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* Common Question.

1. Explain Bayesian theory in detail ~~(S-22, W-22~~ S-22 1a, W-22 2b, S-23 4C.

2. Role of pharmacist in clinical p'kinetic. S-22 1b, ~~c~~

3. ~~Population p'kinetic (S-22 1c,~~

3. Significance of population p'kinetic (S-22 1c)

~~Define population p'kinetic. Explain NOMENCLATURE~~

- Explain the Sampling design used in population kinetic study (W-23 1c)

- Define population p'kinetic (S-23 6b)

4. Explain p'kinetic correlation in drug therapy. S-22 2a.

- Define clinical p'kinetic. write S.N on p'kinetic parameter affecting drug action. (W-22 1a)
- Give importance of clinical p'kinetic S-23 - 4b

5. Write about determine of dose & dosing interval S-22 2b, W-22 4C → (Small 4a unit.

6. Indication of TDM S-22 2c, W-22 3c, S-23 7c. written before.

Written before

7. Inhibition of Biliary Excretion (S-22 3a, W-22 3b,

8. Note on enzyme inhibition (S-22 3b,

9. IV to oral (S-22 3c, W-22 5a, S-23 3a)

10. Explain TDM in drug in CVS (S-22 4a, S-23 1b)

11. Define pharmacogenetic & it application (S-22 4b) (S-23 7b)

- Importance of genetic Polymorphism of CYP isoenzyme P450 & example W-22, 2a (S-22 7a)

12 TDM of carbamazepine (S-22 4c)
" " Cyclosporine & carbamazepine (W-22, 1b)
" " Na^+ valproate & lithium (W-22 3c)

13 Write in detail drug dosing in obese patient S-22 5a,

- Obese & Geriatric patient (W-22 7a).
- BEER's criteria used in geriatric patient (S-23 2c)

14 Drug interaction at elimination site (S-22 5b)

15. Note on effect of hepatic diseases (S-22 5c)

- Enlist various factor for hepatic ~~diseases~~ impairment. Discuss in detail p'kinet in hepatic diseases (W-22 1 5c).
- Hepatic clearance (S-23, 3c)

16. Explain detail about role in genetic polymorphism in drug target (S-22 6a)
- Genetic polymorphism in drug transport & target (W-22 5b), S-23 5a)

17. Cristi-Hoyton dosage adjustment in uremic patient (S-22 6b, W-22 7b)

18 Extracorporeal removal of drug (S-22 6c) (W-22 7c). (S-23 1c)

19. <-7a

20 Analysis of population P'kinetic (S-22 7b)
- NONMEM method (W-22 3a)

21 Dosage adjustment in renal diseases (S-22 7c). S-23 4a.

Different.

W-22

2c Explain influence of drug interaction in metabolism phase ε example
- Discuss drug interaction to protein binding & metabolism (S-23 2a)

4b what is clearance? Explain relation ε Drug dose & AUC.
= ~~Creatinin clearance S-23 7a~~

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6(a) Various marker used to measure GFR, Advantage & disadvantage & measure for CR clearance
S-23 Q9)

6(b) Nomogram S-23 Q9

S-23

2b) Factor for individualize dose - dosage regimen.

5b Define interindividual variation.

W-22

Q.7(c) Detail: Different method of extracorporeal removal of drug

Pg. 62.

Alternatively, if the normal total body clearance, Cl, and fe are known, the above equation is modified after substitution as

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

5.8.1 THE WAGNER METHOD

The method for renal dose adjustment discussed in the previous sections all 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 be assumptions, the equations should be demonstrated as statistically reliable in practice. A statistical approach was used by 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 previous edition.

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

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

5.9 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

5.9.1 OBJECTIVE

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

5.10 METHODS AVAILABLE FOR DRUG REMOVAL

- Haemodialysis
- Peritoneal dialysis
- Hemofiltration
- Hemodiafiltration
- Hemoperfusion

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

5.10.1 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 solutes across a semipermeable membrane

How Does Haemodialysis Work?

- A dialysis machine pumps small blood out of the body, mixed with anticoagulant and circulated through a filter called dialyzer. blood
- Inside the dialyzer, a porous artificial membrane separates blood from the dialysis fluid
- Diffusion of extra fluid and wastes from the blood into dialysate
- The 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.

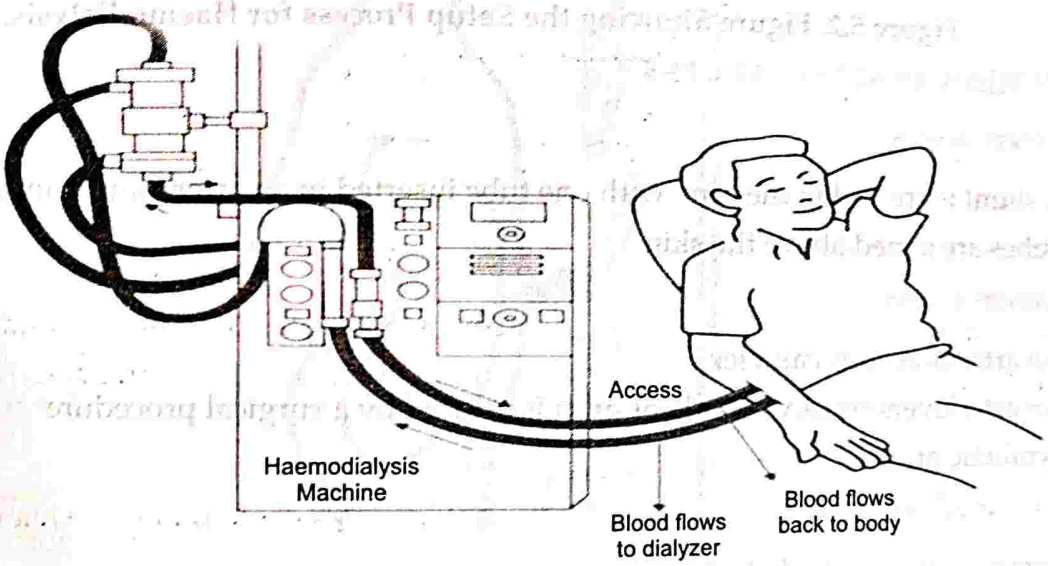

Fig 5.1: Figure Showing The working of Haemodialysis.

- 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

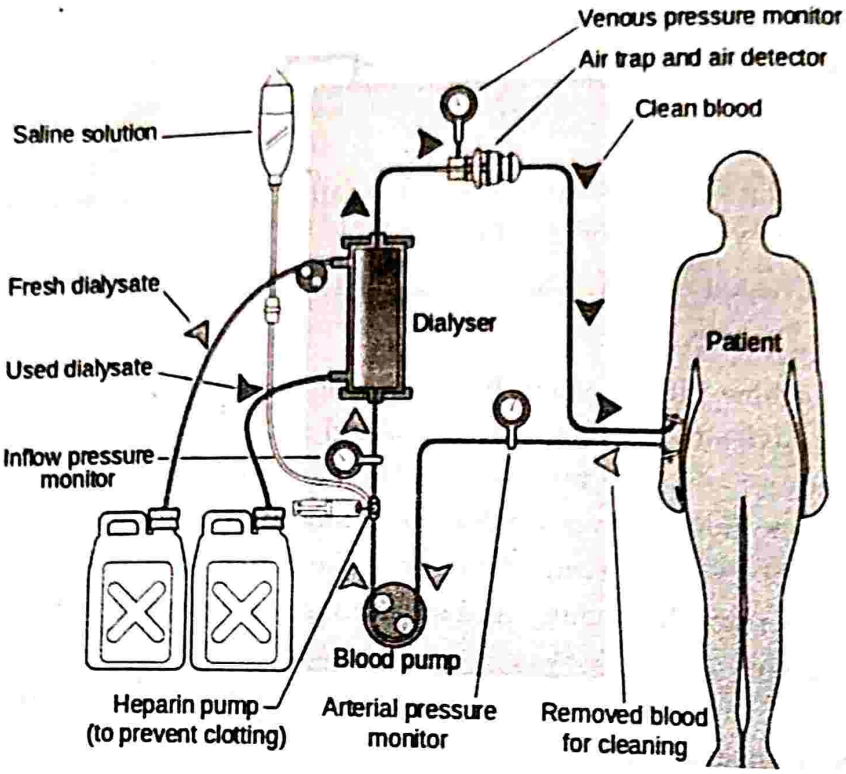

Figure 5.2: Figure Showing the Setup Process for Haemodialysis.

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 catheter
- An arteriovenous (AV) fistula or graft is created by a surgical procedure
- synthetic graft

Types of haemodialysis

- conventional haemodialysis
- daily haemodialysis
- nocturnal haemodialysis

Conventional haemodialysis

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

Daily haemodialysis

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

Nocturnal haemodialysis

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

Applications

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

5.10.2. 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

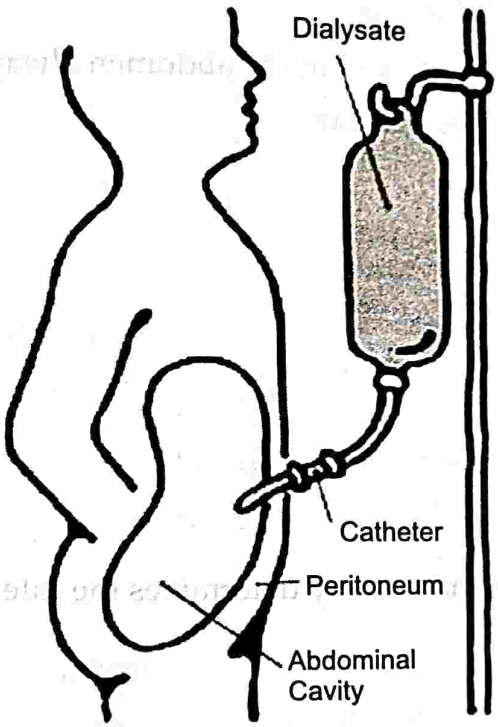

Figure 5.3: Figure Showing Peritoneal Dialysis.

- The process uses the patient's peritoneum in the abdomen and dissolved as a membrane across which substances (electrolytes, urea, glucose, albumin, and other small molecules) are exchanged from the blood. fluids movement of formed
- Membrane restricts the elements (e.g. erythrocytes) and large molecules (e.g. protein) but allows the movement of smaller molecules according to the concentric. Gradient.

Techniques used for peritoneal dialysis

- Manual intermittent peri. Dialysis
- Automated cycler intermittent peri. Dialysis
- Continuous ambulatory peritonealdialysis

Manual intermittent peri. Dialysis

Bags containing fluid are warmed to body temperature; 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 always
- 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 100oml

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

5.10.3. HEMOFILTRATION

- Convective solute transport i.e. 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.

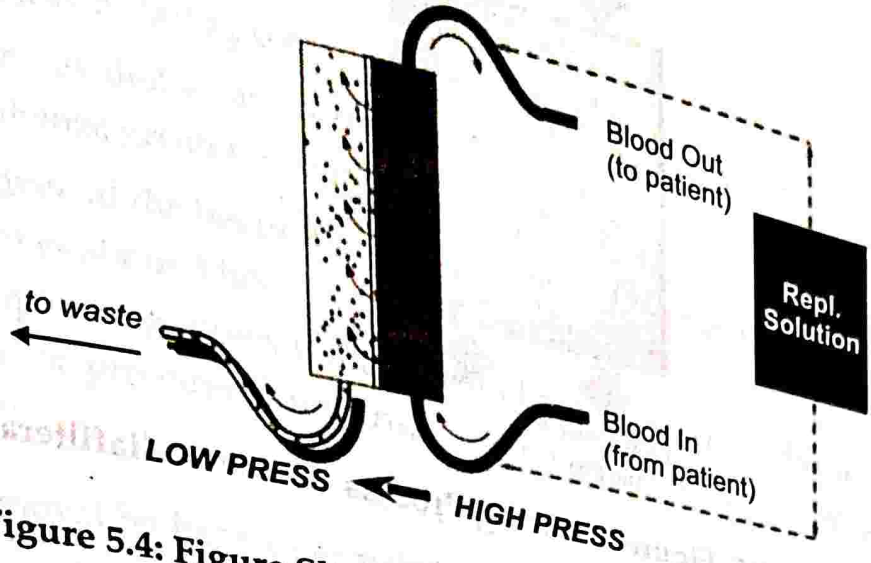

Figure 5.4: Figure Showing the Process of Haemofilteration

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

Types of hemofiltration

Continuous veno-venous hemofiltration

haemofilter is placed between cannulated femoral, subclavian, or internal jugular veins.

Continuous arteriovenous hemofiltration blood passes through a haemofilter that is placed between a cannulated femoral artery and vein

5.10.4 HAEMODIAFILTRATION

Hemofiltration in combination with haemodialysis .

- 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

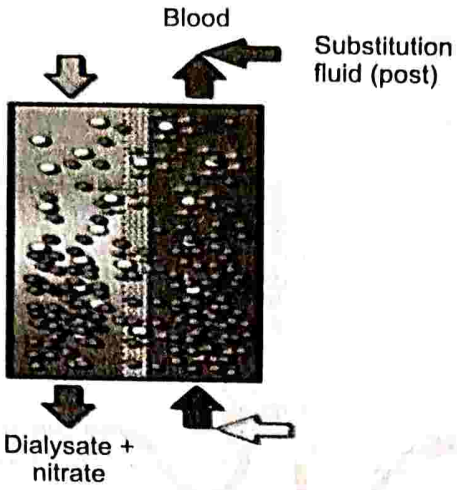

Figure 5.5: Figure Showing Process of Haemodiafilteration

- Access is achieved through a catheter
- Good removal of both large and small mole.wgt solutes

Q.4.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 flowOut of the column

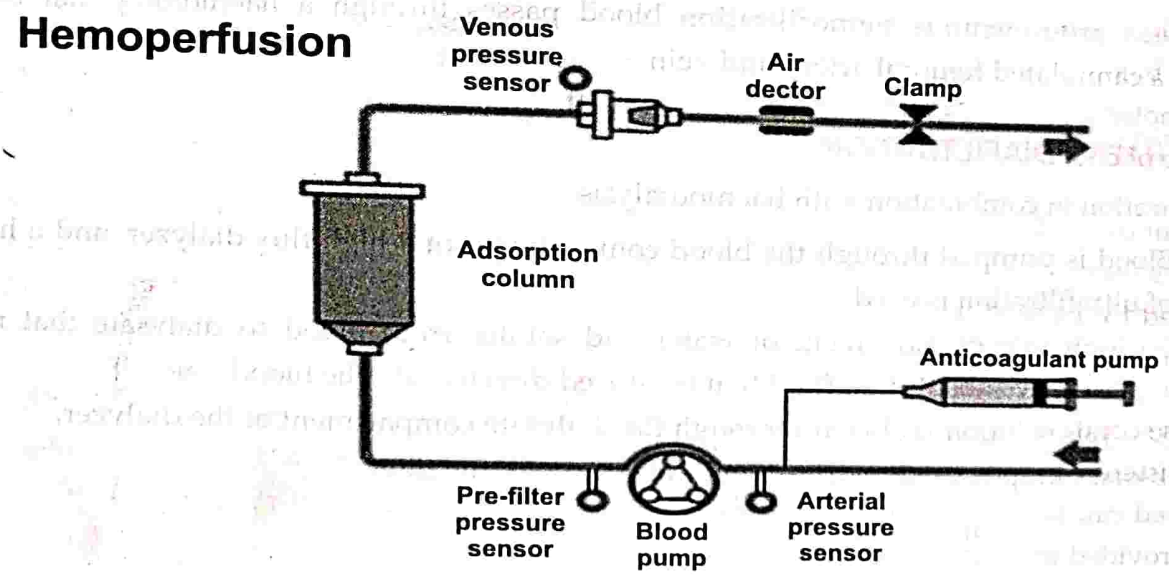

Figure 5.6: Figure Showing Hemoperfusion

Adsorbents used:

a. Activated charcoal

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

-Activated charcoal adsorbs both polar and nonpolar drugs

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

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

Factors for drug removal by haemoperfusion:

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

Q7(b) Note on Giusti-Hyton method for dosage adjustment in uremic patient

→ Dose adjustment for drug in uremic or renally impaired patients should be made in accordance ~ changes in p'dynamic & p'kinetics of the drug in individual patient.

→ Whether renal impairment will alter p'kinetic of the drug enough to justify dosage adjustment is a an important consideration.

→ Active metabolites of drug may also be formed & must be considered for additional pharmacologic effect when adjusting dose.

→ The dosage adjustment for Uremic Patients are done by 3 methods

- Nomogram - Chennavasin, Welling
- Giusti - Hoyton Method.
- General Clearance Method.
- The Wagner Method.

uremic dose = $\frac{Kq}{Kn} \times$ Molar

① Cristi Haytom method.

⇒ It is also known as the Cristi-Hayton equation.

⇒ It is a PK kinetic dosing method used for adjusting drug dosages in patients c renal impairment, particularly those c uremia.

⇒ This method provide a simple yet effective approach to modify drug doses based on patient's renal function.

* Principle of Cristi - Hayton Method.

1. Renal function Assessment :-
   - The Cristi - Hayton method relies on estimating the patient's renal function, typically determined by measuring creatinine clearance (CrCl) or calculating estimating eGFR using equation like Cockcroft - Gault formula.

2. To categorize patient based on renal impairment

3. Drug dosage adjustment :- The Cristi - Hayton Equation provide formula to dosage adjustment.

- The Giusti - Hayton equation is

$$C_R = 1 - fe\left[1 - \frac{CL_{CT}^{U}}{CL_{CT}^{N}}\right]$$

Here C_R is Giusti - Hayton symbol also it written as.

$$C_R = \frac{K_U}{K_N} = 1 - fe\left[1 - \frac{CL_{CT}^{U}}{CL_{CT}^{N}}\right]$$

where, K_U is uremic elimination rate constant.

K_N is normal renal excretion rate constant.

f_e is drug excreted in unchanged form

CL_{CT}^{U} uremic creatinine clearance

CL_{CT}^{N} Normal creatinine clearance.

* Application

① Assessment of Renal function

② Categorization of Adjusted dose

③ Calculate dosing.

④ Clinical monitoring.

* Advantage.

① Simplicity

② Individualization

③ Safety.

④ Cost effective

* disadvantage

① limited Validation

② Resource Intensive

③ Time consuming

④ Variability in Renal function.

Q7(a) Dosage regimen for Obese & Geriatric patient.

ω The geriatric population is often defined as patient who are older than 65 year.

ω There is an increasing number of people who are living more than 85 year.

as older elderly population

- Aging process is more associated w physiologic changes during aging rather than purely chronological age.
- There are 3 categorys in geriatric population according to age

① 65 - 75 → young old

② 75 - 85 → old.

③ 85 & more → very old.

- The elderly population tend con multiple drug therapy due to concomitant illness

- Yes cognitive function in some geriatric lead to complicated drug schedule

↓

Higher drug therapy cost

↓

Poor drug compliance

↓

Yes drug efficacy

↓

Possible drug toxicity or multidrug regimen

→ P' kinetics.

① Absorption :- This include

- A decline in splanchnic blood flow.
- Altered GI Motility
- ↑es gastric pH
- Alteration in GI absorptivity surface

ii) The incident of Achlorhydria effect disab of weak bases drug in geriatric patien

② Distribution : Bind to protein decrease due to decrease in albumin conc^n.

ii) The apparent Vd may change due to ↓ decrease in muscle mass & ↑es body fat.

③ Metabolism

ii) Decrease in hepatic cell & blood flow.

iii) Drug biotransformation may decrease ↓ age

④ Excretion.

ii) Renal drug excretion - generally decline ↓ age as result of decrease in the GFR and/or tubular secretion.

iii) ↓es in number of receptor which will change in receptor binding process.

iii) Organ specific changes.

iv) Changes in baroreceptor sensitivity.

Further in notes of these.

13 Note on drug dosing in obese patient.

⇝ Obesity has been associated ē HTN, Arthroe- CAD, Diabetes etc. in compare ete nonobese patient.

⇝ Patient or person consider obese if actual body weight exceeds ideal or desirable weight by 20%.

⇝ The ideal or desirable body weight are based on avg body weight & height of males & female of same age.

⇝ Obesity also defined by BMI body mass index, a value that normalized body weight based on height.

⇝ BMI unit is kg/m^2.

⇝ It equation is

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

⇝ By two main content the dosing depends
(a) Body composition & drug clearance
(b) Volume of distribution.

(a) Body Composition & drug clearance :- It changes with body weight.

- Normal patient house 4:1 ratio of lean to adipose body weight.

- In obese patient adipose weight increase by 20-40% & ratio of lean : adipose become 3:2.

- Clearance represent capacity of body to metabolise & excrete drug.

- Clearance correlate to lean weight rather than adipose weight.

- When lean weight increase, the clearance Yes & finally the dose should be increased.

(b) Volume of distribution :- It related the structural aspect of body.

- Hydrophilic drug have high plasma conc^n, & low volume of distribution

- lipophilic drug have rapid distribution in adipose tissue thus low plasma conc^n & ↑es volume of distribution

- Here lipophilic drugs, V_d is more likely to relate ∝ TBW.

- Moreover larger V_d requires High loading dose followed by constant dose

12) TDM for carbamazepine

ans It is an iminostilbene derivative related to TCA.

- It is used in tonic-clonic & other seizure
- Generally 4-12 µg/ml is used for t/t

- Need of TDM for carbamazepine is for
  1. Due to binding ∝ albumin & α1-acid glycoprotein (AAP) cause variation in plasma binding among individual.

Q6(c) TDM of Na^+ Valporate & Lithium.

Ans Sodium Valporate :-

- Valporic acid is an anti-convulsant, which is used to treat seizure.
- Sometimes used in combination ± other drug.

* Uses :-
  - Treat various seizure.
  - Treat Manic episode
  - Treat Bipolar disorder.
  - Treat Migraine headache.

* MOA.

(i) Valporic acid ↑es GABA availbility, an inhibitory neurotransmitter

(ii) It may also enhance the action of GABA.

(iii) Valporic acid also block voltage dependent Na^+ channel.

* P'kinetic.

① Absorption

Absorption is rapid.

Oral → 1-3hr.

Meal → 6-8 hr.

Enteric coated → absorbed delay.

② Distribution :-

- Distribution & Protein binding.

$V_d = 0.15 L/kg$.

③ Metabolism

>95% hepatic metabolism.

④ Excretion :-

∴ 1-3% renal excretion.

- Oral clearance is 7-2ml/h/kg.

$t_{1/2}$: 12-18 hours in adult

⑤ ADR/Toxic effect :-

>75mcg/L.	Ataxia, lethargy
>100mcg/L.	Tremor.

⑥ Drug Interaction :-

Phenytoin :- Lamotrigine, rifampin & carbamazepine, Cimetidine.

⑦ Therapeutic range

50 - 100 µg/ml.

30 - 60 µg/ml

55 - 100 µg/ml.

⑧ Toxic range > 100 µg/ml

⑨ Contraindication.
- liver diseases.
- Urea cycle
- known prophriya.
- Pregnancy.

⑩ Assay :- HPLC.

* Lithiums.

w lithium has been used to treat manic episode. since 19th century.

* Uses :-

① Mood stabilizer.
② Manic episode.
③ Bipolar disorder.
④ ~~Acne~~

* MOA :-
w The exact mode of Action of lithium is unknown.

* Pharmacokinetic.

① Absorption :- lithium absorption is rapid & oral bioavailibility is close 100%.

② Distribution :- Vd is 0.7 to 1.0 L/kg
- Not ~~sig~~ significantly protein bound.

⑩ Metabolism :- lithium carbonate is not metabolized before excretion.

⑪ Excretion :- Kidney & feces

* ADR / Toxicity.

① Nausea, diarrhea, polyuria.

② Toxicity :- tremor, nausea, ataxia, reflexes.

③ Non dose :- Diabetes, hypothyroidism, ~~hyperthyroidism~~ hypercalcemia.

* Drug interaction.

→ Diuretic
→ NSAID
→ ACE
→ CCB.

* Therapeutic range.

Acute therapy :- 1500 - 2400 mg/dl.

* Toxic level :- 1.5 mEq/L

* Contraindicator

:- CVS drug, diuretic, dehydration
Renal diseases, sodium depletion.

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* Assay : AAS, flame photometry.

Q6(b) Same S-23 Q1(a)

Q6(a) Various marker used to measure GFR & advantage & disadvantage, formula of Cr clearance

Several drugs and endogenous substance have used as marker to measure GFR.

1. The drug must be freely filtered at glomerules.
2. The drug must neither be reabsorbed nor actively secreted by renal tubules.
3. The drug should not be metabolized.
4. The drug should not bind significantly the plasma protein.
5. The drug should be nontoxic.
6. The drug may be infused in sufficient dose to permit simple & accurate quantitation in plasma & in urine.

* Changes in GFR reflect changes in kidney function that may be determinished in uremic condition.

- Clearance of insulin may be measured by the rate of infusion divided by the steady

State plasma insulin concentration.

⇒ Creatinine is an endogenous substance formed from creatinine phosphate during muscle metabolism.

⇒ Small amount of creatinine may be actively secreted by renal tubules & the values of GFR obtained by creatinine clearance tend the higher GFR measured in insulin.

⇒ BUN is commonly used to diagnosis of renal diseases.

⇒ Renal clearance of urea by GFR & partial reabsorption in renal tubes.

⇒ Hence, the renal clearance of urea is less than creatinine & insulin.

$$GFR = \frac{\text{Urine concentration} \times \text{Urine Flow}}{\text{Plasma concentration}}$$

IMPORTANCE OF GFR MEASUREMENT

In day to day clinical practice an estimation of glomerular filtration rate (GFR) is required for various reasons viz,

a) assessment of renal function.

b) severity of renal disease

c) calculation of proper drug dosage and

d) appraisal of renal involvement in systemic diseases.

METHODS USED FOR MEASURING GFR

I. CLEARENCE METHODS:
   -EXOGENOUS SUBSTANCE
   -ENDOGENOUS SUBSTANCE
II. FROM PLASMA CREATININE
III. BY NEW ENDOGENOUS MARKERS

A) Exogenous Substances

i) Inulin:- (MW 5200 dalton), a polymer of fructose is considered the gold standard for the estimation of GFR. It is freely filtered by glomerulus, and is neither reabsorbed nor secreted by the renal tubules. It is metabolically inert and cleared only by the kidney. It requires constant IV infusion to maintain plasma level and once steady state has been achieved, plasma and timed urine specimen levels are measured. However, analysis of inulin is technically demanding, time consuming, labour intensive, costly and unsuitable for out patient use. The reference ranges for the GFR in normal individuals given by Smith are 88 to 174 ml/min/1.73m^2 for males and 87 to 147ml.min/1.73m^2 for females .

ii)Non-radiolabelled contrast media:- In addition to inulin, radiolabelled contrast media infusion (iothalamate / iohexol) ... been used to measure GFR. One advantage is that urography and an estimation of GFR can be done at a single examination (3). Cumbersome measurement makes it unsuitable for day to day clinical practice.

iii)Radiolabelled compounds:- A number of radiolabelled chelates have been used to assess the GFR in man, as very small non-toxic amounts of the compound can be given and can be measured even at very low concentrations using conventional counters. Amongst these are [^{51}Cr] EDTA, [^{125}I] iothalamate, [^{99}Tc^{m}] DTPA, [^{131}I] Hippuran to mention a few . Disadvantages are that some radiation is administered, radiopharmaceuticals are more expensive, Gamma camera and skilled personnel are needed. Hence these chelates cannot be used routinely to assess GFR.

- **B) Endogenous Substances**

i) Urea (MW 60 dalton) was one of the f... markers for assessing GFR (6) but at present is not used in clinical practice due to several reasons. Urea production is variable and varies with protein intake. It is readily reabsorbed by tubules and again amount of reabsorption is variable. Hydration status of the individual also affects urea clearance markedly, increased plasma levels accompany decreased urine flow in patients with depleted intravascular volume. In addition many substances may interfere with its estimation.

Q7(a) Define CR clearance. Enumerate various formulas used for measurment of creatin clearance

=> The problems of obtaining a complete 24 hr. urine collection from a patient, the time necessary for urine collection, & the analysis time preclude a direct estimation of creatinine clearance.

=> Serum creatinine concentration Cl_s., is most often estimated from the patient's C_{Cr}, Several methods are available for calculation of creatinin clearance from serum creatinine concentration.

-> The more accurate methods are based on patient's age, height, weight & gender.

=> These methods should be used only for patient's ~~age~~ with intact liver function & no abnormal muscle disease, such as hypertrophy or dystrophy.

=> Moreover, most of method assume a stable creatinine clearance.

=> Unit for Cl_{Cr} is ml/min.

→ For adults, the method of Cockcroft and Gault is used to estimate creatinine clearance from serum creatinine concentration.

→ This method consider both the ages & weight of patient.

For males :

$$Cl_{cr} = \frac{[140 - age(year)] \times body\ weight\ (kg)}{72 \times C_{cr}}$$

For females, use 90% of Cl_{cr} value obtained in males.

→ The Sierskark - Nielsen et al give nomogram method to estimates creatinine clearance on the basis of age, weight & Sr creatinine concentration.

→ Cockcroft & Gault compared their method in adult males of various ages.

→ Creatinine clearance estimated by both methods were comparable, both method demonstrated an age related linear decline in Cr excretion which may due to decrease in muscle mass & age.

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- For children, Schwartz gave the method for the calculation of creatinine clearance based on body length & Serum creatinine concentration.

$$Cl_{cr} = \frac{0.55 \times \text{body length (cm)}}{S_{cr}}$$

- The unit is mL/min/1.73m^2
- 0.55 represent a factor used for children aged 1-12 years.
- Traub & Johnson gave nomogram ~~method~~ method for calculating creatinine clearance.
- The nomogram is based on observation from 81 children aged 6-12 yr & requires the patient's height & serum creatinine concentration.

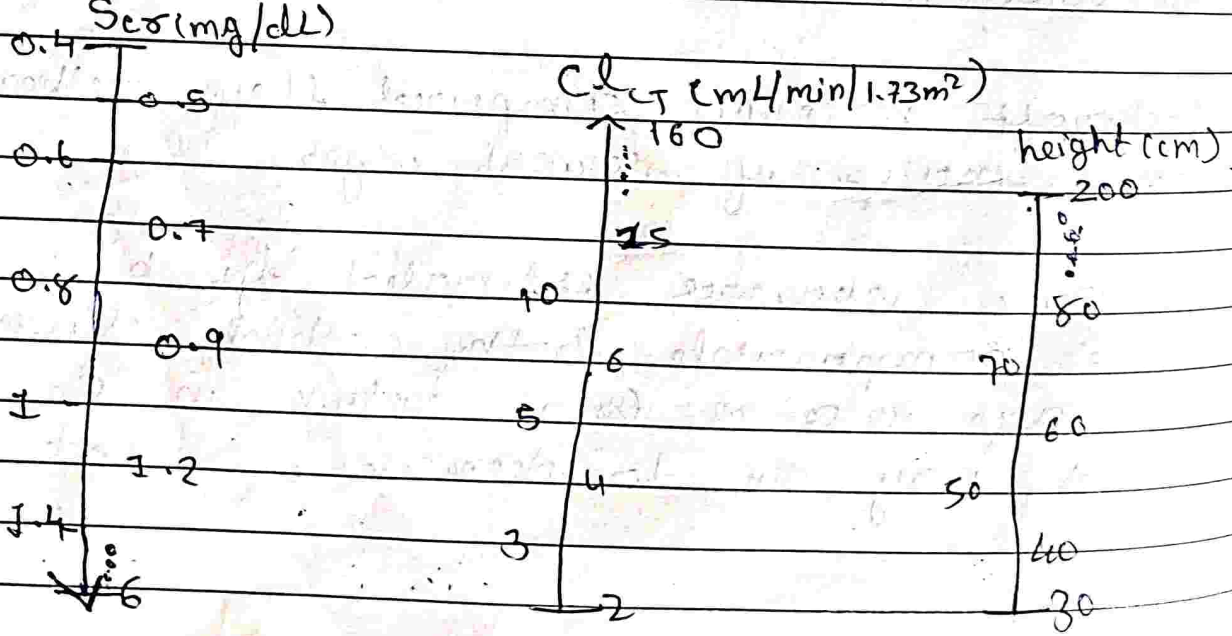

Table 1: Formulas for rapid estimation of Cl_{cr}.

Author(s)		Formula	Units
Cockcroft & Gault (15)	♂	$\frac{(140-age).B.W.}{S_{cr}\ 72}$	ml/min
	♀	Correction factor 0.85	
Hull *et al* (14)	♂	$\frac{145 - age}{S_{cr}} - 3$	ml/min/70kg
	♀	Correction factor 0.85	
Jelliffe (16)	♂	$\frac{100}{S_{cr}} - 12$	ml/min/1.73m²
	♀	$\frac{80}{S_{cr}} - 7$	
Barnesksay *et al* (17)		$\frac{4,420}{P_{cr}} + 88 - age$	ml/min
Salazar & Corcoran (18)	♂	$\frac{(137-age).(0.285.BW).(12.1.Ht^2)}{51.\ S_{cr}}$	ml/min/
	♀	$\frac{(146-age).(0.287.BW).(9.74.Ht^2)}{60.\ S_{cr}}$	

Scr = Serum Creatinine (mg/dl); BW=Body weight (kg); Ht=Height (m)

Measuring Cl_{cr}

- Pediatric equation (0- 1 Year)

$$Clcr = \frac{0.48 * height\ (cm)}{Sr.cr\ (mg/dL)} * \frac{BSA.}{1.73}$$

- Age 1- 18
- $$Clcr = \frac{0.55 * Height\ (cm)}{Sr.cr\ (mg/dL)} * \frac{BSA.}{1.73}$$

III: GFR estimation by new endogeno... markers:-

- **a)** ß2-Microglobulin (M.W 11815 dalton) is filtered at glomerulus like water. Subsequently >99.9% is reabsorbed and degraded in renal tubule. Because it is filtered so readily, its plasma concentration in health is low(average 1.5mg/ L). The plasma concentration increases as the glomerular filteration rate declines reaching about 40mg/l in terminal uremia. The logarithm of the plasma concentration is linearly related to the logarithm of glomerular filtration rate throughout the whole range so that it provides an excellent marker for renal dysfunction. The plasma concentration of ß2-microglobular is not affected by muscle mass nor by sex of individual. As its estimation involves expensive radioimmunoassay it has not yet become more useful in clinical practice. Also in patients with some tumors and inflammatory diseases there may be increase in plasma concentration due to increased production rather than reduced clearance (19).

- **b)** Cystatin C is a 13-KD protease inhibitor which is produced by all nucleated cells and is independent of muscle mass and sex. Its production, unlike ß2-microglobulin is not affected by inflammatory states or malignancies. Cystatin C is eliminated by glomerular filtration and metabolized by proximal tubular cells. Its measurement has been proposed as an alternative and more sensitive marker of GFR than creatinine particularly in patients with slight to moderately decreased GFR .

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25(c) Enlist factor for hepatic impairment. Detail the pharmacokinetic consideration in hepatic diseases.

Ans Factors contributing to hepatic impairment.

1) Liver Disease Etiology :- Various factor can lead to hepatic impairment, include viral hepatitis, Alcoholic liver diseases, etc.

2) Severity of liver Disease :- Severity of hepatic impairment can range from mild to severe, & stages such as compensated cirrhosis, acute liver failure etc challenges in drug therapy.

3) Co-existing Condition :- Patient & hepatic impairment may have comorbidities such as renal dysfunction, CVS diseases, etc.

4) Drug induced liver injury :- Certain medication, herbal supplement or toxin can cause liver damage, leading to hepatic impairment.

5) Alcohol Consumption :- Excessive alcohol consumption is leading cause of liver disease contributing to condition such as alcoholic hepatitis, fatty liver etc.

6) Viral infection :- Chronic viral infections, particularly hepatitis B & C can lead to liver damage & impairment of hepatic function.

7) Metabolic disorder :- Metabolic condition such as obesity, diabetes & dyslipidemia can contribute to the development & progression of hepatic steatosis.

* P'kinetic Consideration :-

① Absorption :- May not directly affect absorption of drug unless drug undergo 1st pass metabolism.

② Distribution :- Alteration in plasma protein binding due to hypoalbuminemia and changes in blood flow affect drug distribution.

③ metabolism :- liver play central role in drug metabolism primarily through cytochrome P450 enzyme system.
- Hepatic impairment can lead to impaired drug metabolism result in ↓ clearance & ↑ systemic exposure to certain drug.

EAPS

PI

④ Excretion :- Drug excreted primarily via biliary route may accumulate in patient z hepatic impairment due to impaired biliary excretion.

- This lead to Tes drug conc" & potential hepatotoxicity.

⑤ Enzyme induction / Inhibition :- liver disease can alter that activity of drug metabolizing enzyme, leading to enzyme induction or inhibition.

⑥ Half-life :- Elimination half life of drug may be prolonged in patient c hepatic impairment due to ~~decrease~~ reduced hepatic clearance

⑦ Pro drug activation :- Antiviral medication or Chemotherapeutic agent require hepatic metabolism for activation. & result in non or partial activation due to hepatic ~~metabolism~~ impairment.

⑧ Individual Variation :- The extent of pk'inetic alteration in hepatic diseases can vary widely among patients based con severity & etiology ~~such~~ as. concl other factors such as.

(a) Nature & severity of

(b) Drug elimination

(c) RoA

(d) Hepatic blood flow

(e) Protein binding

(f) Clearance.

(g) Therapeutic range.

Q5(b) Genetic polymorphis in transport & target

Ans Before in notes.

Q5(a) IV to oral → before in notes

Q4(c) Determining dose & dosing interval → before in notes.

Q4(b) What is clearance? Explain relationship b/w Clearance, Drug dose & AUC

→ Clearance is p'kinetic refers to the rate at which a drug is removed from body, typically expressed as volume per unit time.

- It represent the combined processes of drug elimination, including metabolism, renal excretion, billary excretion etc.
- It defined as the volume of plasma cleared of the drug in a unit time.
- It expressed in ml/min
- Total clearance = $CL_{renal} + CL_{hepatic} + CL_{other}$.

$CL = Vd \times K_{el}$ → elimination rate constant.

$= \frac{Dose}{AUC}$

$= \frac{Dose}{C_p}$ plasma conc^n

- The relationship b/w CL, Drug Dose & AUC are as.

1. Clearance & drug dose :- Clearance play imp role in determining effective concn of drug in body.
- If drug dose ↑es, rate of drug elimination may become saturated if elimination path are limited

2) Clearance & AUC relationship :-

- AUC represent the total exposure of drug in body over time & is influenced by both drug absorption & elimination
- With non linear p/kinetic, clearance may decrease as dose increase due to saturation.

(3) Clearance is inversly affect AUC.

$$Cl = \frac{Dose}{AUC}$$

:- Higher clearance - lower AUC. & vice versa

3) Non linear Pkinetic & clearance :-

- Non linear P'kinetic occur when change in drug conc" are not proportional to changes in dose
- With non linear p'kinetic, clearance may decrease as dose increase due to saturation

(4) Effect of Cl on half life :- Clearance influences the half life of a drug, which represent the time required for the conc" of drug in body to be reduced by half.

- Drug & low clearance have long half-lives because they are eliminated more slowly.

5. Clearance in drug Elimination :-

- Clearance represent the efficiency of drug elimination from body and is essential for maintaining drug conc^{n} within therapeutic range.

6. Clearance in Drug Metabolism & Elimination.

- metabolic clearance involve biotransformation of drug enzymes in liver & other tissue.

- In Excretion, drug undergo both hepatic & renal clearance & relative contribution of each pathway depending on drug's properties & ROA.

Q(a) Classify & explain p'kinetic drug-drug interaction & example.

⇒ P'kinetic is "what body does to drug" ; these interaction occur when one drug alter the conc^{n} of another drug & clinical consequences.

⇒ P'kinetic interaction occur when the ADME or elimination process of object drug is altered by precipetent drug & such interaction called ADME interaction.

- P'kinetic drug interaction identified & classified as.

① Absorption interaction

② Distribution "

③ Metabolism "

④ Excretion "

① Absorption.

- Since the oral route is one of most commonly used to administer drugs, interction influence the absorption.

- The net effect of interaction is

(a) Faster or slower absorption

(b) More or less drug absorption.

- Clinical significance interaction occurs due to factors such as.

① Change in GI pH:- Absorption change due to change in gut pH, lipid solubility & pKa

e.g.
→ H_2 blocker, PPI or antacid change GI pH result in malabsorption of ketoconazole & Itroconazole.

② changes induced by chelation :-

∴ Absorption occur due to formation of insoluble complexes.

e.g. ① Tetracyclin or ciprofloxacin ∓ Ca, Al & Fe
② Penicillamine ∓ Antacid.

③ Changes in GI Motility.

- Alteration of GI emptying time affect

e.g. Propanthelin increase slow dissolving digoxin absorption ↑ by 30%.

② Drug distribution.

→ Major mechanism of drug distribution interaction is alteration in protein drug binding.

e.g. → Interaction due to displacement of one drug by other

e.g. Warfarin ∓ phenylbutazone. as Phenylbutazone displaced warfarin from binding

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③ metabolism

(a) Stimulation of metabolism :- Certain drug stimulate activity of microsomal enzyme which is also called induction of enzyme.

⇒ This induction result in fast metabolism & reduce effect of drug.

e.g Warfarin & phenobarbital.

(b) Inhibition of metabolism :- Certain drug inhibit or prolong the action of enzyme also called inhibition of enzyme

e.g. Alcohol & disulfiram.

④ Elimination Reaction

- Majority of drug excretion are carried out by kidney & liver via bile.

⇒ Drug excreted by kidney involved in drug interaction by change pH, GFR, tubular reabsorption or active secretion

e.g. Probenecid. Ses renal excretion of MXT & Penicillin.

→ Some drug excreted in bile & interaction occur due to alteration of residence time & AUC.

e.g ~~Quinidine~~ Quinidine inhibit or alter Digoxin action.

Q3(c) TDM & it protocol :- Before in notes.

Q3(b) What is Bilary excretion? Explain effect of inhibition of Biliary excretion of drug ? example.

→ Biliary excretion is a crucial pathway for the drug elimination, where drugs & their metabolities are actively transported from hepatocytes into bile & eventually excreted into intestine.

⇒ From intestine, these compound can either be reabsorbed or eliminated via feces, contributing to overall elimination of drug from body

→ Inhibition of bilary excretion can have significant effect on drug disposition & p'kinetic, leading to altered drug conc" in the body & potential changes in therapeutic efficacy or toxicity.

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- Biliary excretion play a crucial role in eliminating drug & their metabolites from body, particularly for compound that undergo extensive hepatice excretion. metabolism

- M.O.A.

- Biliary excretion involve transport of drugs & ether metabolites from hepatocyte into bile canaliculi, ultimately leading to elimination via bile into GI tract.

- This process is mediated by various transporter such as ATP binding cassette, P glycoprotein etc.

- The inhibition of biliary excretion occur via 3 mechanism.

① Competitive inhibition :- Drug or endogenous substance may competitively inhibit the transporter involved in biliary excretion

② Non-competitive inhibition :- Inhibition of transporter function through direct interaction with transporter protein can impair biliary excretion independent of substrate competition.

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② Indirect inhibitor :- Certain drug or compound may induce change in the hepatocyte function or bile composition, indirectly affecting the efficiency of bile excretion pathway.

* Effects of Bile Excretion inhibition.

1. Increased hepatic accumulation
2. Prolonged Systemic Exposure
3. Altered P'kinetic
4. D-D interaction.

	Transporter	Drug	Inhibitor	Result
①	P-gp	Digoxin	Quinidine	↓ bilia excretio
②	MRP 2	SN-38	Probenicid	↓ bile excretion

iv) Example :① Inhibition of BSEP substrate by cyclosporine A lead to ↓ biliary excretio & ↑ systemic exposure of tacrolimus.

v) ② Verapamil & cyclosporin : are both p-gp, but through different mechanism. Verapamil is competitive inhibitor where as

cyclosporin inhibit transport function of substrate

③ Decrease in vincristin clearance in presence of verapamil.

④ Decrease in paclitexal clearance in presence of thromapheere

⑤ Rifampicin enhance the clearance or excretion of digoxin lead to less availability of digoxin for action.

Q3(o). Population Pkinetic. Explain analysis using NONMEM method.

⇒ Population P'kinetic is the study of variability in plasma drug concentration b/w & within patient population receiving therapeutic dose of drug.

⇒ Popk examine the relationship of demographic genetic, pathophysiological, environmental & other drug related factor that contribute to variability observed in safety & efficacy of drug.

⇒ The resolution of issue causing variability in patients allows for the development of an optimum dosing strategy for population, subgroup etc.

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- The importance of developing optimum dosing strategies has led to an increasing in use of PoPk approach in new drug development.

- The non linear mixed effect model (NONMEM) is also called because the model uses both fixed and random factor to describe the data.

- Fixed factor such as patient weight, age, gender & creatinine clearance are assumed to have no error, whereas random factor include inter & intraindividual difference.

- NONMEM is a statistical program written in fortran that allows Bayesian Pkinetic parameter to be estimated using an efficient algorithm called first order (FO) method.

- Multiplicative coefficient or parameters for patient factor may also be estimated.

- NONMEM fit plasma drug concentration data for all subject in the group simultaneously & estimate the population parameter & its variance.

- The model describe the observed plasma drug concentration (C_i) in terms of model with.

1. P_k = fixed effect parameters, which include p'kinetic parameter or patient factor parameters. e.g. P_1 is Cl, P_2 is multiplicative coefficient including creatinine factor, P_3 is multiplicative co-efficient for weight.

2. Random effect parameter: including.

(a) the variance of structral (kinetic) parameter P_k or intersubject variability within the population ω_k^2.

(b) the residual intrasubject variance or variance due to: measurement errors, fluctuation in individual parameter values, and all other error not accounted for the other parameter.

→ One approach is the standard two stage (STS) method, which estimate parameter from the plasma drug conc" data for an individual subject during the 1st stage.

→ Second approach, the first-corder method, is also used but is perhaps less well understood. The estimation procedure is based on minimization of an extended least-square criterion, which was defined through an FO taylor series expansion of response vector about the fixed effect & which utilized a Newton-Raphson like algorithm.

ans) factor include body weight, creatinine clearance & a clearance factor P_1 equation.

$$Cl_{drug_j} = P_1 + P_2(C_{creatinine_j}) + P_3(weight_j) + \eta_{cl_j}$$

where η_{cl_j} is intersubject error of clearance & it variance is $\omega^2_{cl_j}$

Q2(a) Explain influence of drug interaction in metabolism phase of drug ? example

Further

Q2(b) what is Bayesian theory :- Further.

Q2(a) Importance of polymorphism of cytochrome P450 :- Further

Q1(c) Explain the sampling design used in population p'kinetic study.

ans) Population p'kinetic studies aim to characterize the p'kinetic variability of drug in diverse patient population.

- The sampling design used in these studies play a crucial role in obtaining representative data to develop robust population p'kinect model.

* Sampling Design in population p'kinetic studies.

1. Purpose of Sampling Design.
- The sampling design in population p'kinetic studies is designed to collect p'kinetic data from a diverse population of patient to capture variability in drug disposition across different demographic & clinical subgroup.

- The design aim to balance the need for sufficient data point to develop reliable p'Kinetic model while mimizing the ~~data~~ burden on study participating & resource required for sample collection & analysis

2. Sampling Strategy.
- Population P'kinetic studies often employ a prespective, longitudinal sampling strategy, where p'kinetic sample are collected from patients at multiple time point following drug administration.

3. Patient Selection Criteria:-

→ Patient included in population p'kinetic studies are typically selected based on predefined inclusion & exclusion criteria to ensure the study population is representative of target patient population.

4. Sampling Time Points:-

→ Sampling time point are strategically selected to capture key pkinetic such as Cmax & Cmin & terminal elimination phase.

5. Sampling Frequency.

→ The frequency of sampling depend on the drug p'kinetic profiling & the study objective.

6. Sample Size Considerations.

→ Sample size calculation are performed to determine the number of patient & p'kinetic sample needed to archieve study objective such as parameter estimation precision & model validation.

7. Sampling Methodology

→ P'kinetic sample are typically collected via venipuncture or peripheral catheter insertion, depending on study protocol, & patient characteristics.

8. Data Analysis & Modeling.

→ P'kinetic data collected from study participant are analyzed using population p'kinetic modeling technique to estimating population parameter & characterize interindividual variability.

9. Validation & Interpretation.

→ The validity & robustness of population p'kinetic models are assessed through validation procedure, including goodness-of-fit diagnostic, visual predictive check, & sensitivity analyse.

Q1(b) TDM & process in patient cyclosporin & carbamazepine.

Further.

Q1(a) P'kinetic, note on parameter affecting drug action

Further.

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27(c) Describe general approach for dosage adjustment in renal diseases.

Further.

2(b) Write about Analysis of population p'kinetic data.

⇒ Traditionaly p'kinetic studies involve taking multiple blood samples periodically over time in a few individual patients & characterizing basic p'kinetic parameter such as K, VD & Cl.

⇒ Traditional p'kinetic parameter estimation is very accurate, provided that enough samples can be taken for individual patient.

⇒ The disadvantage is only a few relatively homogeneous healthy subject are including in p'kinetic studies from which dosing in different patient must be project.

⇒ In this clinical setting, patient are usually less homogeneous patient vary in sex, age & BW, they may have contaminant diseases & may be receiving multiple drug treatment

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→ The vital information needed about the p'kinetics of drug in patient at different stages of their diseases & various therapies can only be obtained from the same population, or from collecting of pooled sample.

→ The advantage of population p'kinetic analysis using pooled data were reviewed by Sheiner & Beden and included a summary of population p'kinetic for dozen of drug.

→ P'kinetic 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.

→ The further is NONMEM.

Q7(a) Explain role of cytochrom & genetic polymorphism further.

6(c) Explain detail the different method of extracorpeal removal.

Book & further.

Q3(c) IV to oral.

Further

Q3(b) Note on enzyme inhibition = example

Further in yellow book

Q3(a) Inhibition of Biliary Excretion.

Further

Q2(c) Indication of TDM

Further

Q2(b) Determining Dose & dosing interval

Further in yellow book

Q2(a) Explain P'kinetic correlation in drug therapy.

→ P'kinetic correlation in drug therapy refers to the relationship b/w drug concentration in body & clinical outcomes, including efficacy & safety.

→ The correlation in drug therapy.

TVS

PRT IV IC & D

GCS DIV PRT

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1. P'kinetic Parameter

⇒ P'kinetics parameter such as absorption, distribu, Meta, Excre -- determine the conc" of a drug as it site of action & in systemic circulation.

2. Relationship B/w drug conc" & effect

⇒ The conc" effect relationship describes the correlation b/w drug conc" & pharmacological effect.

⇒ In general, increasing drug conc" lead to greater pharmacological response, up to certain point where maximal effect is achieved.

3. Therapeutic Range :-

⇒ The therapeutic range represent the range of drug concentration within which the desired therapeutic effect is achieved without causing significant toxicity.

4. Pharmacokinetic Variability :-

⇒ Interindividual variability in p'kinetics parameter can lead to difference in drug conc" among patient receiving the same dose.

5. Individualized dosing.

- Individualized dosing aims to account for p'kinetic variability & achieve target drug conc^n in individual patients.

- p'kinetic modeling & ~~therapeutic~~ & TDM are tools used to optimize dosing regimen based on patient specific factor and drug conc^n.

6. Clinical Applications.

- Pk kinetic correlation inform dosing decision in various clinical scenario such as adjusting drug dose in patient c renal or hepatica impairment optimizing dosing in special population.

7. Pharmacogenomic.

- P'genomic factor such as genetic variation in drug metabolizing enzymes & drug transporters, can influence drug p'kinetic & responses.

8. Predictive Modeling.

→ P'kinetic modeling & Stimulation technique can predict drug conc^n & p'dynamic response based on patient characteristic

and dosing regimen.

9. Safety Monitoring.

→ Monitoring drug concentration and P'kinetic parameter can help identify patient at risk of toxicity and guide ~~to~~ intervention to prevent ADR.

10. C.T design.

→ ~~Understanding~~ Understanding P'kinetic correlation inform the design of C.T, including dosing regimens, sample schedules & endpoint.

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Q7(c) Give any 4 indication of TDM.

⇒ TDM is generally defined as clinical laboratory measurement of a chemical parameter that with appropriate medical interpretation, will directly influence the drug prescribing procedure.

⇒ The use of drug conc^n measurement in body fluid as can aid to the management of drug therapy for cure, alleviation or preventing of diseases.

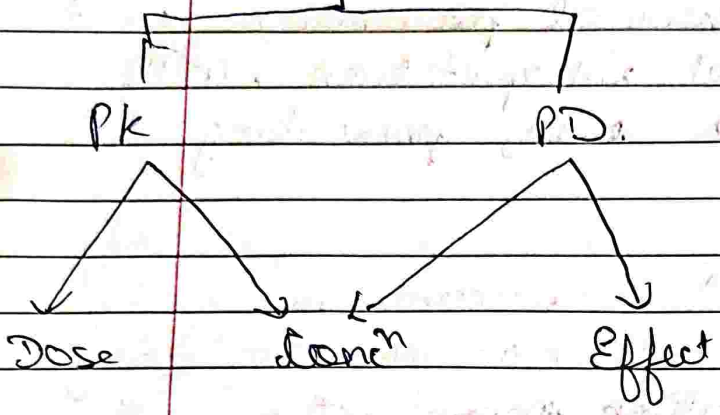
⇒ The goal of this process is to individualize therapeutic regimens for optimal patient benefit.

⇒ TDM is based on principle that for some drug there is a close relationship b/w plasma level of drug and its clinical effect.

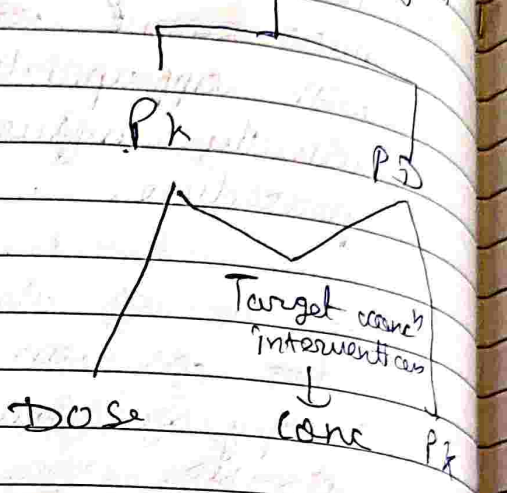
⇒ Such a relationship does not exit TDM is of little value.

⇒ The algorithm show difference b/w TDM & target concentration intervention.

TDM
↓
Therapeutic Regimen



TCI
↓
Therapeutic regimen



* Indication.
* Table.

	Effect	Drug
①	Relationship b/w dose & plasma is unpredictable	Phenytoin
②	Drug ε Steep dose response curve	theophylline
③	Difficult to interpreting clinical evidence of therapeutic or toxic effect	digitalis
④	Drug interaction	Lithium & thiazide Anti epileptic Cyclosporin A
⑤	~~Contd~~ Eliciting withdrawal of therapy	

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Q7(c) Give any 4 indications of TDM

1. Drug efficacy difficult to establish clinically
2. Suspected toxicity
3. Inadequate therapeutic response
4. Compliance concern
5. Dosage change
6. Chance in co-medication
7. Manifestation to toxicity

Indication for TDM	Drug	Purpose
(1) Plasma concentration		
Drug of narrow therapeutic range	lithium, Digoxin, Vancomycin	→ For find dose related toxicity
Drug showing conc-dependent kinetic in therapeutic range	phenytoin, Antibiotic	For adjustment of dose
To check bioavailability		To find out unanticipated dose related toxicity

B. Pharmacodynamic consideration.

1) Drug showing wide interindividual various metabolism	TCA depressant	Maintain plasma conc within therapeutic range.
2) Drug c prophylactic purpose	TCA depressant	To capture biochemical & clinical endpoint
3) Drug in patient c comorbidities.	Aminoglycoside, Theophyllin.	To compensate diseases mediated half life & clearance.
C. Toxicity		
1) Distinguish b/w drug related ADR from diseases condition.	Digoxin	To assist in differential diagnosis.
2) Drug - drug related interaction	Quinidine - digoxine	To avoid toxicity
3) To check patient compliance	-	To explain therapeutic failure c Standard doses of drug.

Q7b) Define pharmacogenetic & 2 suitable e.g

i) Define :- Study of variability in drug response determined by single gene.

ii) In other words, it is the study of how gene affect the way people respond to drug therapy.

Pharmacogenetic ⟷ The study of variation in gene that determine an individual respons to drug therapy

Genetic Polymorphism ⟷ Common variation in DNA sequence

Potential target genes are those that encode

PK
① - Drug metabolizing enzyme
② - Transporters
③ - Drug Target

PD
(i) - Receptors
(ii) - Ion channels
(iii) - Enzyme
(iv) Immune molecule

polymorphism on.

(4) Genetic metabolism of

- Cytochrome P450 (CYP450) enzyme involved in phase I metabolism of large number of drug.

- It has superfamily of 57 related isoenzyme.

- It superfamily has subfamilies categorized according to AA sequence.

- CYP450 exists in many forms due genetic variation in individual

- the most important families are

CYP1A2
CYP2C9
CYP2C19
CYP2D6
CYP3A4.

- CYP1A2 :- Responsible for metabolism of 5% drug.

- Most frequent variant CYP1A2* 1F allele - result in increased expression

- CYP1A2* 1C - result in decrease expression.

- Drugs are - fluvoxamine, clonazapine, olanzapine, theophylline.

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- CYP2C9 :- It has 30 different variants.
- Most common is CYP2C9*2*3, both variant result in les activity.
- Major contributer is Warfarin.

- CYP2C19 :- It is highly polymorphic drug metabolizing enzyme.
- It has 30 different variant.
- The poor metabolizer enzyme variant is CYP2C19*2*3
- Mainly found in Asian.
- In this enzyme most common example is Omeprazole.
- CYP2C19*17 type result in ultra metabolizing capacity.

- CYP2D6 :- large Isoenzyme family with more than 70 variants.
- Most common example is Antidepressant & antiarrhythmic
- It was 1st invented & debrisoquine result in exaggerated hypotensive response.

⇒ CYP3A4 :- Abdunttly found in liver.
- Metabolize 50% of drugs
⇒ 20 variants are known.
⇒ CYP3A4 * 1B influence gene expression
CYP3A4*2 ↓es nifedipine clearance

(2) Polymorphism in Drug Transporter.

→ There are 2 superfamilies of protein that have effect on ADME of drugs

(i) ATP Binding Cassette (ABC) :- Present in cellular & intracellular membrane & responsible for importing & exporting of substance.
- The 3 familes are important.

(a) ABCB1 gene encoding MDR1 :- code for efflux of protein & associate c drug resistance e.g. digoxin & docetaxel.

(b) ABCC family :- Also known as multidrug resistance proteins (MRPs), mainly found in brain, liver, kidney & intestine
⇒ Mainly effect tamoxifen transport

(c) ABCG2 :- Known as breast cancer resistance protein (BCRP).
⇒ Include organic cation transporter (OCT) & Organic cation transporter prot (OATP)
⇒ OATP1B1 effect response of Simvastatin

Drug transporter

→ Transporters are protein that carry either endogenous compound or xenobiotics across membrane

→ Transporter can either influx or efflux protein.

⇒ Genetic variation such as SNPs of transporter can cause difference in influx & efflux of drug.

→ Atleast 66 SNP's in ABCB1 gene
- 3 most studied SNPs include 2 synonyms & 1 synonymous varied which cause decrease expression of PGP & cause unstable mRNA.

→ MRPs 1, 2 & 3 are commonly known to effect in drug disposition.

→ It is imp in limiting bioavailability of certain drug, const drugs in breast milk & protecting fetus from drug.

⇒ Highly expressed in GI, liver, placenta & influence the absorption & distribution.

(iii) Solute carrier Protein

- Transport ions & organic substances across biological membranes.
- These includes organic cation transporter (OCT) & organic anion transporter proteins (OATPs).
- Available throughout the body.
- OATP1B1 is a hepatic influx transporter & atleast 40 SNP reported that result in either altered expression or activity of OATP1B1.
- Among them one SNP has been associated & an increased risk of simvastatin induced myopathy.

(3) Drug ~~too~~ targets.

- Drug target include receptors enzyme, ion channels & intracellular signalling protein.

- Drug target is an biological agent in which the drug is directed and or bind to it resulting in a change in its behaviour or function e.g. protein & nucleic acid.

⇒ Genetic polymorphism occur commonly for drug target proteins, including receptor, ion channel, enzyme.

⇒ Receptor genotype & drug response

→ β_1 receptor are located in heart & kidney, where they are involved in regulation of heart rates, cardiac contractility & B.P.

⇒ Two common nonsynonymous SNPs in β_1 receptor gene located at codon 49 & 389.

⇒ The influence of the β_1 receptor gene on blood pressure response to β_1-receptor blockade ē metoprolol.

→ β_2 receptor are located on bronchial smooth muscle cells, where ethey mediate bronchodilation upon exposure to β_2-receptor agonist.

⇒ Inhaled β_2 agonist are most effective agents for acute reversal of bronchospasm.

⇒ More than 11 SNPs have been identified in the β_2 receptor gene, three of which occur frequently and result in AA changes.

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- Two common nonsynonymous SNPs are found in the gene's coding block region, at codons 16 & 27 & a 3rd occur upstream from coding block in gene's promoter region.

- Enzyme genes & drug response.

1. Vitamin K epoxide reductase (VKOR) is an example of an enzyme & genetic contribution to drug response.

- The vitamin k epoxide reductase complex subunit 1 gene (VKORC1) encode which cause warfarin resistance.

- Further there are various subfamily of VKORC1 are.

  VKORC1 *1
  VKORC1 *2
  *3
  *4

- A common SNP occur in the gene for the inhibitory G protein β_3-subunit & has been associated & enhanced intracellular signal transduction.

- The epithelial sodium channel (ENaC) is an example of an ion channel genetic contribution to drug response.

2(b) Enlist factor for individualize adverse-dosage regimen.

i) Human are reasonably homogeneous but differences among people exist including their responsiveness to drug.

ii) There is a frequent need to tailor drug administration to individual patient.

iii) A failure to do so lead to ineffective therapy in some patient & toxicity in other.

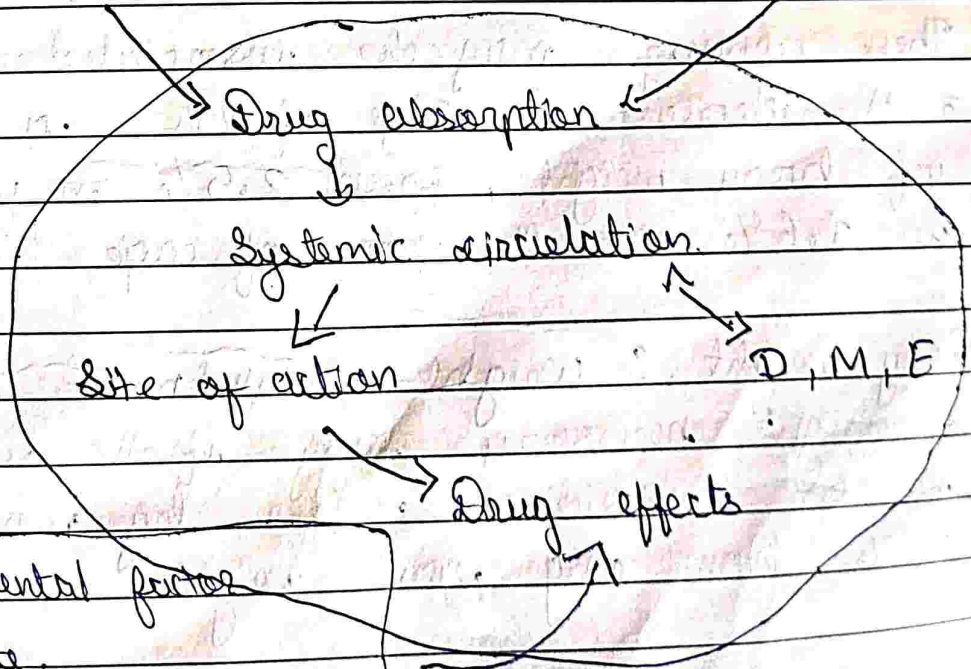
- Understanding the source of this variability & adjusting drug dose accordingly is area in which pharmacist can make a major impact on risk managment & patient care.

- Avg data are useful as a guide, but ultimately information pertaining to individual patient is important - interindividual variability.

* Factors are

Biological factor
- Age
- Gender
- Genetics
- Diseases

cultural factor
- Attitude
- Beliefs
- family influence



Environmental factor
- Climate
- Parasite
- Pollutant
- Smoking & alcohol

I Biological factor

1. Age :- Aging is characterized by periods of growth on development, is can additional source of variability in drug response.

→ Drug absorption doesn't appear to change dramatically with age but the factor that affect drug absorption, including gastric P^H, gastric emptying, intestinal motility & blood flow change ~ age.

→ These changes tend to be less apparent in elderly than in very young.

→ A major exception is for some 1st pass drug given to elderly, where oral bioavailability increase ~ age.

→ These changes may be associated in part, to the decrease in size of liver, as proportion of body weight, from 2.5% in young adult to 1.6% at 90 year of age.

2. Body weight & weight adjustment is generally thought necessary only if the weight of an individual differ by more than 30% from avg adult weight.

→ Dose correction must be considered for thin & obese patients.

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- The difference in loading dose may not be as great as anticipated from body weight alone.
- The use of total body weight to determine a drug dosage regimen could result in toxic effect if the patient is grossly obese.
- It is expressed as mg/kg.
- For child dose $= 1.4 \times \left[\frac{\text{weight of child in kg}}{70}\right]^{0.7} \times$ maintance dose

3. Gender :- Genetic & physiological difference b/w male & female can have effect on pkinetic & p'dynamic of drug.
   - Genomic imprinting, body size, organ size, body fat, ADME can also effect p'ology outcome.
   - other factor such as GI transit time, liver enzyme function and urinary creatinine clearance are influenced by both age & sex
4. Genetics :- Genetic polymorphism effect dead to the production of isoenzyme ∴ reduced activity of multiple copies of an enzyme ∴ higher activity make a major contribution etc

variability in dose requirement of drug that eliminated by hepatic metabolism.

⇝ CYP450 enzymes, P-glycoprotein are increasingly being recognized for their importance to PK variability.

5. Disease condition :- Disease is major source of variability in drug response.

⇝ The PK & PD of some drugs have been shown to be influenced by presence of concurrent diseases other than the one for which drug is used.

e.g.

① Cirrhosis → Theophylline :- shows fall in plasma conc^{n}

② Uremia → Gentamycin :- ↑es toxicity & renal clearance.

II Environmental factors

① Drug interaction :- many of clinically significant interactions b/w drugs are p'kinetics in origin, often due to induction & inhibition of metabolizing enzyme or transporter protein.

- However interaction can also occur between drug & food supplement or herbal remedies.

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② Absorption :- It can altered by drug interaction with in gut that result from binding to other drug such as cholestyramine or antacid to enteral feed in case of phenytoin.

③ Distribution :- can be altered by interaction that cause displacement from plasma protein binding.

④ 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 individual basis

⑤ Excretion :- Probenecid reduces the renal excretion of many antibiotic by competing for anion secretion transport mechanism.

→ Changes in biliary secretion & entero-hepatic circulation.

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Influence of D interaction in protein binding & metabolism.

* ~~Protein binding~~

Drug interaction is defined as the pharmacological activity of one drug is altered by the concomitant use of another drug or by the presence of some other substance.

In other words, it is the modification of the effect of one drug (the object drug) by the prior concomitant administration of another.

The drug whose activity is effected by such an interaction is called as a "Object drug".

The agent which precipitates such as interaction is referred to as Precipitant.

The interacting molecules are generally the macromolecules such as protein, DNA or adipose.

The protein are particularly responsible for such an interaction.

⇒ The phenomenon of complex formation of drug with protein is called protein binding of drug.

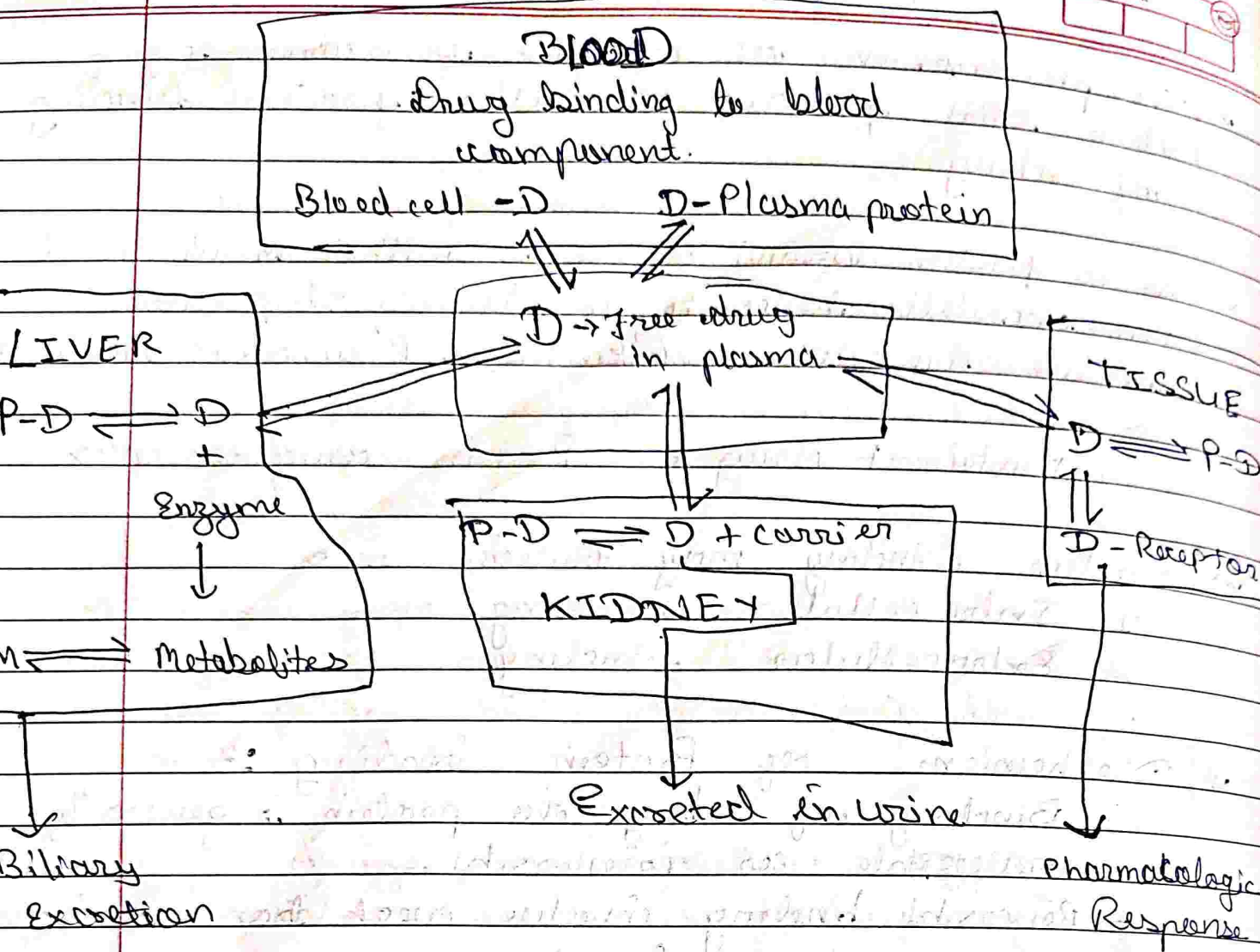
⇒ As a protein bound drug is neither metabolized nor excreted hence it is pharmacologically inactive due to it P'kinetic & P'dynamic inertness.

Protein + drug ⇌ Protein - drug complex.

⇒ Protein binding may divided into
1. Intracellular binding
2. Extracellular binding

⇒ Mechanism of Protein binding :-
- Binding of drug to protein is generally reversible or irreversible
- Reversible binding involve weak bond such as
1. Hydrogen bond.
2. Hydrophobic bond
3. Ionic bond
4. Van der waal's force.

- Irreversible drug binding through covalent bonds is a result of covalent binding & it often a reason for carcinogenicity



1. Binding of drug to blood component.

A. Plasma protein - drug binding :-
The binding of to plasma protein - is reversible.

Albumin > α^1 - acid glycoprotein > lipoprotein > Globulins.

* Albumin.
- Site 1 :- Warfarin & Azapropazone.
- Site 2 :- Diazepam
- Site 3 :- Digitoxin.

Site 4 :- Tamoxifen.

2. Binding of drug to α-1 acid glycoprotein
→ Basic interaction imipramine, lidocaine etc.

3. Binding of drug to lipoprotein :-
→ Basic interaction Diclofenac, cyclosporin A etc.

B. Binding of drug to blood cell.

→ Major component is RBC, the rate & extent of entry into RBC is more for lipophilic drugs.
→ 3 component
(a) Hb :- Drug M.W of 64,500 Dal.
Phenytoin, pentobarbital.
(b) Carbonic anhydrase :- Carbonic anhydrase inhibitor drug are bind to acetazolamide
(c) Cell membrane :- Imipramine & chlorpromazine

2. Binding of drug to extravascular tissue protein.
- Factor affecting :- lipophilicity, structural feature of drug.

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II Metabolism.

- Drug metabolism is metabolic breakdown of drugs by living organism → usually through specialized enzymatic system.

- More generally xenobiotics metabolism is set of metabolic pathway that modify chemical structure of xenobiotics.

- Biotransformation reaction most often act to detoxify poisonous compound.

- Metabolism of drug - a component of P'kinetic is an imp aspect of pharmacology & medicine.
  e.g. Rate of metabolism determine duration & intensity of p'cological action.

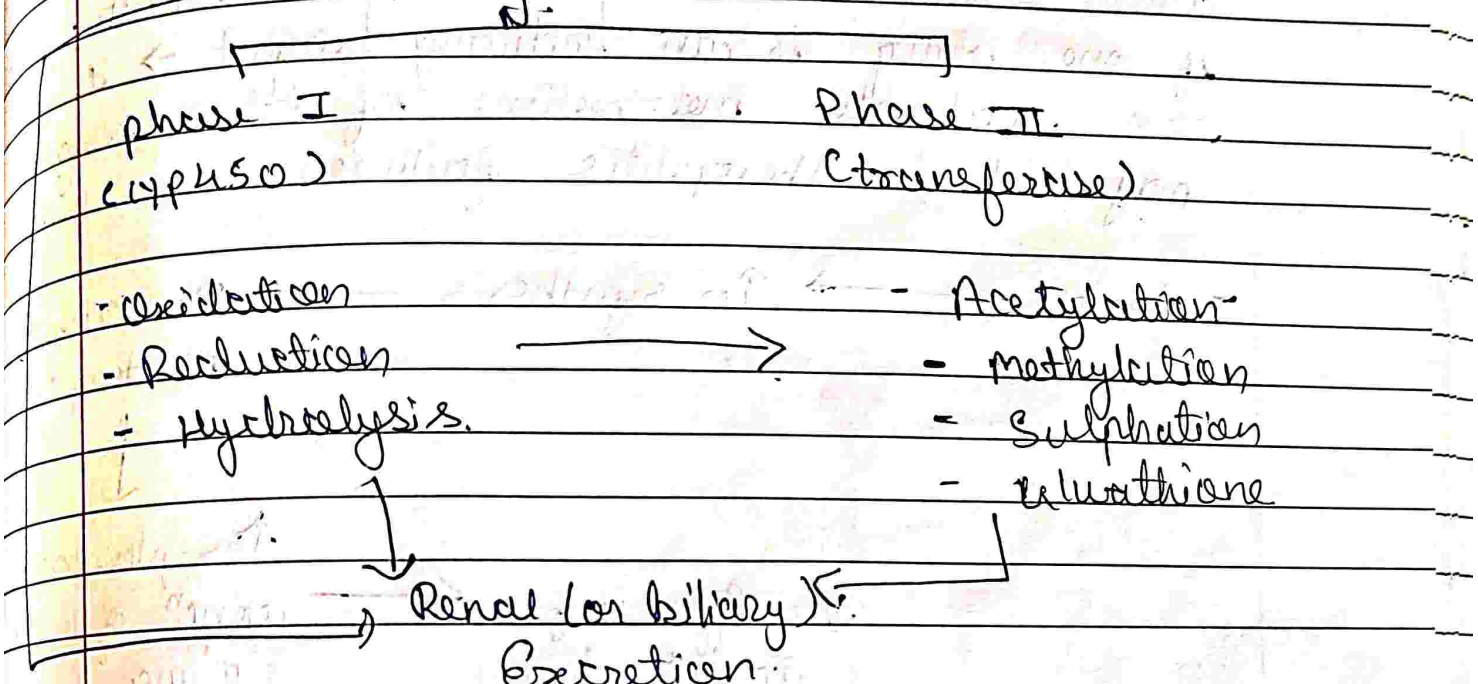
- It is one of I° mechanism by which drug are inactivated e.g. phenytoin

- Some cases, drug activity increases e.g. enalapril & in some case drug provide long-lasting effect due to increased metabolism time e.g. diazepam.

- Metabolism has 2 phase.

Phase I:- It is non synthetic reaction involve in metabolic modification of drug.

Phase II :- It is synthetic phase reaction are synthetic conjugation & increase polarity compared to parent drug & are more readily excreted in urine.



↳ In metabolism, the drug effect 2 activity.

(I) Enzyme induction :- It is a process by which enzyme activity enhanced → usually ↑ enzyme synthesis

- Increase in enzyme synthesis is often caused by xenobiotic binding to nuclear receptor → which then act as positive transcription factor for certain CYP450 isoenzyme.

⇒ Exogenous inducing agents including drugs, but also halogenated insecticides e.g. DDT, herbicides, polycyclic aromatic hydrocarbon, dyes, food preservative etc.

⇒ A practical consequence of enzyme induction → when 2 or more drug are given simultaneously if one drug is an inducing agent → it can accelerate metabolism of other drug → may lead to therapeutic failure.

Inducer ⟶ ↑es synthesis ⟶ ↑es metabolism of target drug ↓ ↑es plasma conc^{n} of target drug ⟵ ↓es Effect of target drug.

(II) Enzyme inhibition

⇒ Allopurinol, MXT etc are other drug exert their therapeutic effects by enzyme inhibition.

- Apart from such direct action inhibition of drug - metabolizing enzyme by a concurrently Administered drug can lead to drug accumulation & toxicity.

e.g. Cimetidine inhibit CYP450 system & of warfarin.

Inhibitor — Rapid → Direct inhibition of CYP450 isoenzyme → ↓es metabolism of target drug → ↑es Plasma conc^{n} of target drug → ↑es Effect / ↑es toxicity } of target drug.

↳ Specificity of enzyme inhibition is sometimes incomplete.

e.g. Coumarin & phenytoin compete c one another for metabolism.

→ Metronidazole is a non competitive inhibitor of microsomal enzyme → inhibit phenytoin

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21. Dosage adjustment in renal diseases.

⇒ The kidney is an important organ in regulating body effluid, electrolyte balance, removal of metabolic waste, and drug excretion from body.

⇒ Impairment or degeneration of kidney function affects the P'kinetic of drug.

⇒ Some of the diseases are

- Pyelonephritis
- HTN
- DM
- ~~Drugs~~
- Hypervolemia
- Nephro allergens.

⇒ Acute diseases or trauma of kidney can cause uremia in which GFR is impaired, lead to accumulation of excessive fluid & blood nitrogenous product.

⇒ Decline renal function leads to disturbance in electrolyte, fluids result in alter p'kinetic & dynamic of drug.

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- Several approaches are available for estimating the appropriate dosages regimen for patient ∴ renal impairment.
- most of methods assure that the required therapeutic plasma drug 'conc" in uremic patient is similar to required in patient ∴ normal renal function.
- The method for dose adjustment in uremic patients are based on accurate estimation of drug clearance.
- Two general ~~methods~~ p'kinetic approach for dose adjustment.

(i) Dose adjustment based on Drug Clearance

(ii) " " based on changes in the Elimination Rate constant.

1) Dose adjustment based on drug clearance

- With multiple oral doses the average steady State concentration (C^{ss}_{av}) is calculated as

$$C^{ss}_{av} = \frac{FD_0}{Cl_T T} \quad -(1)$$

- For patient ∴ uremic/renal impairment total body clearance change to Cl_T^u & dosage interval changed to τ^u, at dose D_0^u

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

Combining (1) & (2)

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

(v) If dosage interval kept constant than final equation will be.

~~$D_0^{u} = D_0^{N} Cl_T^{N}$~~

$$D_0^{u} = \frac{D_0^{N} \cdot Cl_T^{u}}{Cl_T^{N}}$$

(vi) For IV same desired C_{ss} is maintained at Rate of infusion (R^N) & Rate of infusion in uremic / renal impaired patient (R^u)

$$\therefore R^{u} = \frac{R^{N} Cl_T^{u}}{Cl_T^{N}}$$

(vii) Dose Adjustment Based on change in Elimination Rate constant

(viii) Dosage regimen may designed either by reducing the normal dose of drug or by prolonging the dosage interval.

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⇒ To estimate a multiple dosage regimen in the normal patient is to maintain a desired can be calculated

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

⇒ Assuming the V_d is same in both normal & uremic patient & τ & kept constant then dire uremic dose D_0^u.

$$D_0^u = \frac{D_0^N K^u}{K^N} \quad \text{--- (2)}$$

⇒ Assumption for calculation of dosage regimen are:-

- The renal elimination rate constant decreases proportionely as renal function decreases.
- The non-renal route of elimination remain unchanged.

⇒ The overall elimination rate constant the sum of total of all ROA in body which is given

$$K^u = K_R^u + K_{NR} \quad \text{.... (3)}$$

where K_R is renal excretion rate constant

K_{NR} is non renal elimination rate constant

$Cl_R^u = K_R^u V_d^u$

$K_R^u = \frac{K_{NR}^N}{V_d^u / V_d^N}$

- Rearrangment

$$K^u = K_{NR}^N + \frac{Cl_R^u}{V_d^u}$$

14.) Drug interaction at elimination site.

⇒ Drug interaction are a significant concern in moderen p'therapy.

⇒ This occur when the administration of one drug alter the p'kinetic profile like A.D.M.E of another, potentially leading to therapeutic failure & ADR

⇒ The elimination phase, the final stage where drugs are removed from body, presents a critical window for potential interaction.

⇒ understanding these interaction is crucial for pharmacist & healthcare professionals to ensure optimal drug therapy & patient safety.

- Mechanism of drug interaction at Elimination Site:

⇒ (i) Reduced Elimination :-

(a) Renal competition :- The kidneys play vital role in drug elimination, primarily through glomerular filtration & tubular secretion.

- This competition can significantly decrease the elimination of one or both drugs.

- Probenecid used for gout, competes ē penicillin for secretion via (OAT) system in proximal tubules.

(b) Decreased renal blood flow :- Some medication like NSAID can have vasoconstrictive effect, reducing renal blood flow.

- This translate to a decreased GFR, the rate at which blood is filtered by kidney.

- The elimination of other drug primarily dependent on glomerular filteration, such as Nit. lead to toxicity

(c) p^H alteration in urine :- The elimination of ionizable drug, which exist in both charged & uncharged forms, can be significantly influenced by urine p^H.

- Drugs that alter urine p^H can indirectly affect the elimination of other drugs.

- For example, Acetazolamide, diuretic, increases urine p^H.

(ii) Increased Elimination

(a) Enzyme induction :- The liver is primary site for drug metabolism, where enzyme like CYP450 system play a crucial role in biotransforming drug into inactive metabolite for excretion.

- A classic example is Rifampin, induce CYP enzyme specially CYP3A4.

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eg when rifampin is co-administered & warfarin, an anticoagulant drug, the increased CYP3A4 activity accelerate warfarin metabolism

(iii) Clinical implication of Elimination Site interactions

(a) Increased risk of toxicity :- when a drug elimination is reduced due to mechanism like renal competition or decreased GFR, the drug accumulate in body, potentially reaching toxic level & causing ADR.

(b) Decreased therapeutic effect :- If a drug is eliminated too quickly due to enzyme induction, it may not reach therapeutic conc^{n} in body for sufficient duration to exert its desired effect.

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13) BEER'S in geriatric Patient.

⇒ Prescribing for older patients present unique challenges.

- Premarketing drug trial often exclude geriatric patients.
- Approved doses may not be appropriate for older adult.

⇒ The beers criteria, also known as beers list.

⇒ It is a valuable tool developed by American Geriatrics Society to promote safe & effectiveness medication use in older adults.

⇒ It not a definitive list of medication to avoid but rather a set of recommendation.

⇒ Older adults are particularly susceptible to medication-related problems due to several factor :-

(a) Physiological changes :- Aging besties experience a decline in kidney & liver function, which can affect drug metabolism & elimination.

(b) Polypharmacy :- Geriatric patient often have multiple chronic conditions, leading to use of several medication simultaneously, increasing the risk of interaction.

(c) Increased sensitivity :- Older adult may be more sensitive to affect of medication even at standard dose, due to change in body composition & drug distribution.

Key component of the Beer's criteria.

The Beers criteria is not a static list but is updated periodically by AGS based on emerging evidence.

It currently include several category of medication to consider for geriatric patients.

- Potentially inappropriate medication (PIMs). These are medication with a higher likehood of causing ADR in older adult compared to their potential benefits.
  e.g. Antipsychotics, benzodiazepines.

- Medication to Use c Caution :- These medication require careful monitoring due to increased risk of side effect in older adult.
  eg. NSAIDs

- Medication for which dosage adjustment may be needed ; The std dosage of some medication may need to be adjusted for geriatric patients due to reduced organ function e.g. Diuretic & anticoagulant

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(iv) Applying the Beers criteria in Geriatric Care.

- The beers criteria is not meant to be a rigid set of rules.

- Instead, it serves as a guide for healthcare professional when making medication decision for older adults.

- Individualized Assessment :- A comprehensive review of patient's medical history, current medications, & overall health is crucial.

- Risk Benefit Analysis :- The potential benefit of a medication are weighed against the potential risk of side effect and interaction & other medication the patient is taking

- Shared Decision-Making :- Healthcare professionals discuss the finding & recommendation & the patient & their caregiver, involving them in the decision-making process.

(v) Benefits of Utilizing the beer's criteria.

- Improved medication safety :- By identifying potentially inappropriate medication, the criteria help reduce the risk of ADR & hospitalizati in older adult.

- Optimized medication regimens :- It encourages healthcare professional to consider safer alternative & adjust dosage when necessary.

• Enhanced communication :- The criteria promote open communication b/w healthcare professionals, patients, & caregiver. about medication use

- Limitation :-

① Not a one-size-fits all approach

② Focuses on specific medication

③ Regular updates required.

- TDM

12] Lithium

- Lithium has been used to treat manic episode.
- It mechanism is still unknown & has narrow therapeutic range & so careful monitoring regu

- Use
  - Mood stabilizer, to treat manic episode
  - maintenance of bipolar disorder
  - Use as monotherapy in mani & in combination in bipolar.

- MOA
  - Unknown
  - Proposed as alteration of intraneuronal metabolism of catecholamine & alteration of Na+ transport in nerve cell

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P'kinet

A :- Rapid absorb & oral bioav ≥ 70%
D :- Vd is 0.7 to 1.0 L/kg
- Not significant bind to protein
M :- Not metabolize before excretion
E :- ↓ via kidney & elimination in feces.

• $t_{1/2}$:- 15 - 36 hr.

ADR :- ~~Polyuria, polydipsia~~ Myopathy.

• ADR :-

(a) Therapeutic level :- N & V, D., Polyuria, polydipsia, tremor

(b) Toxicity :- Slurred speech, confusion, coma, arrhythmia, hypotention

(c) Non dose related - DM I, goiter, hypercalcemia, acne, leukocytosis.

• Interaction

① Diuretics
NSAID, ACE, CCB

• Dose.

① Acute therapy :- 1500 - 2400 mg/day
Maintainance :- 900 - 1500 mg/day

* C/I.
  ① CVS risk
  ② Use diuretics
  ③ Renal dysfunction
  ④ Sodium depletion

* Monitoring.

- Thinking & thought of patient must have absent suicidal, depression thought.
- Sx Cx
- ECG
- Vitals.
- Renal function :- BUN.
- CBC
- weight record.
- ~~BP~~ Serum Ca^{2+}

* Assay
  - flame photometry
  - IAS.

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* Cyclosporin

→ It is a steroid - sparing immunosuppressant used in organ & bone marrow transplant as well as inflammatory condition such as RA, dermatitis, UC etc.

* Use
- Immunosuppressive agent.
- For prophylaxis of organ rejection in kidney, liver & heart transplant.
- Treatment of RA & inadequate response to Mx for severe recalcitrant & psoriasis.

* MoA
- Act on helper T-cells, which inhibit the activation of calcineurin & production of interleukin-2, thus reducing cell-mediated immune response.

* Pkinetic

- A :- Mainly absorb in intestine.
  - 1st Bioavailability 30% within 1-8 hr
  - Cmax at 3.5 hr.
- D :- Blood consist 33% - 47%, plasma 4% - 9%, lymphocyte 5% - 12%.
  - Vd - 4-8 L/kg

- Protein binding 50% to erythrocyte 2.34% lipoprotein

- M :- Metabolized in intestine & by liver.

- E :- 1° biliary excretion 90% rest by 34% urine.

Half life :- 19 hr.

* ADR.
  - Headache
  - CVS :- Hypertension.
  - Dermato Rashes, hypertrichosis.
  - GTI :- Nausea, diarrhea, Abd distress.
  - Infection :- viral infection
  - Renal :- Scr level increase
  - Respi :- URTI.

* Interaction.
  - Doxycycline, erythromycin
  - Carbamazepine, INH, phenytoin
  - methylprednisolone
  - NSAID, ciprofloxacin, Amphotericin B, melphalan

* Toxic range.
  - Oral in human is 12mg/kg

C/I
- Hypersensitivity.
- R.A
- Renal function imbalance.
- Concomitant administration of PUVA, MXT, autoimmune disease.
- Pregnancy.

Monitoring parameter.
- Renal function
- CBC
- B.P
- Vitals
- Hypersensitivity reaction.

Assay.
- Monoclonal RIA
- HPLC.

9. IV to oral.

⇒ The ideal RoA for any medication is one that achieves serum conc^n sufficient to produce the desired effect without producing undesired effect.

- Importance of conversion.

→ In in previous sessions, patient were switched to oral therapy to continue t/t after an already adequate course of IV therapy was administered.

⇒ In Recent, it is not uncommon to convert a patient to PO therapy as part of initial t/t course.

⇒ The available oral formulation on market are easier to administer, safe, & achieve desired therapeutic conc^n thus making the PO route an ideal choice.

⇒ Patients are more comfortable if they do not have an IV catheter in place

⇒ Attachment to an IV pole can restrict movement, which can hinder early and/or frequent ambulation.

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iv) Patient who continue to receive parenteral therapy are at the increased risk for infusion - related adverse events.

v) In addition, the presence of an IV catheter provide a portal for bacterial & fungal growth.

vi) Using PO therapy also reduces hidden expenses such as cost of IV sets & pumps, laboratory monitoring & nursing & pharmacy personnel time.

vii) There are 3 type of method for conversion.

(i) Sequential therapy

(ii) Switch therapy

(iii) Step down therapy.

(i) Sequential therapy

$C_{ss} = SF.D_0 / KV_d \tau$

$D_0 / \tau = C_{ss} KV_d / SF$

→ Refers the act of replacing a parenteral version of a medication with it oral counterpart

Eg. Conversion of famotidine 20mg IV to 20mg PO.

ii) There are many classes of medication that have oral dosage form that are therapeutically equivalent to the parenteral form of same medication.

2. Switch therapy

- It is used to describe a conversion from an IV medication to the PO equivalent that may be within the same class and have the level of potency, but is a different compound.

e.g. Conversion of IV pantoprazole to rapidly dissolving lansoprazole tablets or omeprazole capsules.

3. Step-down therapy.

- Refers to converting from an injectable medication to an oral agent in another class or to a different medication within the same class where frequency, dose & spectrum of activity may not be exactly the same.

e.g. Converting from ampicillin/sulbactum 3g IV to amoxicillin/clavulanic acid 875mg PO.

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* Ideal characteristics for conversion.
- The oral dosage form should be excellent bioavailability
- Be well tolerated upon administration.
- Its use should be supported by clinical data.
- other optimal properties include the availability of multiple oral dosage form.
- Dosing at or frequency equivalent to or less than IV formulation.

* Medication Converting IV to oral

1) Sequential/Switch.
   ① Antibiotic - Azithromycin
   Ciprofloxacin -
   clindamycin -
   doxycyclin etc
   ② Antifungal :- Fluconazole
   ③ Antiviral :- Acyclovir
2) Step down :- Ampicillin/sulbactum.
   piperacillin/Tazobactum.

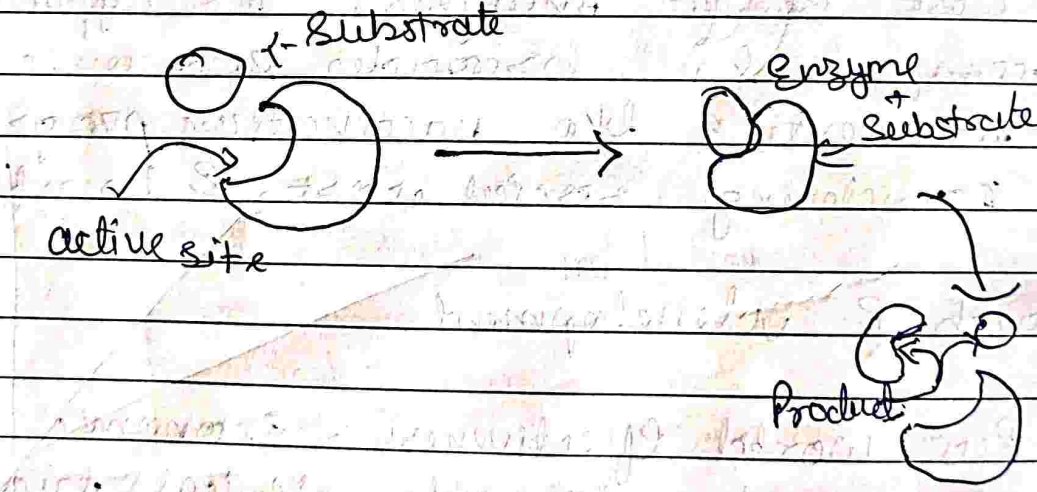
Q. Note on enzyme inhibitions.

→ Enzyme are bio catalysts present in cell that speed up biochemical reaction without getting itself destroyed in reaction.

→ Enzyme catalyse a reaction by reducing the activation energy needed for the reaction to occur.

→ However, enzymes need to be tightly regulated to ensure that level of the product do not rise to unwanted levels.

→ This is accomplished by enzyme inhibition



→ Enzyme inhibition are molecule that bind to enzyme and decrease their activity.

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Type of Enzyme inhibitors

- Reversible
  - Competitive
  - Non competitive
  - Uncompetitive
- Irreversible
  - ↓
  - Suicidal inhibitor
- Allosteric

① Reversible inhibition

» Inhibitor bind non-covalently to Enzyme.

» Inhibition can be reversed on removal of inhibitor from enzyme.

$$E + I \rightleftharpoons EI$$

» Not all molecules that bind to enzyme are involved in regulation of metabolism.

» Not all molecules that bind to enzyme are inhibitors, enzyme activators bind to enzyme to increase their activity

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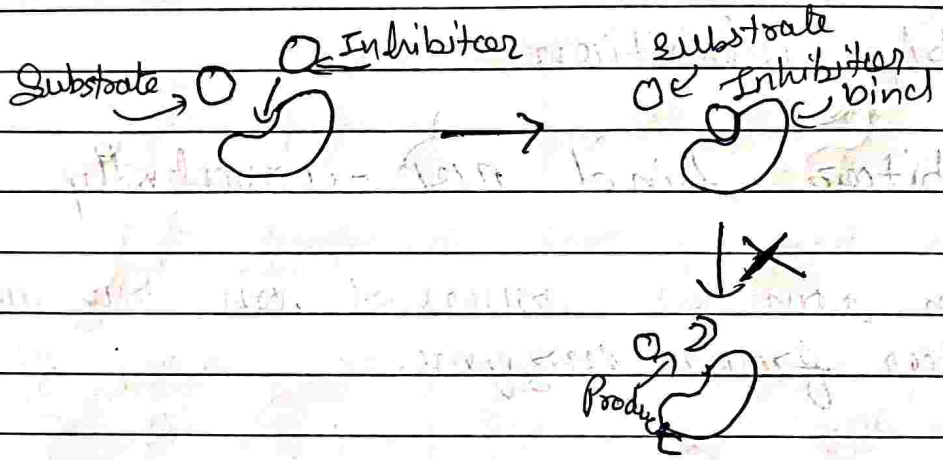
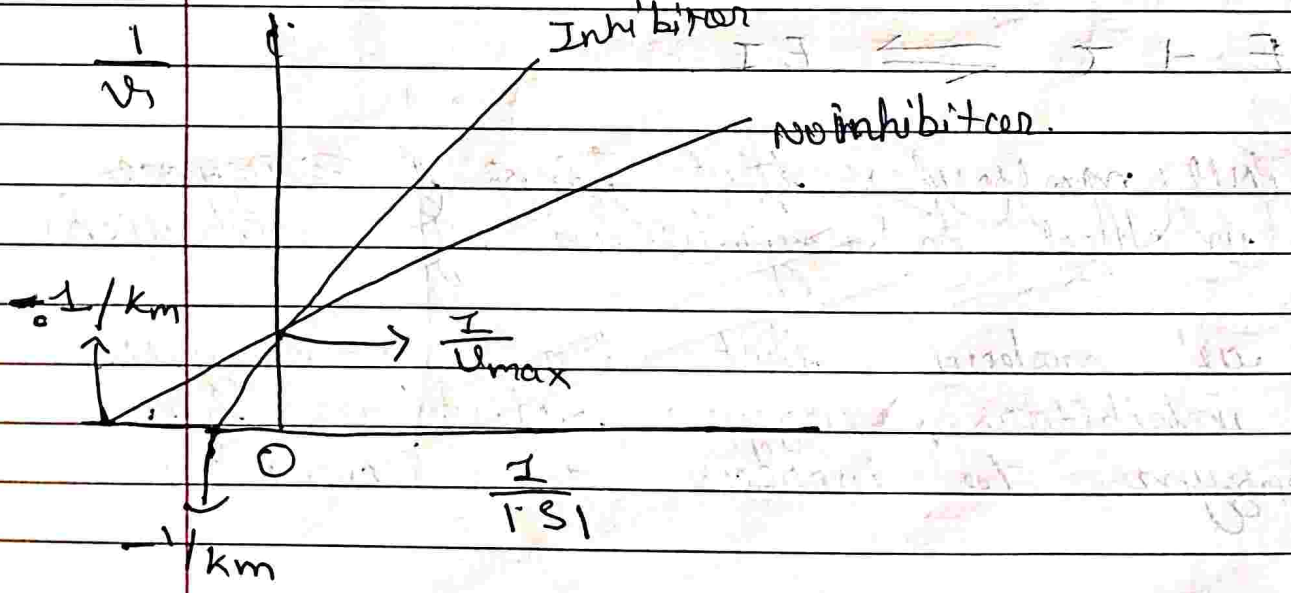
⇝ 3 type of reversible inhibition

(a) Competitive inhibition :- Inhibitor bind reversibly to the same site that the substrate bind to active site.

⇝ Binding of inhibitor inhibit the reaction & does not produce any product.

$$E + I \rightleftharpoons EI$$





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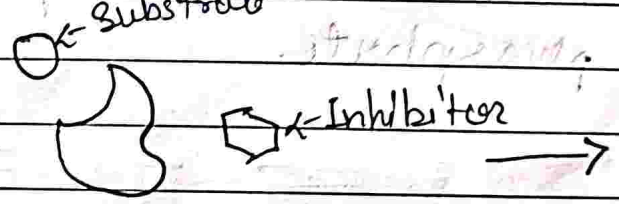
e.g. ① Malonate is competitive inhibitor for succinate dehydrogenase.
② Allopurinol for xanthine oxidase.
③ Atorvastatin.
④ methotrexate.

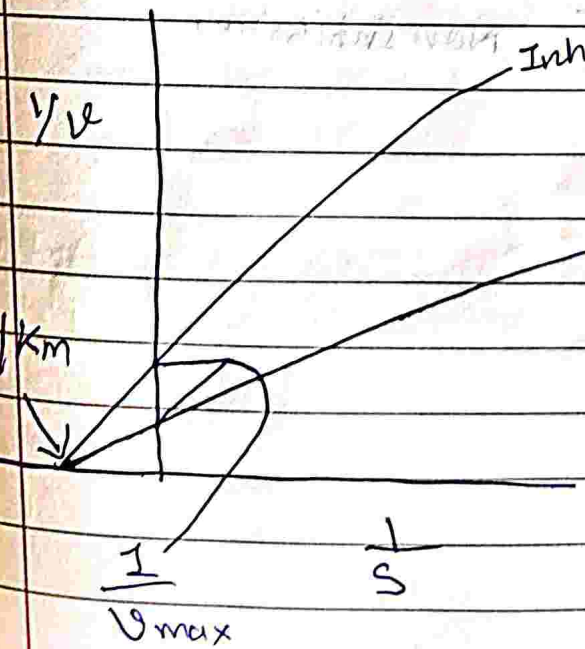
(b) Non-competitive inhibition.

Inhibitor bind to enzyme at a site other than active site and cause inhibition.

It may bind to free enzyme forming complex

$$E + I + S \rightleftharpoons ESI$$



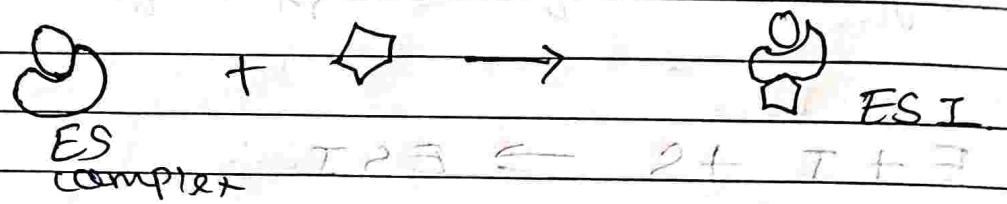


e.g. Heavy metals
- Pepstatin
- Trypsin
- Ethanol.

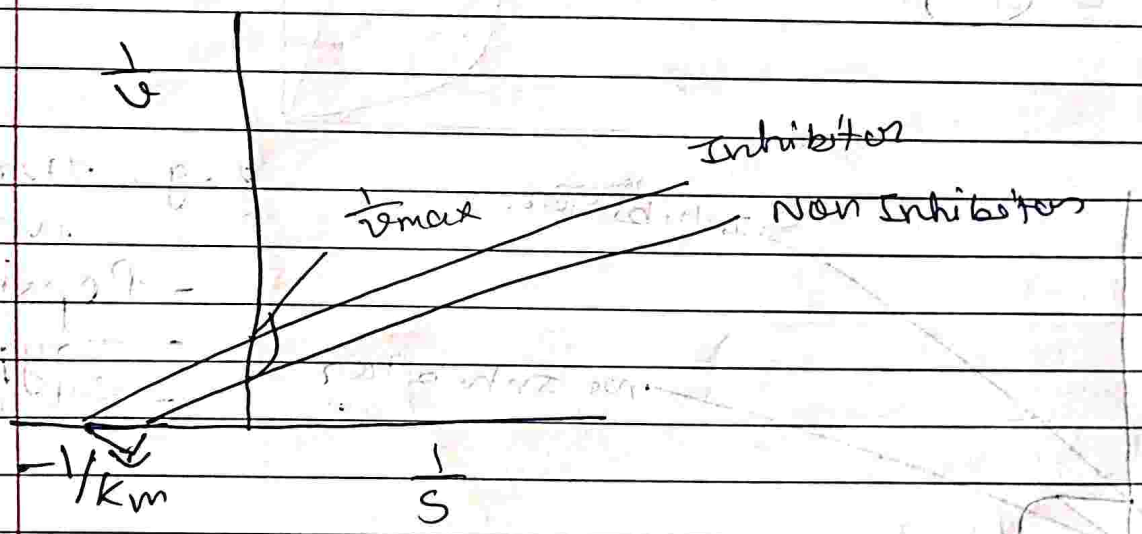
(c) Uncompetitive :- The inhibitor binds to enzyme at a site other than the active site.

» The inhibitor can bind only to the ES complex & not free enzyme

$$ES + I \rightleftharpoons ESI$$

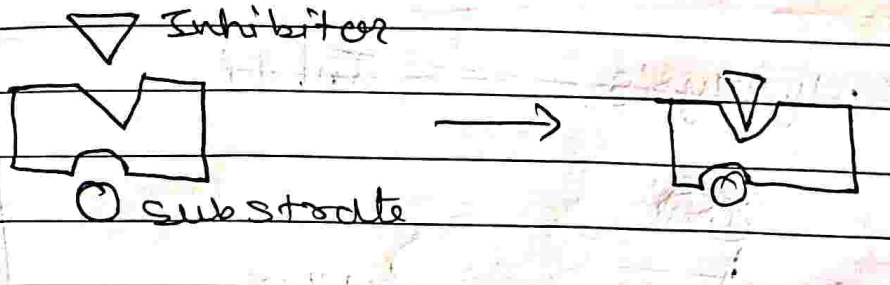


» e.g. Phenylalanine inhibit placental alkaline phosphate.



(2) Irreversible inhibition

- Inhibitor bind covalently with enzyme irreversibly so it can't dissociate from enzyme.
- Inhibitor cause conformation change at active site of E destroying their capacity to function as catalysts.
- Enzyme activity not regained by dialysis.



e.g. Disulfiram
cyanide
Fluoride
BAL :- British anti lewisite.

(3) Allosteric inhibition :-

- Some Enzyme possess additional site other than active site called allosteric site E
- They are unique protein molecule.
- It has positive & negative allosteric site in which +ve Ves activity & -ve ves activity

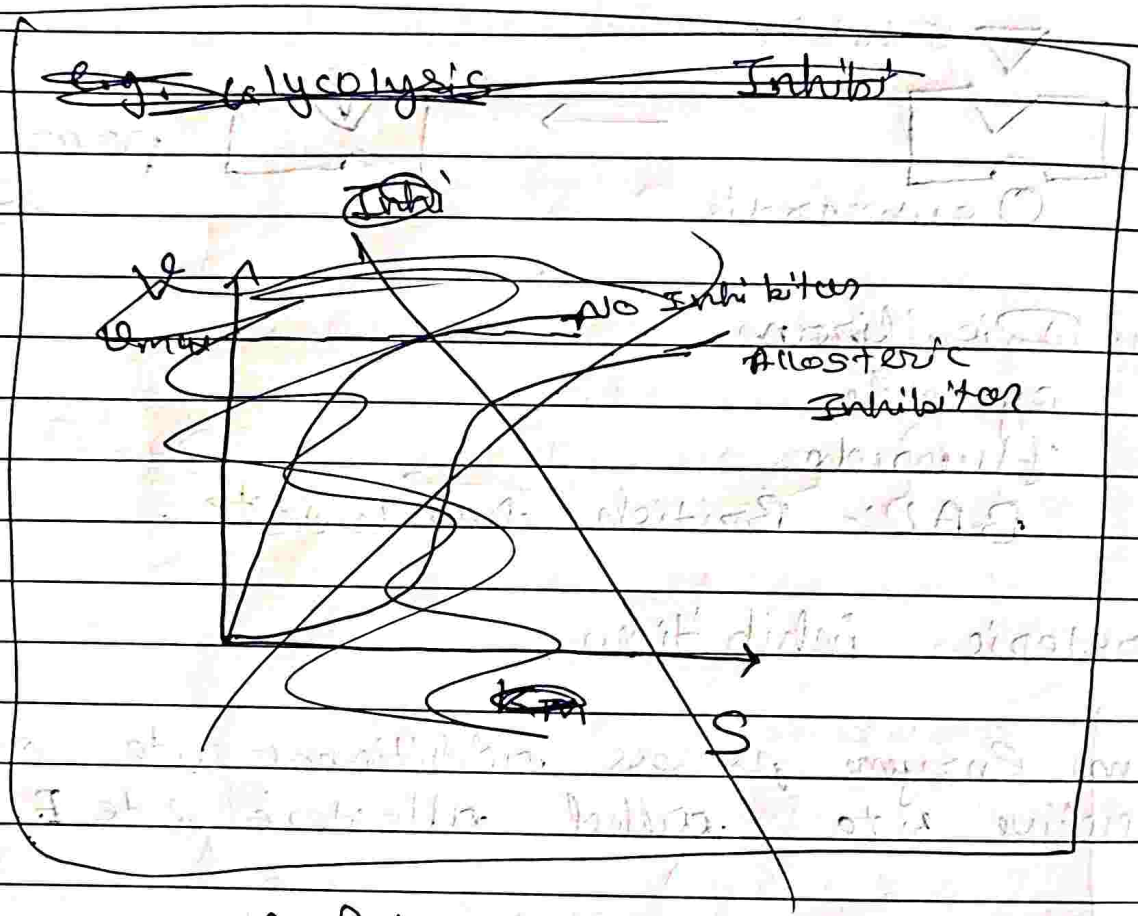
⇒ It is partially reversible.

⇒ It has 2 state in p'kinetic that low affinity than T S.rate where high & high affinity than R state.

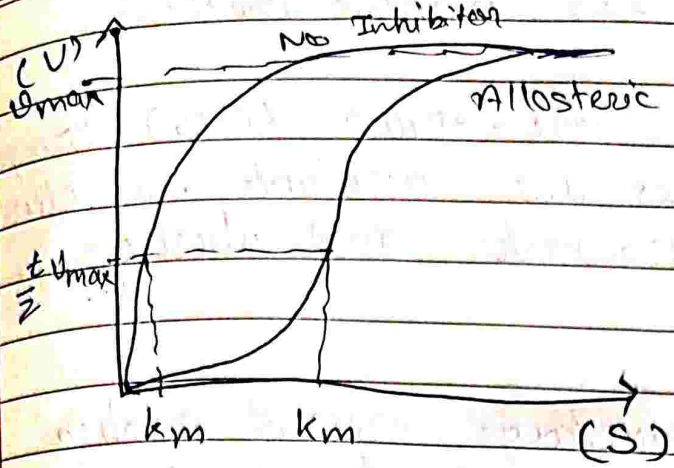
R - relax & T is tense.

Allosteric Inhibitor/activator

substrate.



e.g. • Pathway — Inhib. — Activa
- Glycolysis — ATP & Citrate — AMP
- TCA — ATP — ADP
- fatty acid synthesis — — Acetyl COA.



Q. Population p'kinetic Adaptive method or dosing with feedback

- In dosing drug with narrow therapeutic ratios, an initial dose is calculated based on mean population p'kinetic parameter.
- After dosing, plasma drug conc are obtained from patient.
- As more blood sample are drawn from patient, the calculated individualized patient p'kinetic parameter 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-square algorithm is used.

(A) Software used for Adaptive method.

- Many ordinary least-square (OLS) computer software packages are available to clinical practice for parameter and dosage calculation.

- Some software package record medical history & provide adjustment for weight, age & in some cases, disease factor.

- A common approach is to estimate the clearance & volume of distribution from intermittent infusion.

- Abbott base P'kinetic System is an example of patient-oriented ~~System~~ software that records patient information & dosing history based on 24 hr.

- An adaptive-type algorithm is used to estimate p'kinetic parameters include

  - Population clearance
  - Volume of distribution of drug
  - Patient Specific CL & V_D
  - Serum creatinine concentration

- The software package allows specific parameter estimation for digoxin, theophylline & aminoglycosides, although ~~often~~ other drugs can also be analyzed manually.

(B) Algorithms involved.

- many least-square (LS) & weighted least square (WLS) algorithms are available for estimating patient p'kinetic parameter.

- Their common objective involved estimation the parameters with minimum bias and good prediction, often as evaluted by mean predictive error.

- The advantage of Bayesian method is the ability to input known information into program, so that the search for the real p'kinetic parameter is more efficient & perhaps & more precise.

OLS method.

$$C_i = f(P, t_i) + E_i$$

$$OBJ_{OLS} = \sum_{i=1}^{n} \frac{(C_i - C_{ai})^2}{\alpha_i^2}$$

* delirium
* Constipation

7b) What are the factors considered in design of dosage regimen for pediatric pt ? Give any two formulae for calculation of child dose.

* Desiging a dosage regimen for pediatric pt involves multiple considerations due to unique physiological & developmental difference in children compared to adults.

* Factors to be considered :

- Age : Pediatrics range from neonates to adolescents, with significant variations in physiological development. Age influences drug metabolism & p'kinetics
  - Neonates (Birth to 28 days)
  - Infant (28 days - 23 months)
  - Young child (2-5 years)
  - Older child (6-11 years)
  - Adolescent (12-18 yr)
- Wt : It impacts drug distribution & metabolism
- Body Surface Area (BSA) : Dosing in cases like chemotherapy, to account for variations in body composition
- Developmental Stage : Diff stages of growth affect ADME
- Drug metabolism & excretion : They have varying levels of enzyme activity & renal function, affecting drug clearance
- ROA : Choice of drug formulation & delivery method influenced by age & ability to accept diff routes
- Therapeutic Goals & Safety : It's crucial to balance efficacy with safety, considering the ↑ sensitivity of pedia pt to certain drugs.

Kinetics

Absorption:

1) Diff in GI function: Pedia pt have diff GI pH levels, motility & enzyme activity
2) ROA: Children → difficulty swallowing pills, so liquid formulation or other delivery methods needed.

Distribution:

1) Body Composition: Children have ↑ water content, ↓ fat content compared to adults. affect distribution of hydrophilic & lipophilic drugs
2) Protein Binding: Levels of plasma protein like albumin ↓ in children, affect

Metabolism:

1) Enzyme activity: activity of liver enzyme responsible for drug metabolism such as CYP450 family can vary by age. Neonates ↓ enzym (slower) ↓ metabolism
2) Developmental Stages: M ↑ with age, reaching adult level in adolescen

Excretion

1) Renal function: RF ↓ in younger children, affect drug E. Leads to prolong drug action & ↑ toxicity risk
2) Hepatic function: Plays role in drug E, vary in pedia pt

Formula

1) Clark's Rule (Wt Based)

$$\text{Child's Dose} = \text{Adult Dose} \times \frac{\text{Child wt (kg)}}{70}$$

2) Young's Rule (Age Based)

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Child age (yr)}}{\text{age} \times 12}$$

3) Body Surface Area [BSA]

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Child's BSA } (m^2)}{1.73}$$

(2) What is the role of pharmacists in clinical pharmacokinetics?

→ pharmacokinetics is defined as the kinetics of drug absorption, distribution, excretion & their relationship to the pharmacologic, therapeutic or toxicological response in man & animals.

→ clinical pharmacokinetics
– The applications of pharmacokinetic principles in the safe & effective management of individual patient are called as clinical pharmacokinetics.

(1) Therapeutic drug monitoring
⇒ This involves measuring drug conⁿ in the blood to ensure they stay within therapeutic range not too high & not too low.

(2) Dose adjustment - Based on individual Patient characteristics such as age, weight, organ function (especially liver & kidney) & genetics, pharmacists can recommend appropriate dose modifications.

(3) Drug Interaction Analysis
→ Pharmacist evaluate potential drug interactions that might alter the the pharmacokinetics of drug, leading

to increased toxicity or reduce efficacy.

(4) pharmacokinetic consultations.
→ they provide advice to other healthcare professionals about drug metabolism, clearance, volume of distribution, & other pharmacokinetic parameters.

(5) Patient specific modelling
→ pharmacist might use software & pharmacokinetic models to predict individual patient responses to drugs & optimize dosing.

(6) Pharmacogenomics:
→ some drugs are metabolized or act differently based on genetic variations.

(7) Education
→ pharmacists educate both healthcare professionals & patients about pharmacokinetic principles, which can influence drug efficacy & safety.

(8) Research & development
→ pharmacist might be involved in pharmacokinetic research, contributing to our understanding of drug behavior in the body.

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(9) Kinetics in special popn
→ Patient like the elderly, pregnant women, infants, or those with certain diseases (eg HIV, cancer) might have unique pharmacokinetic considerations.
→ Pharmacist ensure these special popn receive appropriate & safe drug regimen.

(10) Adverse drug reaction monitoring
→ monitoring & reporting of potential adverse reactions related to pharmacokinetic variations or interactions.

KLE
Dr. Ramesh Bhandari
Asst. Profesor

Factors to be considered while selecting dosage regimen for children

i. Age
ii. Weight or Body surface area
iii. Dosage form or formulation
iv. Route of administration
v. Pharmacokinetics
vi. Interactions

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Asst. Profesor

Some useful formulas for Calculating child dose

✓ Fried's rule for infants

$$\frac{\text{Age in months} \times \text{Adult Dose}}{150} = \text{Dose for Infant}$$

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✓Young's rule

$$\frac{\text{Age (in Years)} \times \text{Adult Dose}}{\text{Age (in years)} + 12} = \text{Child dose}$$

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✓Child dose based on BSA

$$\frac{\text{BSA of child } (m^2) \times \text{Adult Dose}}{1.73\ M^2} = \text{Child dose}$$

Haycock formula for BSA:

$$BSA = 0.024265 \times W^{0.5378} \times H^{0.3964}$$

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Asst. Profesor

✓Clark's Rule

$$\frac{\text{Weight (in lb)} \times \text{Adult Dose}}{150 \text{ lb}} = \text{Child dose}$$

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Asst. Profesor

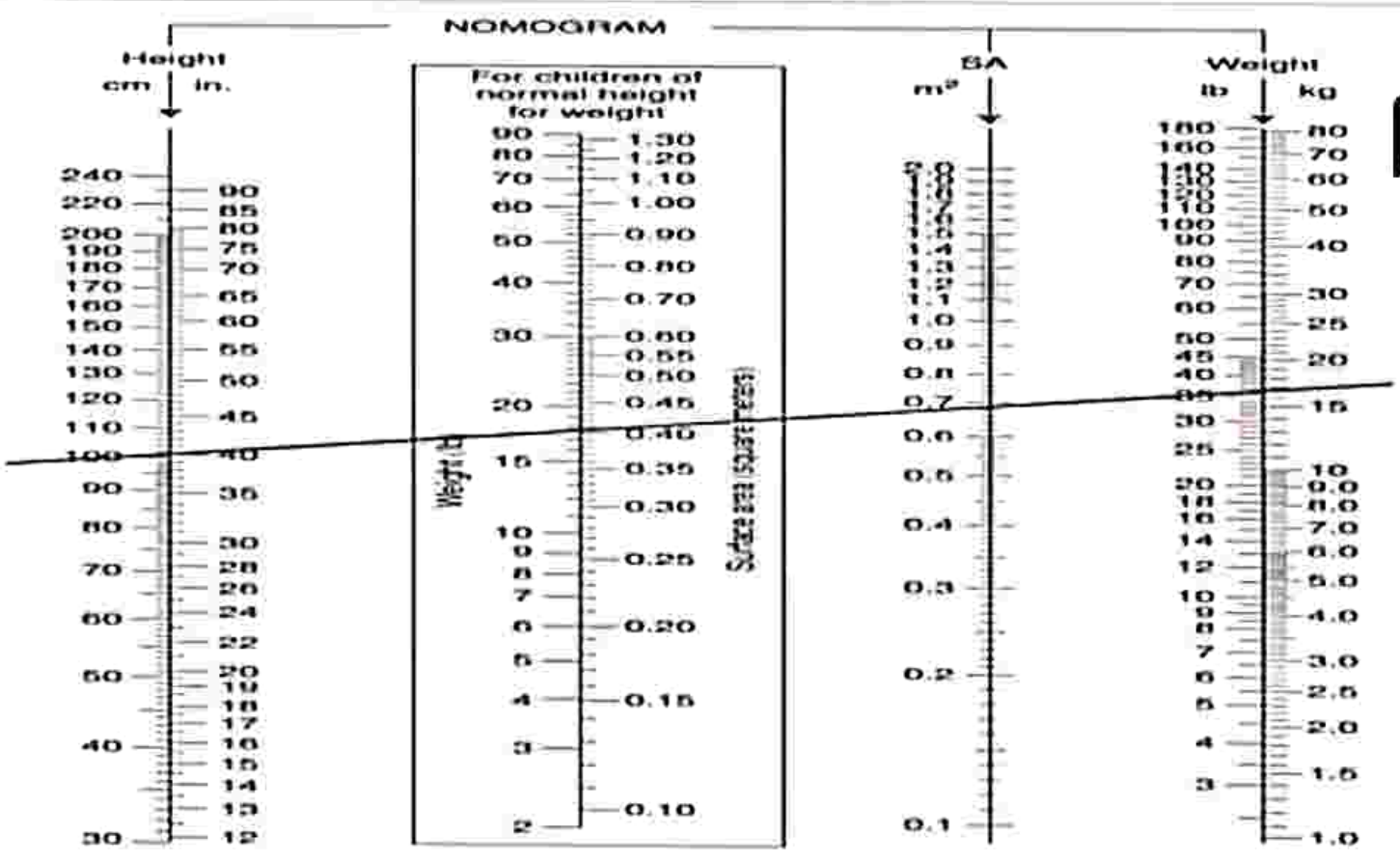
Practice Problem

✓The elimination half-life of penicillin G is **0.5 hour** in adults and **3.2 hours** in neonates (0–7 days old). Assuming that the normal adult dose of penicillin G is **4 mg/kg every 4 hours, calculate the dose of penicillin G** for an **11-lb infant**.

DOSE CALCULATION BASED ON BODY SURFACE AREA

Child dose= [Child's body surface area / Average adult body surface area] × Adult dose

(An average adult of 70kg, 175cm has a body surface area of 1.73m2. Child body surface area obtained from nomogram that determine body surface area using the height (cm or in) and weight (kg or lb) of the child.)



Pediatric doses of medications are generally based on body surface area (BSA) or weight. To calculate a child's BSA, draw a straight line from the height (in the left-hand column) to the weight (in the right-hand column). The point at which the line intersects the surface area (SA) column is the BSA (measured in square meters [m^2]). If the child is of roughly normal proportion, BSA can be calculated from the weight alone (in the enclosed area).