned to the patient



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

Types of hemofiltration

Continous veno-venous hemofiltration

hemofilter is placed between cannulated femoral, subclavian or internal jugular veins

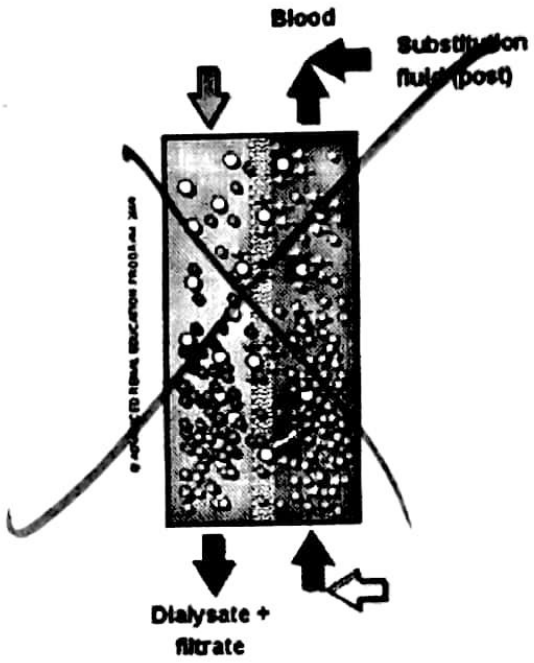
Continous arteriovenous hemofiltration

blood passes through a hemofilter that is placed between a cannulated femoral artery and vein

4. HEMODIAFILTRATION

Hemofiltration in combination with hemodialysis

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



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

5) HEMOPERFUSION

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

Q. Various markers used in measurment of GFR with advantage and disadvantage, formula for creatinine clearance

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 GFR

→ -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

- 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 ↓ 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

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.

Creatinine is an endogenous amine produced as a result of muscle catabolism. It is excreted unchanged in the urine by glomerular filtration only. An advantage of this test is that it can be correlated to the steady-state concentration of creatinine in plasma and needs no collection of urine. The method involves determination of serum creatinine levels. Since creatinine production varies with age, weight and gender, different formulae are used to calculate creatinine clearance from the serum creatinine values.

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

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

$= 0.9 \cdot Cl_{cr}$ 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.

A direct method for determining creatinine clearance is determination of the amount of creatinine excreted in urine in 24 hours (to calculate the rate of creatinine excretion) and the mean of serum creatinine from blood samples taken just before and immediately after the urine collection period. Following formula is used:

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

Q. Causes for renal impairment, pharmacokinetic consideration in renal failure patients

Cl.Pharmacokinetics Dosage Adjustment in Renal and Hepatic

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

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

PHARMACOKINETIC CONSIDERATIONS in Renal disease

→ 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

impairment may be found in various reference books, such as the *Physicians' Desk Reference*, and in the medical literature.)

Causes for Renal impairment:

- Blood or fluid loss
- Heart attack
- infection
- liver failure
- use of Aspirin, ibuprofen
- Hypertension
- DM
- hypovolemia
- Nephrotoxic drugs
- Neophroallergens
- Pyelonephritis
- Kidney stone
- enlarged prostate
- Lupus
- Chemotherapy drugs
- drugs and alcohol

Q. various factors for hepatic impairment, pharmacokinetic consideration in hepatic disease patient

Cl.Pharmacokinetics **Dosage Adjustment in Renal and Hepatic**

Because continuous replacement therapies are hemofiltration methods, replacement fluid must be administered to the patient to replace fluid lost to the hemofiltrate, though the volume of fluid removed can be easily controlled compared to intermittent hemofiltration. Heparin infusions are also provided for anticoagulation.

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.

Causes of hepatic impairment

- certain prescription medicine
- some herbal supplement
- toxins
- viral infection (hepatitis A, B, C)
- certain Autoimmune disease
- chemicals
- metabolic disturbance
- immune System abnormality

- Genetics (wilson's disease)
- Cancer
- Chronic alcohol abuse

Q. Discuss genetic polymorphism in drug transports and drug target with example

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

→ *Transporterpharmacogenetics* is a rapidly developing field that is concerned with drug uptake and efflux into or through tissues. Significant problems in the clinical application of drugs result from poor or variable oral drug bioavailability, and high intra- and interindividual variation in pharmacokinetics. Several membrane transporter proteins are involved in the absorption of drugs from the intestinal tract into the body, into nonintestinal tissues, or into specific target sites of action.

→ *Drug efflux* is an important cause of drug resistance in certain types of cells. In cytotoxic chemotherapy for several human cancerous diseases, drugs are generally very effective, but in the case of *intrinsic* or *acquired multidrug resistance*, usually highly effective antineoplastic compounds, eg, vincristine, vinblastine, daunorubicin, or doxorubicin, fail to produce cures. One of the major causes of such multidrug resistance is the appearance of special integral membrane proteins, the *P-glycoprotein multidrug transporter*, or MDR1, which is one of the major causes of low drug level in targeted cells. P-glycoprotein is discussed in .

→ The multidrug resistance-associated proteins (MRPs) are members of the ATP-binding cassette (ABC) superfamily with six members currently, of which MRP1, MRP2, and MRP3 are commonly known to affect drug disposition. MRP1 is ubiquitous in the body. Substrates for MRP1 include glutathione, glucuronide, and sulfate. MRP1 is expressed basolaterally in the intestine,

although its role in extruding drugs out of the enterocytes is still uncertain. There is some substrate overlap between MRP1 and apically located P-glycoprotein. The aminoacid homology between MDR1 and P-glycoprotein was reported to be 15% in some cell lines.

GENETIC POLYMORPHISM IN DRUG TARGETS

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

Clinically Important Genetic Polymorphisms of Drug Targets and Drug Transporters

Gene	Frequency	Drug	Drug Effect
Multidrug resistance gene (*MDR1*)	24%	Digoxin	Increased concentrations of digoxin in plasma
Beta-2 adrenergic receptor gene (*2AR*)	37%	Albuterol	Decreased response to Beta-2 adrenergic agonists
Sulphonylurea receptor gene (*SUR1*)	2â€"3%	Tolbutamide	Decreased insulin response
Five genes coding for cardiac ion channels	1â€"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. genetic polymorphism of cytochrome P-450 isozymes on drug metabolism

GENETIC POLYMORPHISM IN DRUG METABOLISM: CYTOCHROME P450 ISOZYMES:

(1) 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.

(2) **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.

(3) **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 ([redacted]) were found to be overrepresented in patients stabilized on low doses of warfarin. These patients had an increase incidence of major and minor hemorrhage.