[redacted]

• Impairment or degeneration of kidney function affects the pharmacokinetics of drugs. Some of the more common causes of kidney failure include disease, injury and drug intoxication.

• Acute disease or trauma to kidney can cause uremia, in which glomerular filtration is impaired or reduced, leading the accumulation of excessive fluid and blood nitrogenous products in the body.

• Uremia, generally reduces glumerular filtration and/or active secretion, which leads to decrease in renal drug excretion resulting in a long elimination half life of administered drug.

• Pharmacokinetic process, such as distribution and elimination may also be altered by

renal impairment.

- Overall, uremic patient have special dosing consideration to accounts for such pharmacokinetics and pharmacodynamic alterations

[redacted]

Pyelonephritis:

Inflammation and deterioration of pyelonephrons due to infection, antigens or other causes.

Hypertension: Chronic overloading of kidney with fluid and electrolytes may leads to kidney insufficiency.

DM: The disturbance of sugar metabolism and acid-base balance may lead or pred-

- High blood pressure can damage blood vessels in the kidneys, reducing their ability to work properly. If the kidneys' blood vessels are damaged, they may stop removing wastes and extra fluid from the body. Extra fluid in the blood vessels → raise BP even more. (cycle)

ispose a patient to degenerative renal disease

DM → damage blood vessel
↳ damage nerve → difficulty in emptying your bladder

Hypovolemia: Any condition that cause a reduction in renal blood flow which lead to renal ischemia and damage.

□ Pharmacokinetic alterations:

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

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

• Bioavailability: The oral bioavailability of

a drug such as propranolol (which has a high first pass effect) may be increase in patient with renal impairment as a result of decrease in first pass hepatic metabolism.

Volume of distribution:

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

Protein binding:

The plasma protein binding of weak acidic drugs in uremic patient is decreased and whereas protein binding of weak basic drugs less affected. The decrease in

protein binding, result in larger fraction of free drugs and increase in volume of distribution.

- Elimination half life:

The net elimination half-life is generally increase as a result of dominant effect of reduced glumerular filtration.

- In clinical practices, estimation of drug dosage in renal impairment is based on an estimate of remaining renal function of patient and prediction of total body clearance.

Assumption	Comment
Creatinine clearance accurately measures the degree of renal impairment	Creatinine clearance may be biased. Renal impairment should be verified by physical diagnosis and other clinical test.
Drug follows dose-independent pharmacokinetics	pharmacokinetic should not be dose-dependent (nonlinear)
Non-renal drug elimination remains constant	Renal disease may also affect the liver and cause a change in non-renal drug elimination (drug metabolism)
Drug absorption remains constant	unchanged drug absorption from GIT
Drug clearance, Cl_u, declines linearly with creatinine clearance Cl_{cr}	Normal drug clearance may include active secretion and passive filtration and may not decline linearly
Unaltered drug protein binding	Drug protein binding may be altered due to accumulation of urea, nitrogenous wastes and drug metabolites

Target drug concentration remains constant	changes in electrolyte composition such as K^+ may affect sensitivity to effect of digoxin. Accumulation of active metabolite may cause more intense pharmacodynamic response compared to parent drug alone

I. Dose adjustment based on drug clearance:-

Method based on drug clearance try to maintain the desired C^{∞}_{avg} after multiple oral doses or multiple iv bolus injection as total body clearance, Cl_T, changes; C^{∞}_{avg} is calculated as:

$$C^{\infty}_{avg} = \frac{FD_0}{Cl_T \cdot \tau} \quad \text{.1}$$

τ = Dosing intervals

for a patient with a uremic condition, total body clearance of uremic patient will change to new value, Cl_T^u so to maintain the same desired C_{avg}^{∞}, the dose must be changed to uremic dose, D_o^u or dosage interval must changed to τ^u, as shows as:

$$C_{avg}^{\infty} = \frac{D_o^N}{Cl_T^N \cdot \tau^N} = \frac{D_o^U}{Cl_T^U \cdot \tau^U} \quad .2$$

N = Normal condition

U = uremic condition

·Rearranging the equation 2, given:

$$D_o^U = \frac{D_o^N \, Cl_T^U \, \tau^U}{Cl_T^N \, \tau^N} \quad .3$$

·If the dosage interval is kept constant, then the uremic dose D_o^U is equal to a fraction of

normal dose as:

$$D_0^U = \frac{D_0^N \, Cl_T^U}{Cl_T^N} \quad .4$$

• For iv infusion, the same desired C_{ss} is maintained both for patient with normal renal function and for patient with renal impairment. So, the rate of infusion R must be changed to new value R^u, for uremic patient, as

$$C_{ss} = \frac{R^N}{Cl_T^N} = \frac{R^U}{Cl_T^U} \quad .5$$

Normal Uremia

II. Dose adjustment based on changes in the elimination rate constant:

• The overall elimination rate constant for many drug is reduced in the uremic patient.

• Doses of drug, with a narrow therapeutic range should be reduced.

• The usual approach to estimating a multiple dosage regimen in the normal patient is to maintain a desired C^{∞}_{avg} as shown.

Assuming the V_D is the same both normal and uremic patients and is constant, then the uremic dose D^U_0 is a fraction (K^U/K^N) of normal dose

$$D^U_0 = \frac{D^N_0 K^U}{K^N} \qquad .6$$

• When the elimination rate constant for a drug in uremic patient can not determined directly, indirect method are available to calculate the predicted elimination rate constant based on renal function of patient.

• The assumption on which these dosage regimens are calculated included the following:

1. The renal elimination rate constant, (K_R)

decrease as renal function decrease ($K_R = K_e$)

2. The non-renal route of elimination remains unchanged.

3. Changes in renal clearance of drug are reflected by changes in creatinine clearance.

$$K^U = K_{nr} + K_R^U \quad -7$$

K_{nr} = non-renal elimination rate constant

K_R = Renal elimination rate constant

K^U = overall elimination rate constant

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

$$Cl_R^U = K_R^U \cdot V_D^U \quad -8$$

Rearranging the equation given

$$K_R^U = Cl_R^U \left(\frac{1}{V_D^U}\right) \quad -9$$

• Assuming if, the apparent volume of distribution and non-renal route of elimination do not change in uremia, then

$$K_{nr}^{U} = K_{nr}^{N} \text{ and } V_D^U = V_D^N$$

• Substituting equation 9 into equation 7 gives:

$$K^U = K_{nr} + \frac{1}{V_D}(Cl_R^U)$$

• From this equation, a change in renal clearance Cl_R^U due to renal impairment will be reflected in a change in the overall elimination rate constant (K^U).

• Cl_R^U is related to the measurement of kidney function by glomerular filtration rate (GFR) & in turn is estimated by change in patient's creatinine clearance.

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

Dosage regimen need not be changed when:
- The fraction of drug excreted unchanged, f_u is ≤ 0.3 and
- The renal function RF is ≥ 0.7 of normal

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

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

$$\text{Drug dose in renal impairment} = \text{Normal dose} \times RF$$

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

$$\text{Dosing interval} = \frac{\text{Normal interval in hours}}{RF}$$

• When the drug is eliminated both by renal and nonrenal mechanisms, the dose to

be administered in patients with renal failure is obtained from equation:

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

$$\text{RF} = \frac{Cl_{cr} \text{ of patient}}{Cl_{cr} \text{ of a normal person}}$$

- The overall elimination rate constant for many drugs may be reduced in case of uremic patient.
- A dosage regimen may be designed for uremic patient by reducing the normal dose of drug and keeping the frequency of dosing constant or by decreasing the frequency of dosing and keeping the dose constant.

- Renal function can be determined by measuring the GFR.
- Both endogenous and exogenous substances have been used as markers to measure GFR.
- In order to be useful as a marker, the agent should entirely get excreted in unchanged form by glomerular filtration only and should be physiologically and pharmacologically inert.
- The rate at which these markers are excreted in urine reflects the GFR and changes in GFR reflects renal dysfunction.

- Tests to estimate GFR:

Endogenous markers
- Urea
- Creatinine

Exogenous markers
- Inulin
- Radioactive Substances

- Blood urea nitrogen:

Normal range: 8-20 mg/dl

BUN is actually the concentration of nitrogen within urea in the serum. It is commonly used for renal disease.

BUN can be reflection of the GFR.

Common causes of elevation of BUN:

Excessive protein intake

Reduced renal blood flow

Common causes of decreased BUN:

Patients who are malnourished

Profound liver damage

- Creatine clearance:

It is used most as measurement of GFR.

- It varies with the age, weight, gender.
- Cl_{cr} is the rate of urinary excretion.

□ Methods of estimation:

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

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

→ page no: 210

2. Using Serum creatine and body length:

$$Cl_{cr} = \frac{KL}{S_{cr}}$$

K = Constant of proportionally that is age specific.
L = Length in cm

3. Estimation of creatinine clearance using Serum creatinine and height.

$$Cl_{cr} = \frac{0.48 \times height}{S_{cr}}$$

4. Jellife's method:

- This is based on age and serum creatinine concentration of the patient.
- This method is not intended for patients under 20 years of age.
- This method is generally applicable for adult patients upto the age of 80 years.

$$\text{Males: } Cl_{cr} = \frac{98 - 0.8\,(Y - 20)}{C_{cr}}$$

Y = age in year and C_{cr} = Serum creatinine concentration in $mg/_{100}{}^{ml}$

$$\text{Females: } Cl_{cr} = (0.9)\,\frac{98 - 0.8\,(Y - 20)}{C_{cr}}$$

5. Cockraft and Gault's method:

This method is based upon the age, weight and serum creatinine concentration of the pt.

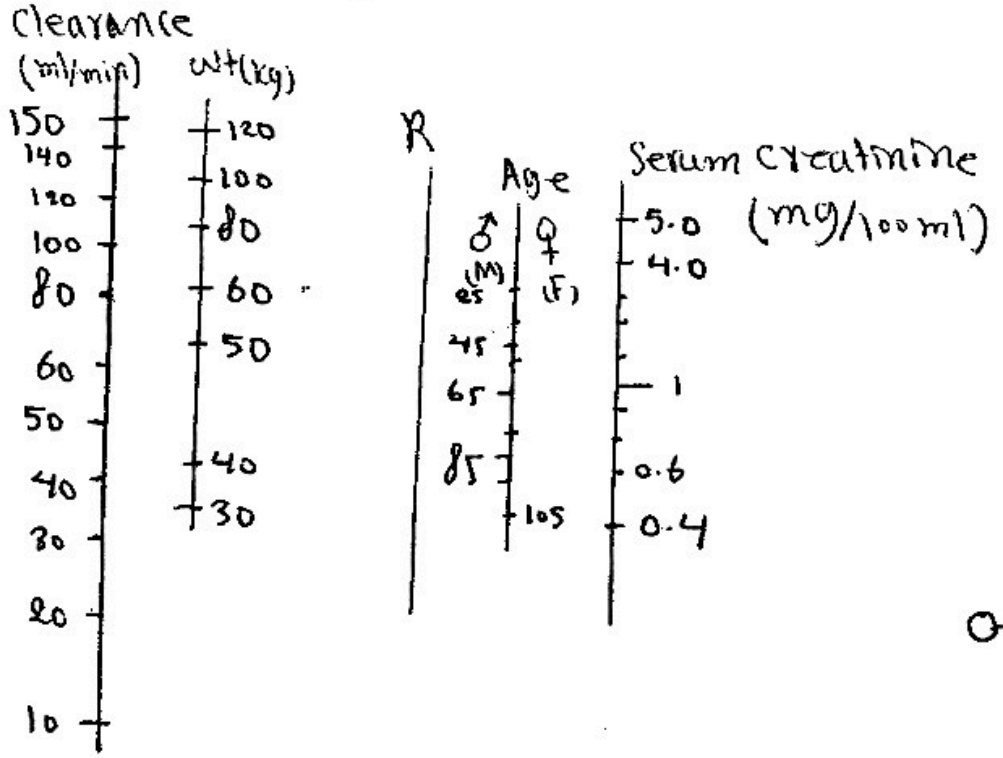
$$\text{Males: } Cl_{Cr} = \frac{(140-y)(W)}{(72)(C_{Cr})}$$

W = weight in kg

$$\text{Females: } Cl_{Cr} = (0.85)\frac{(140-y)(W)}{(72)(C_{Cr})}$$

6. Siersback-nielsen nomogram method:

Here instead of an equation this method uses a nomogram.



• Inulin clearance:

Normal range: M: 127 ml/min/m^2

F: 118 ml/min/m^2

• An inert carbohydrate which is not bound to plasma proteins, inulin is freely filtered through the glomerulus and not metabolized, secreted or reabsorbed and can be regarded as gold standard for measuring GFR in adults and older children.

• The test is fairly invasive because inulin must be administered i.v and it requires special analytical methods that limit the practical application in many health care facilities.

- time consuming.

• Glomerular filtration rate:

- The amount of fluid from the blood into the glomerular capsule per unit time is known as glomerular filtration rate. (GFR)
- The GFR of 130 ml/min is considered normal in healthy state, although a range of 131 ± 22 ml/min is the normal range.
- The filtration process is passive in nature, and drug in the plasma provide its molecular dimension are small will be filtered in the glomeruli.
- Filtration does not occur if the drug is associated with formed elements of blood, or is bound to the plasma protein. This is because association or binding of drug increases not only the size, but also molecular weight of the compound.

□ Factors influencing glomerular filtration:

1. Total surface area available for filtration.

2. Permeability of the filtration membrane
3. Net filtration pressure.

- The net filtration pressure is the glomerular (55 mm Hg) hydrostatic pressure minus the sum of glomerular osmotic pressure (30 mm Hg) and capsular hydrostatic pressure (15 mm Hg).

55 mm Hg − 30 mm Hg − 15 mm Hg = 10 mm Hg

□ Several criteria are necessary to use a drug to measure GFR:

1. The drug must be freely filtered at the glomerulus.
2. The drug must not be reabsorbed nor actively secreted by the renal tubules.
3. The drug should not be metabolized
4. The drug should not bind significantly to

plasma protein.

5. The drug should not have an effect on the filtration rate nor alter renal function.

6. The drug should be non-toxic.

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

$$GFR = \frac{\text{excretion rate}}{\text{Plasma concentration}}$$ unit: $\frac{ml}{min}$

- Glomerular filtration rate is usually expressed as ml/min, although it is not uncommon to express it as L/hr. If a drug is not bound to plasma proteins, it is filtered in the amount equal to:

$$Q = (C_p)(GFR)$$

Q = amount of drug filtered through glomeruli (mg/min)

C_p = Concentration of drug in plasma (mg/ml)

GFR : ml/min

• Creatinine clearance values must be considered carefully in special population such as the elderly, obese, and emaciated patients.

• In elderly and emaciated patients, muscle mass may have declined, thus lowering the production of creatinine.

However, serum creatinine concentration values may appear to be in the normal range, because of lower renal creatinine excretion.

• Thus, the calculation of creatinine clearance from serum creatinine may give an inaccurate estimation of the renal function.

• For obese patient, generally defined as patients more than 20% over ideal body weight, IBW, creatinine clearance should be based on ideal body weight.

Or

• The Sierback-Nielsen method of determining creatinine clearance is similar to the method of cockraft and Gault in that this method also makes use of Serum creatinine concentration, weight, age and gender of the patient, the difference in the two methods is that instead of an equation, this method uses a nomogram. Although use of nomogram is relatively easier than using an equation generally provides a more accurate answer.

• The nomogram consists of five vertical lines, drawn parallel to, and at suitable distances from each other. These lines are labelled (from left to right) as follows: clearance (in ml/min), weight (in kg), R (no units, because this line represents the point of reference), age (in years),

and serum creatinine (in mg/100ml).

• The vertical line labelled "Age" is marked separately for males and females, the markings on right side of this line are for females and markings on the left side are for males.

The nomogram is used as follows:

1- Draw a straight line to connect patient's weight (on the second line from left) to the patient's age (on the second line from right) this gives a point of intersection on the middle line K.

2- Draw a straight line to connect the patient's serum creatinine value (in mg/100ml) on the first line on right to the point of intersection on line K and extrapolate this straight line to the first line on left to read creatinine clearance.

▫Children:

In pediatric practice, determination of creatinine clearance using the relationship b/w urinary creatinine excretion rate and concentration of creatinine in the serum is not used. This is because collection of a 24 hour pooled sample of urine for determination of excretion rate of creatinine in the urine is just not feasible in infants and children.

1. Method of Schwartz and associates:

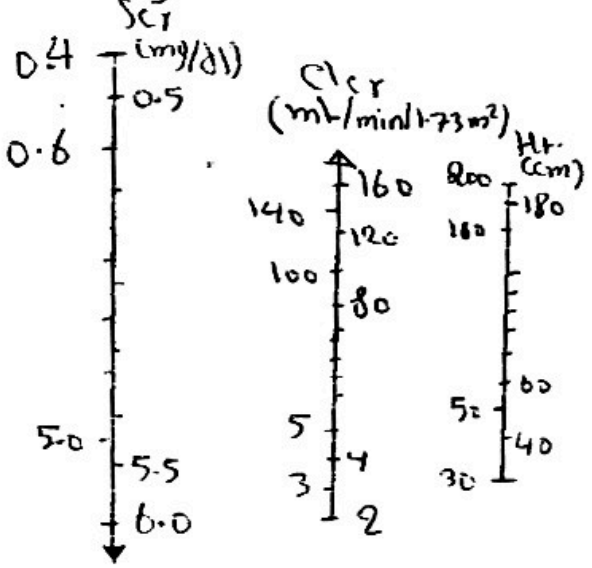
. This method uses the following equation for calculating creatinine clearance in children, the creatinine clearance obtained is expressed in $ml/min/1.73\ m^2$

$$Cl_{cr} = \frac{(0.55)(Hi = \text{height in cm})}{Ccr}$$

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

2- Method of Traub and Johson:

- This method uses a nomogram which require the height and serum creatinine concentration of the patient.
- This nomogram is consists of three vertical straight lines, drawn parrallel to each other and suitable distances from each other.
- These straight lines are as follow:



a-The vertical line on the left represent serum creatinine concentration. This straight line is subdivided into units expressing serum creatinine concentration in mg/100 ml.

b-The vertical line on the right represents height. This straight line is subdivided into units heigtht of the child in centimeters

c)The vertical line in the middle of these two lines represents creatinine clearance. This straight line is subdivided into units and expresses creatinine clearance in ml/min/1.73 m^2.

. In Traub and Johnson for the administration of creatinine clearance of a child does not take into consideration the age or weight of the patient

It means this method will yield the same creatinine clearance for all children regardless of their age or weight, as long as these children have the same height and same serum creatinine concentration.

- This nomogram is used as follows:

- Draw straight line to connect the patient's serum creatinine value (in mg/100mL) to the patient's height (in cm). The point of intersection of this straight line and the vertical line in the middle of nomogram indicates creatinine clearance of the patient in ml/min/1.73 m^2

☐ Dose adjustment for uremic patients

- Dose adjustment for drugs in uremic or renally impaired patients should be made in accordance with changes in pharmacodynamics and pharmacokinetics of the drug in the individual patient.
- Active metabolites of the drug may also be formed and must be considered for additional pharmacologic effects when adjusting dose.
- The following methods may be used to estimate an initial and maintenance dose regimen.
- After initiating the dosage, the clinician should continue to monitor the pharmacodynamics and pharmacokinetics of the drug.
- He or she should also evaluate the patient's renal function, which may be changing.

oBasic for Dose Adjustment in Uremia:

- The loading drug dose is based on the apparent volume of distribution of the patient.
- It is generally assumed that the apparent volume of distribution is not altered significantly, and therefore that the loading dose of the drug is the same in uremic patients as in subjects with normal renal function.
- The maintenance dose is based on clearance of the drug in the patient.
- In the uremic patient, the rate of renal drug excretion has decreased, leading to a decrease in total body clearance. Most methods for dose adjustment assume nonrenal drug clearance to be unchanged.
- The fraction of normal renal function remaining in the uremic patient is estimated from creatinine

clearance.

- After the remaining total body clearance in the uremic patient is estimated, a dose regimen may be developed by:

1- Decreasing the maintenance dose

2. increasing the dosage interval or

3. Changing both maintenance dose and dosage interval.

- Although total body clearance is a more accurate index of drug dosing, the elimination half-life of the drug is more commonly used for dose adjustment because of its convenience.

- Clearance allows for the prediction of steady state drug concentrations, while elimination half-life yields information on the time it takes to reach steady-state concentration.

1. Nomograms:

Nomograms are charts available for use in estimating dosage regimens in uremic patients.

- The nomograms may be based on serum creatinine concentrations, patient data (height, weight, age, gender) and the pharmacokinetics of the drug.
- Most methods for dose adjustment in renal disease assume that nonrenal elimination of the drug is not affected by renal impairment and that the remaining renal excretion rate constant in the uremic patient is proportional to the product of a constant and the creatinine clearance, Cl_{cr}:

$$K_u = K_{nr} + \alpha Cl_{cr}$$

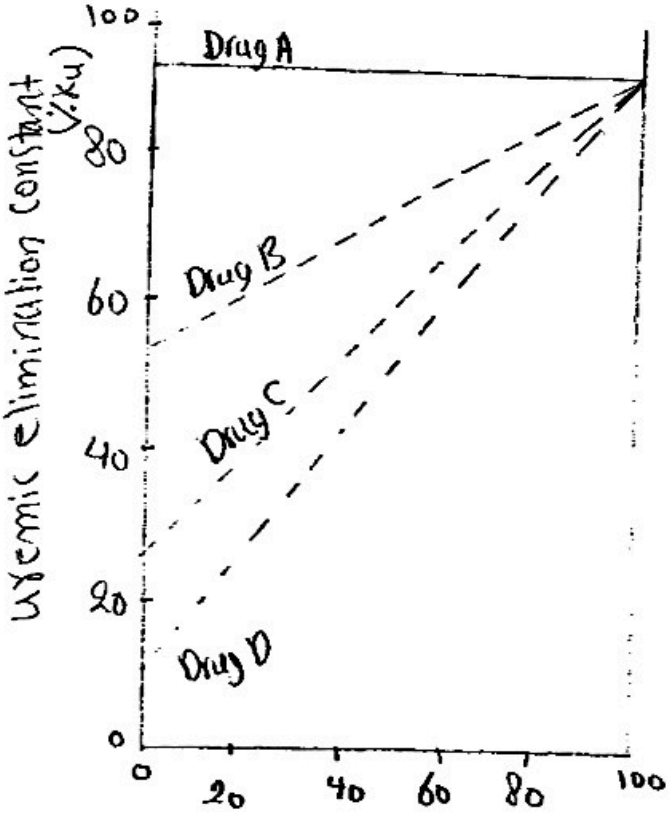
where K_{nr} is the nonrenal elimination rate constant and α is a constant.

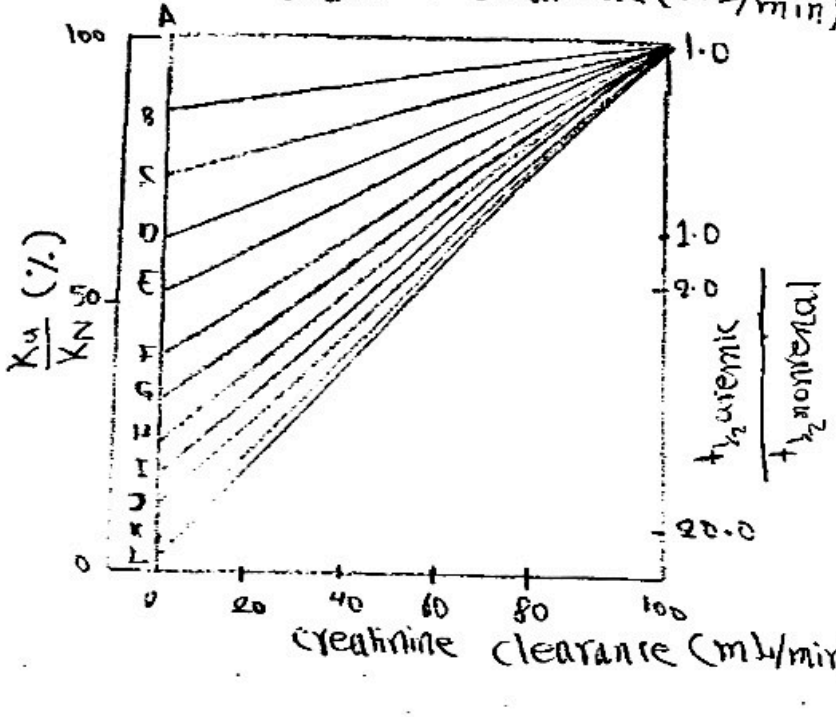
. A graphical representation of this equation for four different drugs, each with a different renal excretion rate constant. The fractions of drug excreted in the urine unchanged, fe, for drug A, B, C and D are 5%, 50%, 75% and 90% respectively.

A creatinine clearance of 80 $^{mL}/_{min}$ is considered an adequate glomerular filtration rate in subjects with normal renal function. The uremic elimination rate constant (K_u) is the sum of the nonrenal elimination rate constant and the renal elimination rate constant, which is decreased due to renal impairment.

. If the patient has complete renal shutdown (ie, creatinine clearance = 0 $^{mL}/_{min}$), then the intercept on the y axis represents the percent of drug elimination due to nonrenal drug elimination routes. Drug D, which is excreted 90% unchanged in the urine, has the steepest

Slope and is most affected by small changes in creatinine clearance, whereas drug A, which is excreted only 5% unchanged in the urine (i.e., 95% eliminated by nonrenal routes), is least affected by a decrease in creatinine clearance.





The nomogram method of provides an estimate of the ratio of the uremic elimination rate constant (K_u) to the nonrenal elimination rate constant (K_N) on the basis of creatinine.

. From the $\frac{K_u}{K_N}$ ratio, the uremic dose can be estimated according to Equation:

$$\text{Uremic dose} = \frac{K_u}{K_N} \times \text{normal Dose}$$

. When the dosage interval is kept constant, the uremic dose is always a smaller fraction of the normal dose.

. Instead of reducing the dose for a uremic patient, the usual dose is kept constant and the dosage interval is prolonged according to the following equation:

$$\tau_U = \frac{K_N}{K_U} \times \tau_N$$

- where τ_U is the dosage interval for the dose in uremic patients and τ_N is the dosage interval for the dose in patients with normal renal function.

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

$$\frac{K^U_r}{K^N_r} = \frac{Cl^U_{Cr}}{Cl^N_{Cr}}$$

$$K^U_r = \frac{Cl^U_{Cr} \cdot K^N_r}{Cl^N_{Cr}}$$

- where K^U_r is the uremic renal excretion rate constant and K^N_r is the normal renal excretion rate constant.

• Because the overall uremic elimination rate constant, K_u, is the sum of renal and nonrenal elimination.

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

$$K_u = K^u_{nr} + K^N_r \left(\frac{Cl^u_{cr}}{Cl^N_{cr}} \right)$$

• Dividing Equation by K_N on both sides yields:

$$\frac{K_u}{K_N} = \frac{K^u_{nr}}{K_N} + \frac{K^N_r}{K_N} \cdot \frac{Cl^u_{cr}}{Cl^N_{cl}}$$

Let $f_e = K^N_r / K_N$ = fraction of drug excreted unchanged in the urine and $1 - f_e = K^u_{nr} / K_N$ = fraction of drug excreted by nonrenal routes.

Substitution into Equation yields the Giusti-Hayton equation, where G is the Giusti-Hayton factor, which can be calculated from the f_e and the

ratio of uremic to normal clearance:

$$\frac{K_u}{K_N} = (1 - f_e) + f_e\left(\frac{Cl_{cr}^{u}}{Cl_{cr}^{N}}\right)$$

or

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

- The ratio $\frac{K_{nr}^{u}}{K_N}$ can be calculated from the fraction of drug excreted by the kidney, normal creatinine clearance, and the creatinine clearance in the uremic patient.

3. General Clearance Method:

The general clearance method is based on the methods discussed above. This method is popular in clinical settings because of its simplicity. The method assumes that creatinine clearance, Cl_{cr}, is a good indicator of renal function and

that the renal clearance of a drug, Cl_R, is proportional to Cl_{cr}. Therefore, renal drug clearance, Cl_R^u, in the uremic patient is:

A. $$Cl_R^u = \frac{Cl_{cr}^u}{Cl_{cr}^N} \cdot Cl_R$$

B. $$Cl_u = Cl_{nr} + Cl_R \cdot \frac{Cl_{cr}^u}{Cl_{cr}^N}$$

- where Cl_u is the total body clearance in the uremic patient.
- If the ratio $\frac{Cl_{cr}^u}{Cl_{cr}^N}$, Cl_{nr} and Cl_R are known, the total body clearance in the uremic patient may be estimated using Equation (B).
- Alternatively, if the normal total body clearance Cl, and f_e are known, Equation (C) may be obtained by substitution in Equation (B):

C. $$Cl_u = Cl_{(1-fe)} + fe \cdot Cl \cdot \frac{Cl^u_{cr}}{Cl^N_{cr}}$$

Equation C. calculates drug clearance in the uremic patient using the fraction of drug excreted unchanged (f_e), total body clearance of the drug (Cl) in the normal subject, and the ratio of creatinine clearance of the uremic to that of the normal patient.

Dividing Equation C. on both sides by Cl yields, the ratio $\frac{Cl_u}{Cl}$, reflecting the fraction of the uremic/normal drug dose.

$$\frac{Cl_u}{Cl} = (1-fe) + fe \cdot \frac{Cl^u_{cr}}{Cl^N_{cr}} \quad (D)$$

4. The Wagner Method:

This method takes advantage of the fact that

the elimination constant for a patient can be obtained from the creatinine clearance as follows.

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

The values of a and b are determined statistically for each drug from pooled data on uremic patients.

- The method is <u>simple to use</u> and should provide accurate determination of elimination constants for patients when a good linear relationship exists b/w elimination constant and creatinine concentration.
- The theoretical deviation of this approach is as follows:

$K\%$ = total elimination rate constant

K_{nr} = non renal elimination rate constant

K_r = renal elimination rate constant

Cl: total body clearance

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

$$Cl = R Cl_{cr}$$

$$K = K_{nr} + \frac{R Cl_{cr}}{V_d}$$

$$K = K_{nr} + \frac{R}{V_d} Cl_{cr}$$

$$100K = 100K_{nr} + \frac{100R}{V_d} Cl_{cr}$$

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

□ Comparison of the various methods for Dose Adjustment in uremic patients:

- All of the methods mentioned previously have similar limitations.
- For example, the drug must follow dose-independent kinetics and the volume of

distribution of the drug must remain relatively constant in the uremic patient.

- It is usually assumed that the nonrenal routes of elimination, such as hepatic clearance do not change. Because no correction for metabolites is made, any drug having an active pharmacologic metabolite must be additionally modified.

- Another assumption in the use of these methods is that pharmacologic response is unchanged in the uremic patient. This assumption may be unrealistic for drugs that act differently in the disease state.

- For example, the pharmacologic response with digoxin is dependent on the potassium level in the body, and the potassium level in the uremic patient may be rather different from

that of the normal individual. In a patient undergoing dialysis, loss of potassium may increase the potential of toxic effect of the drug digoxin.

- For many drugs, studies have shown that the incidence of adverse effects is increased in uremic patients.
- It is often impossible to distinguish whether the increase in adverse effect is due to a pharmacokinetic change or to a pharmacodynamic change in the receptor sensitivity to the drug.

Considering these assumption, dose adjustment must be regarded as a preliminary estimation to be followed with further adjustments in accordance with the observed clinical response.

□ Introduction:

Patients with end stage renal disease (ESRD) and patients who have become intoxicated with a drug as a result of a drug overdose require supportive treatment to remove the accumulated drug and its metabolites.

- The objective of these methods is to rapidly remove the undesirable drugs and metabolites from the body without disturbing the fluid and electrolyte balance in the patient.

There are 3 methods:

- Hemoperfusion
- Hemofiltration
- Dialysis

- Extracorporeal: Situated or occurring outside the body.

□ Dialysis:

Dialysis is an artifical process in which the

accumulation of drugs or waste metabolites is removed by diffusion from the body into the dialysis fluid.

- There are 2 subdivisions under dialysis:

1. Peritoneal dialysis
2. Hemo dialysis

- Both processes work on the principle that as the uremic blood or fluid is equilibrated with the dialysis fluid across a dialysis membrane waste metabolites from the patient's blood or fluid diffuse into the dialysis fluid and are removed.

- The dialysate contains:

- Water, dextrose, electrolytes, potassium, sodium chloride, bicarbonate, acetate, calcium, etc) and other elements similar to normal

body fluids without the toxins.

1. Peritoneal dialysis.

Peritoneal dialysis uses the peritoneal membrane in the abdomen as the filter. The peritoneum consists of visceral and parietal components.

The peritoneum membrane provides a large natural surface area for diffusion of approximately 1-2 m in adults. The membrane is permeable to solute of molecular weights= 30,000 Da

- Total Splanchnic flow is 1200 ml/min at rest but only a small portion, approximately 70ml/min comes into contact with the peritoneum.

- Placement of a peritoneal catheter is surgi-

→ in water, substances in water tend to move from an area of high concentration to an area of low concentration.

cally simpler than hemodialysis and doesn't require vascular surgery and heparinization.

- The dialysis fluid is pumped into the peritoneal cavity, where waste metabolites in the body fluid are discharged rapidly. The dialysate is drained and fresh dialysis fluid is reinstilled and then drained periodically.
- Peritoneal dialysis is also amendable to self-treatment.

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

- Continuous ambulatory peritoneal dialysis (CAPD) is the most common form of peritoneal dialysis.

- Many diabetic patients become uremic as a result of lack of control of their diabetes. About 2L of dialysis fluid is installed into the peritoneal cavity of the patient through a surgically placed resident catheter.
- The objective is to remove accumulated urea and other metabolic waste in the body. The catheter is sealed and the patient is able to continue in an ambulatory mode.

Every 4-6 hours the fluid is empties from the peritoneal cavity and replaced with the fresh dialysis fluid. The technique uses about 2L of dialysis fluid; it does not require a dialysis machine and can be performed.

2. Hemo dialysis:

Hemo dialysis uses a dialysis machine and filters

blood through an artifical membrane.

- Hemodialysis requires access to the blood vessels to allow the blood flow to the dialysis machine and back to the body.

- For temporary access, a shunt is created in the arm with one tube inserted into an artery and another tube inserted in a vein. The tubes are joined above the skin.

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

- At the start of hemodialysis procedure an arterial needle, allows the blood flow to the dialysis machine, and blood is returned to the patient to the venous side.

- Heparin is used to prevent blood clotting

during the dialysis period.

• During hemodialysis, the blood flows through the dialysis machine, where the waste product is removed from the blood by the diffusion through and artificial membrane before the blood is returned to the body.

• Hemodialysis is preferred in situations when:

→ Rapid removal of drug from the body is important.

→ In overdose or poisoning

• Dialysis may be required from once every 2 days to 3 times a week with each treatment period lasting 2 to 4 hours.

• The time required for dialysis depends on the amount of residual renal function in the patient, any complicating illness (eg, diabetes mellitus), the size and the weight of the patient, including muscle mass, and the efficiency of

the dialysis process.

- Dosing of drug in patients receiving hemodialysis is affected greatly by the frequency and type of dialysis machine used and by the physiochemical and pharmacokinetic properties of the drug..

- **Factors affecting dialysability of drugs:** 2M

Physicochemical and pharmacokinetic properties of drug

Water Solubility	Insoluble or fat-soluble drugs are not dialysed eg: glutethamide, which is very water insoluble
Protein binding	Tightly bound drugs are not dialyzed because dialysis is passive process of diffusion eg: propranolol is 94% bound
Molecular Weight	only molecules with molecular weights of less than 500 are easily dialyzed e.g vancomycin is poorly dialyzed and has a MW of 1800.

Drugs with large volumes of distribution	Drugs widely distributed are dialyzed more slowly because the rate limiting factor is the volume of blood entering the machine - eg, for digoxin, V_d = 250 - 300 L. Drugs concentrated in the tissues are usually difficult to remove by dialysis

Characteristics of dialysis machine:

Blood flow rate	Higher blood flows give higher clearance rates.
Dialysate	composition of dialysate and flow rate
Dialysis membrane	Permeability characteristics and surface area
transmembrane pressure	ultrafiltration increases with increase in transmembrane pressure

In hemodialysis, blood is pumped to the dialyzer by a roller pump at a rate of 300-450 ml/min.

- The drug and metabolites diffuse from the blood through the semipermeable membrane.
- In addition, hydrostatic pressure also forces the drug molecule into the dialysate by ultrafiltration. The composition of the dialysate is similar to plasma but may be altered according to the needs of the patient.
- Many dialysis machine use a hollow fiber or capillary dialyzer in which the semipermeable is made in to fine capillaries of which thousands are packed into bundles with blood flowing through the capillaries and dialysate is circulated outside the capillaries.
- The permeability characteristics of the membrane and the membrane surface area are

determinants of drug diffusion and ultrafiltration.

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

. Dialysance is defined by the equation:

$$Cl_D = \frac{Q(C_a - C_v)}{C_a} \quad \text{---}$$

where, C_a = drug concentration in arterial blood.

C_v = drug concentration in venous blood

Q = rate of blood flow to the kidney machine

Cl_D = dialysance

□ Hemoperfusion:

Hemoperfusion is the process of removing the drug by passing the blood from the patient through

an adsorbent material and back to the patient. Hemoperfusion is a useful procedure for rapid drug removal in accidental poisoning drug overdose.

- Because the drug molecules in the blood are in direct contact with the adsorbent material, any molecule that has great affinity for adsorbent material will be removed.
- The two main adsorbent used in hemoperfusion include:

1. Activated charcoal: This adsorbs both polar and nonpolar drugs.
2. Amberlite resins: Amberlite resins, such as amberlite XAD-2 and amberlite XAD-4 are available as insoluble polymeric beads. Each bead containing an agglomerate of cross linked polystyrene microsphere.

• The amberlite resins have a great affinity for nonpolar organic molecules than does activated charcoal.

• The important factors for the drug removal by hemoperfusion include:

- Affinity of the drug for the adsorbent
- Surface area of the adsorbent
- Absorptive capacity of the adsorbent rate of the blood flow through the adsorbent and

• The equilibration rate of the drug from the peripheral tissue in to the blood.

□ Hemofiltration:

Hemofiltration is the process by which fluids, electrolytes, and small molecular weights substances are removed from the blood by means of low-pressure flow through hallow

artificial fibers or flat plate membranes. Because fluid is also filtered out of the plasma during hemofiltration, replacement fluid is administered to the patient for volume replacement.

- Hemofiltration is a slow, continuous filtration process that removes no protein bound, small molecules (<10,111 Da) from the blood by convective mass transport.
- The clearance of the drug depends on the sieving coefficient and ultrafiltration rate.
- Hemofiltration provides a creatinine clearance of approximately 10 ml/min and may have limited use for drugs that are widely distributed in the body, such as aminoglycosides, cephalosporin, and acyclovir.
- A major problem with this method is the formation of blood clots within the hollow filter

fibers.

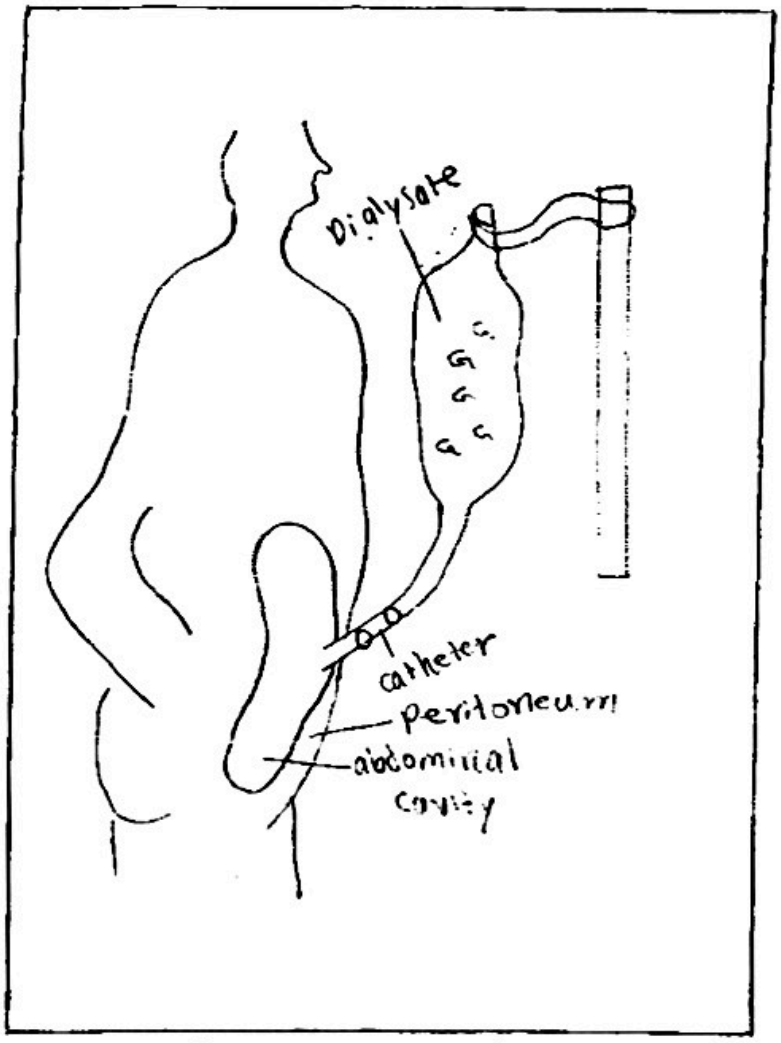


Fig: Peritoneal dialysis

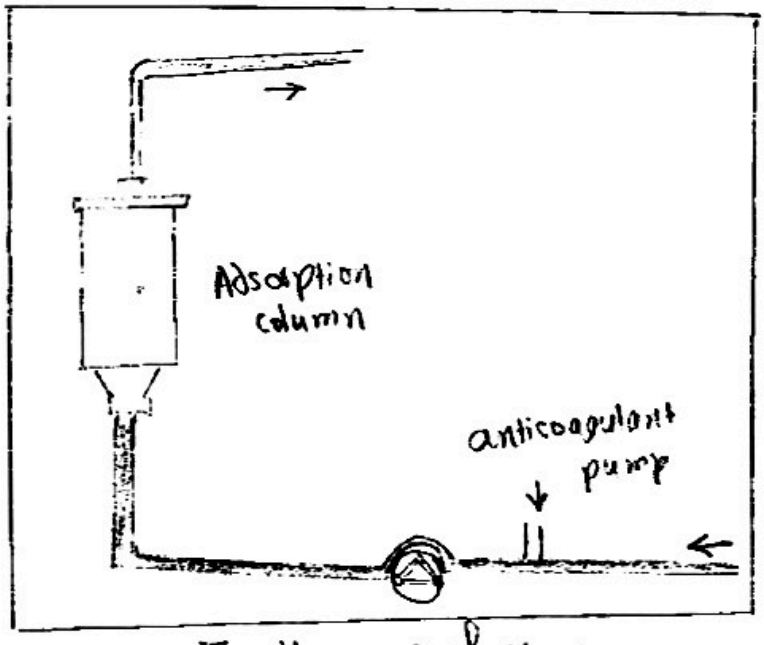


Fig: Hemoperfusion

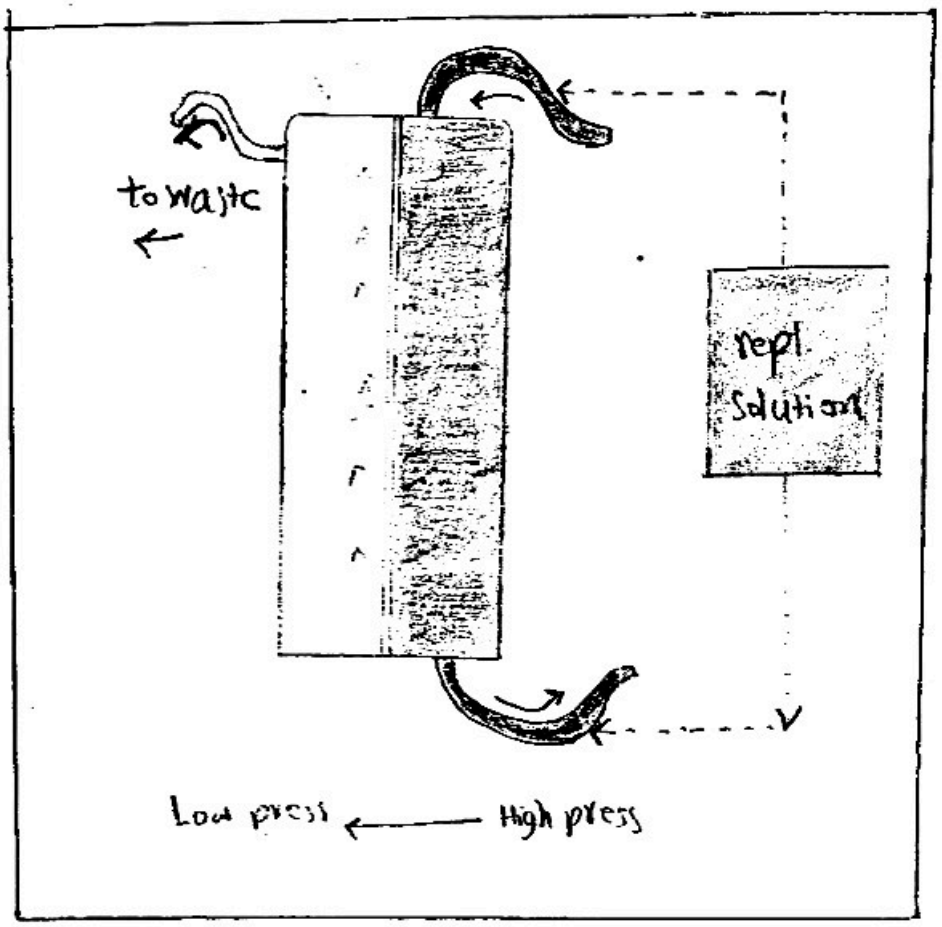


Fig: Hemofiltration

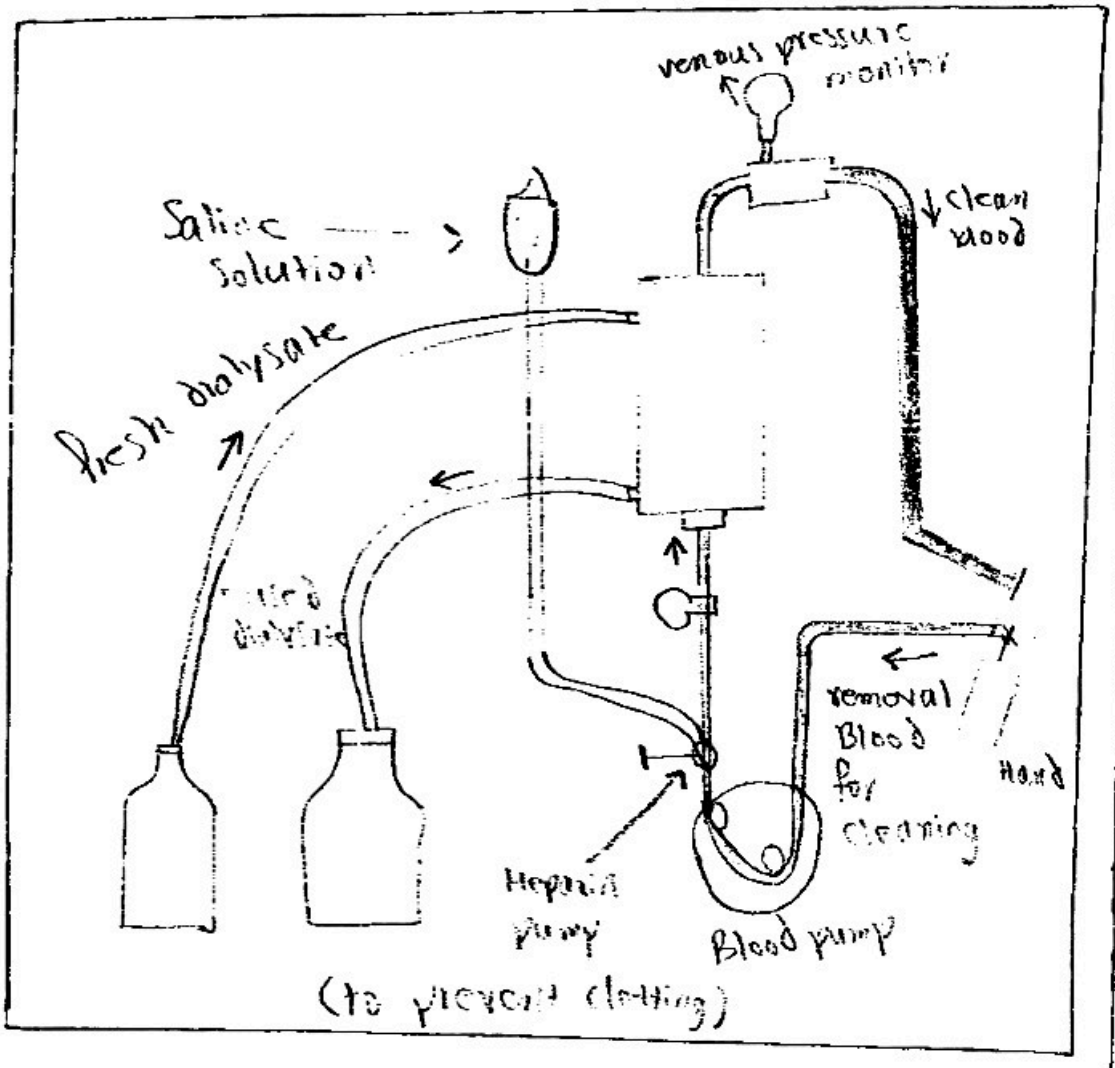


Fig - Schematic of a hemodialysis circuit

-Introduction:

. PharmacoKinetics is defined as the study of time course of drug ADME and their relationship with its therapeutic and toxic effects of the drug.

. PharmacoKinetics is the Kinetics of ADME or KADME.

. Drugs are often metabolized by one or more enzymes located in cellular membranes in different part of liver.

. Drug and metabolites may also be excreted by biliary secretion.

. Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration, and other effects including possible alteration in drug protein binding and kidney function.

. The major difficulty in estimating hepatic

clearance in patients with hepatic disease is the complexity and stratification of liver enzyme system.

- Clinical laboratory test measures only a limited number of liver functions.
- Some clinical laboratory test such as the aspartate aminotransferase (AST) and alanine aminotransferases (ALT), are common serum enzyme test that detect liver cell damage -- rather than liver function.
- Other laboratory tests, such as serum bilirubin are used to measure biliary obstruction or interference with the bile flow. presently, no single test accurately assesses the total liver function.
- A few function test have been used to relate the severity of hepatic impairment to

predicted changes in pharmacokinetic profile of the drug. (FDA guidance for industry, 2003). Example of these test include the ability of the liver to eliminate marker drugs such as anti pyrine, and indo cyanine green, mono ethylglycine, xylidide and galactose. Further more endogenous substrate such as albumin or bilirubin or a functional measures such as prothrombin time have been used for evaluation of liver impairment.

Dosage consideration in hepatic Disease:

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

redirection or detour of hepatic blood circulation liver disease affects the quantitative and qualitative synthesis of albumin, globulins, and other circulating plasma proteins that subsequently affect drug plasma protein binding and distribution.

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

- Considerations in Dosing Patients with Hepatic Impairment

Item	Comments
Nature and severity of liver disease	Not all liver diseases affect the pharmacokinetics of the drugs to the same extent

Drug elimination	Drugs eliminated by the liver > 20% are less likely to be affected by liver disease. Drug that are eliminated mainly via renal route will be least affected by liver disease
Route of drug administration	oral drug bioavailability may be increased by liver disease due to decrease first-pass effects
Protein binding	Drug protein binding may be altered due to alteration in hepatic synthesis of albumin
Hepatic blood flow	Drugs with flow dependent hepatic clearance will be more affected by change in hepatic blood flow
Intrinsic clearance	Metabolism of drugs with high intrinsic clearance may be impaired
Biliary obstruction	Biliary excretion of some drugs and metabolites, particularly glucuronide metabolites may be impaired.
Pharmacodynamic changes	Tissue sensitivity to drug may be altered

Therapeutic range	Drugs with a wide therapeutic range will be less affected by moderate hepatic impairment

• Because there is no readily available measure of hepatic function that can be applied to calculate appropriate doses, enzyme-dependent drugs are usually given to patients with hepatic failure in half-doses, or less.

Response or plasma levels then must be monitored.

• Drugs with flow-dependent clearance are avoided if possible in patients with liver failure. When necessary, doses of these drugs may need to be reduced to as low as one tenth of the conventional dose, for an orally administered agent. Starting therapy with low doses.

•And monitoring response or plasma levels provides the best opportunity for safe, efficacious treatment.

Fraction of drug metabolized

Drug elimination in the body may be divided into
1- fraction of drug excreted unchanged, f_e
2. fraction of drug metabolized

•The latter is usually estimated from $1 - f_e$; alternatively, the fraction of drug metabolized may be estimated from the ratio of $\frac{Cl_h}{Cl}$, where Cl_h is hepatic clearance and Cl is total body clearance.

Knowing the fraction of drug eliminated by the liver allows estimation of total body clearance when hepatic clearance is reduced.

Drugs with low f_e values (or, conversely,

drugs with a higher fraction of metabolized drug) are more affected by a change in liver function due to hepatic disease.

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

- Assume that all the metabolism occurs in the liver and all the unchanged drug is excreted in the urine.

Active drug and the metabolite

For many drugs, both the drug and the metabolite contribute to the overall therapeutic response of the patient to the drug. The concentration of both the drug and the metabolite in the body should be known.

When the pharmacokinetic parameters of the metabolite and the drug are similar, the overall activity

- **Metabolite:** any substance produced by metabolism or by a metabolic process.

of the drug can become more or less potent as a result of a change in liver function; that is

1- When the drug is more potent than the metabolite, the overall pharmacologic activity will increase in the hepatic impaired patient because the parent drug concentration will be higher.

2. When the drug is less potent than metabolite, the overall pharmacologic activity in the hepatic patient will decrease because less of the active metabolite is formed.

Changes in pharmacologic activity due to hepatic disease may be much more complex when both the pharmacokinetic parameters as well as the pharmacodynamics of the drug change as a result of the disease process. In such cases, the overall pharmacodynamics response may be greatly modified, making it

necessary to monitor the response change with the aid of a pharmacodynamic model.

Table Pugh's Modification of Child's Classification

	1 Point	2 Points	3 Points
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1–2	2–3	>3
Albumin (gm/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (sec > control)	1–4	4–10	>10

[a]Total points: 5–6 = mild dysfunction; 7–9 = moderate dysfunction; >9 = severe dysfunctio

D Hepatic Blood Flow and Intrinsic Clearance:

Blood flow changes can occur in patients with chronic liver disease (often due to viral hepatitis or chronic alcohol use).

In some patients with severe liver cirrhosis, fibrosis of liver tissue may occur, resulting in intra- or extra-hepatic shunt. Hepatic arterial-venous shunts may lead to reduced drug fraction of drug extracted (see) and an increase in the bioavailability of drug.

In other patients, resistance to blood flow may be increased as a result of tissue damage and fibrosis, causing a reduction in intrisic hepatic clearance.

- The following equation may be applied to estimate hepatic clearance of a drug after assessing changes in blood flow and intrinsic clearance (Cl_{int}):

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

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

$$Cl = Q(ER)$$

ER: extraction ratio

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

□ Pathophysiologic Assessment:

In practice, patient information about changes in hepatic blood flow may not be available, because special electromagnetic or ultrasound techniques are required to measure blood flow and are not routinely available. The clinician/pharmacist may have to make an empirical estimate of the blood flow change after

examining the patient and reviewing the available liver function tests.

Severity Classification Schemes for Liver Disease			
	Child-Turcotte Classification		
	Grade A	Grade B	Grade C
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (gm/dL)	>3.5	3.0–3.5	<3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor

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

The clinician may make an assessment based on a acceptable risk criteria on a case-by-case basis. list useful endpoints for assessing the extent of hepatic dysfunction.

In general, basic pharmacokinetics treats the body globally and more readily applies to dosing estimation. However, drug clearance based on individual eliminating organs is more informative and provides more insight into the pharmacokinetic changes in the disease process.

. A practical method for dosing hepatic-impaired patients is still in its early stages of development. While the hepatic blood flow model is useful for predicting blood flow, Q_a and Q_v, extrahepatic changes can also influence pharmacokinetics in hepatic-impaired patients.

. Global changes in distribution may occur outside the liver.

Extrahepatic metabolism and other hemodynamic changes may also occur and can be accounted for more completely by

monitoring total body clearance of the drug using basic pharmacokinetics

For example, lack of local change in hepatic drug clearance should not be prematurely interpreted as "no change" in overall drug clearance.

.Reduced albumin and amino acid glycoprotein (AAG), for example, may change the volume of distribution of the drug and therefore alter total body clearance on a global basis.

•Hormonal influence:

Hormones can also affect the rate of metabolism. In hyperthyroid patients, the rate of metabolism of many drugs is increased, as are, for example, the rates of theophylline, digoxin and propranolol. In hypothyroid disease, the rate of metabolism of these drugs may be decreased.

In children with human growth hormone (HGH) deficiency, administration of HGH decreases the half-life of theophylline.

Drugs with Significantly Decreased Metabolism in Chronic Liver Disease	
Antipyrine	Caffeine
Cefoperazone	Chlordiazepoxide
Chloramphenicol	Diazepam
Erythromycin	Hexobarbital
Metronidazole	Lidocaine
Meperidine	Metoprolol
Pentazocine	Propranolol
Tocainide	Theophylline
Verapamil	Promazine

Example

After IV bolus administration of 1 g of cefoperazone to normal and chronic hepatitis patients, urinary excretion of cefoperazone was significantly increased in cirrhosis patients, from 23.95 ± 5.06% for normal patients to 51.09 ± 11.50% in cirrhosis patients (). Explain (a) why there is a change in the percent of unchanged cefoperazone excreted in the urine of patients with cirrhosis, and (b) suggest a quantitative test to monitor the hepatic elimination of cefoperazone. (*Hint:* consult .)

•Liver function Tests and Hepatic metabolic Markers:

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

Some useful marker compounds are listed below:

1. Aminotransferase

AST: Male: 10-40 U/L ALT: M: 10-55 U/L

female 9-25 U/L F: 7-30 U/L

•Aminotransferases are enzymes found in many tissues that include serum glutamic oxaloacetic transaminase (AST, formerly SGOT) and alanine aminotransferase (ALT, formerly SGPT).

ALT is liver-specific, but AST is found in liver and many other tissues, including cardiac and skeletal muscle.

- Leakage of aminotransferases into the plasma is used as an indicator of many types of hepatic disease and hepatitis.
- The AST/ALT ratio is used in differential diagnosis. In acute liver injury, AST/ALT is 1, whereas in alcoholic hepatitis the AST/ALT > 2 (Greater than 2)

2. Alkaline phosphatase:

Male: 45-115 U/L

female: 30-100 U/L

- Like aminotransferase, alkaline phosphatase (AP) is normally present in many tissues, and is present on the canalicular domain of the hepatocyte

plasma membrane.

Plasma AP may be elevated in hepatic disease because of increased AP production and released into the serum.

In cholestasis, or bile flow obstruction, AP release is facilitated by bile acid solubilization of the membranes. Marked AP elevations may indicate hepatic tumors or biliary obstruction in the liver, or disease in other tissues such as bone, placenta or intestine.

3. Bilirubin:

(normal total = 0-1.0 mg/dl, direct = 0-0.4 mg/dl)

Bilirubin consists of both a water-soluble, conjugated, "direct" fraction and a lipid-soluble, unconjugated, "indirect" fraction.

- The unconjugated form is bound to albumin

and is therefore not filtered by the kidney. Since impaired biliary excretion results in increases in urinary bilirubin.

. Unconjugated hyperbilirubinemia results from either increased bilirubin production or defects in hepatic uptake or conjugation.

. Conjugated hyperbilirubinemia results from defects in hepatic excretion.

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4. Prothrombin time

PT: normal (11.2-13.2 sec)

With the exception of Factor VIII, all coagulation factors are synthesized by the liver. Therefore, hepatic disease can alter coagulation. Decreases in PT (the rate of conversion of prothrombin to thrombin) therefore is suggestive of acute or chronic liver failure or biliary obstruction (vit K

is also important in coagulation, so vit K deficiency can also decrease PT.

Example:

Paclitaxel, an anticancer agent for solid tumors and leukemia, has extensive tissue distribution, high plasma protein binding (approximately 90-95%), and variable systemic clearance. Average paclitaxel clearance ranges from 87 to 503 mL/min/m^2 (5.2-30.2 L/h/m^2) with minimal renal excretion of parent drug 10%. Paclitaxel is extensively metabolized by the liver to three primary metabolites. Cytochrome P-450 enzymes of the CYP3A and CYP2C subfamilies appear to be involved in hepatic metabolism of paclitaxel. What are the precautions in administering paclitaxel to patients with liver disease?

Solution

Although paclitaxel has first-order pharmacokinetics at normal doses, its elimination may be saturable in some patients with genetically reduced intrinsic clearance due to CYP3A or CYP2C. The clinical importance of saturable elimination will be greatest when large dosages are infused over a shorter period of time. In these situations, achievable plasma concentrations are likely to cause saturation of binding. Thus, small changes in dosage or infusion duration may result in disproportionately large alterations in paclitaxel systemic exposure, potentially influencing patient response and toxicity.

Inulin clearance:

- Renal function can be determined by measuring the GFR.

Both endogenous and exogenous substances have been used as markers to measure GFR.

In order to be useful as a marker, the agent should entirely get excreted in unchanged form by glomerular filtration only and should be physiologically and pharmacologically inert.

- The rate at which these markers are excreted in urine reflects the GFR and changes in GFR reflects renal dysfunction.
- Inulin (the exogenous fructose polysaccharide) and serum creatinine level have been used successfully for such purposes.

Inulin clearance provides an accurate measure of GFR but has the disadvantage

of being a tedious method.

Clinically, creatinine clearance is widely used to assess renal function.

Intrinsic Capacity Clearance:

Denoted as Cl_{int}, it is defined as the inherent ability of an organ to irreversibly remove a drug in the absence of any flow limitation. .is known as flow independent clearance.