DOSAGE ADJUSTMENT IN RENAL FAILURE

- Renal excretion is a major route of elimination for many drugs and their metabolites that are excreted prominently by the kidney accumulate in renal failure
- Renal diseases also effect other pharmacokinetic process (ie. Drug absorption, distribution and metabolism)
- Renal impairment cause accumulation of several acidic substances that compete with drug for binding sites on albumin and other plasma proteins. This alters pharmacokinetics of many drugs

Physiological functions of kidneys are

- Maintains extra-cellular fluid volume & osmolality
- Conserves important solutes
- Regulates acid-base balance
- Excretion of exogenous substance

Common Causes of Kidney Failure

- Hypertension:- Chronic overloading of the kidney with fluid and electrolytes may lead to kidney insufficiency.
- Diabetes mellitus:- The disturbance of sugar metabolism and acid-base balance may lead to or predispose a patient to degenerative renal disease.
- Nephrotoxic drugs/metals Certain drugs taken chronically may cause irreversible kidney damage—eg, the amino glycosides, phenacetin, and heavy metals, such as mercury and lead.

- Hypovolemia:- Any condition that causes a reduction in renal blood flow will eventually lead to renal ischemia and damage.
- Nephroallergens:- Certain compounds may produce an immune type of sensitivity reaction with nephrotic syndrome—eg: nephrotoxic serum.

Effect of renal disease on pharmacokinetics

- Pharmacokinetic processes such as drug distribution (volume of distribution and renal excretion), and elimination (biotransformation and renal excretion) are altered by renal impairment.
- Therapeutic and toxic responses may get altered as a result of changes in drug sensitivity at the receptor site.

- Acute diseases or trauma to the kidney can cause uremia , in which glomerular filtration is impaired or reduced, leading to accumulation of excessive fluid and blood nitrogenous products in the body.
- The effect of renal disease on pharmacokinetic processes such as absorption, distribution, metabolism, elimination is as follows.

Effect of renal disease on drug absorption

- Gastric PH is increased in chronic renal failure because urea is cleaved, yielding ammonia with acids and buffers in stomach
- Impaired renal function will result in increased bio availability of drugs exhibiting first-pass metabolism when the function of drug metabolizing enzymes is compromised.

Effect of renal disease on drug distribution

- Impaired renal function is associated with important changes in the binding of drugs to plasma proteins.

♦ Protein binding in serum from uremic patients is decreased.

♦ Most acidic drugs bind to the bilirubin site on albumin.
♦ The reduced binding occurs when renal function is impaired for the following reasons.

a) Reduction in serum albumin concentration.

b) Structural changes in binding sites.

c) Displacement of drug from albumin binding sites by organic molecules that accumulate in uremia.

Effect of renal disease on drug metabolism

- Most drugs are not excreted by the kidneys unchanged but are biotransformed to metabolites that are then excreted.
- Renal failure retard the excretion of metabolites.
- Renal failure alters the metabolic clearance of the drug.

Effect of renal disease on drug excretion

- Many studies shown that there is a linear relationship between the renal clearance of a drug and Creatinine clearance in patients with varying degrees of renal function.

  Renal clearance=A* Creatinine clearance

  A=Drug specific constant

- Patients with renal disease also excrete less unchanged drug in the urine than patients with normal renal function.

Renal function

Commonly employed measure of renal function are based on creatinine. Its usefulness lies in its clearance varying in direct proportion to the renal clearance of many drugs. Estimation of GFR in most critical evaluation required for ascertaining renal function.

Renal clearance

- Renal clearance is the volume of blood or plasma which is completely cleared of the unchanged drug by the kidney per unit time.

$$CL_R = \frac{\text{Rate of urinary excretion}}{\text{plasma drug concentration}}$$

- Renal clearance is the ratio of "sum of glomerular filtration and secretion minus rate of reabsorption " to "plasma drug concentration" (c).

$$CL_R = \frac{\text{Rate of filtration} + \text{Rate of secretion} - \text{Rate of reabsorption}}{\text{plasma drug concentration}}$$

Estimation of creatinine clearance

- The method recommended by the Food and drug Administration to estimate renal function for the purposes of drug dosing is to measure creatinine clearance (crcl).
- Creatinine is a by-product of muscle metabolism that is primarily eliminated by glomerular filtration .Because of this property ,it is used to measure glomerular filtration rate..
- Creatinine clearance rates can be measured by collecting urine for a specified period and collecting a blood sample for determination of serum creatinine at the mid point of the concurrent urine collection time

Formula for estimating creatinine clearance as per FDA

$$Crcl(ml/min)=(Ucr \cdot V\ urine)/(Scr.T)$$

Crcl = Creatinine clearance

U_{cr} = urine creatinine concentration(mg/dl)

V_{urine}= volume of urine collected in ml

Scr = serum creatinine

T =time in min. of urine collection

Comparison of creatinine clearance values

Creatinine clearance values	condition
100-125 ml/min	Normal
20- 50 ml/min	moderate renal failure
10>ml/min	severe renal failure

Why do we use creatinine for estimating glomerular filtration rate ?

- Eliminated only by the kidney
- Freely filtered
- Neither secreted nor reabsorbed.
- Easily and accurately measured

Limitations of serum creatinine measurement

- The relationship between the serum creatinine level and ClCr (GFR) also depends on the endogenous production of creatinine by muscle metabolism, which in turn depends largely on muscle bulk.

E.g.. The elderly have less skeletal muscle than do younger persons, as so an elderly person with the same serum creatinine level as a young person can still have a low Clcr (GFR). I.e.. an elderly person can have renal impairment, despite a normal serum creatinine level.

Dose adjustment in renal disease

- In the renal disease, the renal clearance and elimination rate are reduced, the elimination half-life is increased and the volume of distribution is altered.
- The half- lives of some drugs are changed sufficiently in patients with impaired renal function to warrant change in the usual dosage regimen to prevent accumulation of the drug in the body to toxic levels.

- Generally, one should consider a possible, modest decrease in drug doses when creatinine clearance is <50-60mL/min.
- A moderate decrease in drug doses when creatinine clearance is < 25-30 mL/min.
- A substantial decrease in drug doses when creatinine clearance is <15mL/min.

- Decrease the drug dose and retain the usual dosage interval.
- Retain the usual dose and increase the dosage interval.
- Decrease the dosage and prolong the dosage interval.
- The dosage change is usually proportional to the relative difference in half-life between the patients with renal disease and the person with normal renal function.

General rules

- Consider the possibility of renal impairment before drugs are prescribed and use available data to estimate GFR
- Check how drugs are eliminated before prescribing.
- If renal elimination accounts more than 50% of total elimination, then dose reduction will probably be necessary after the 1 st dose i.e. for maintenance dose
- Monitor therapeutic and adverse effect If possible
- Avoid nephrotoxic drugs. If such drugs are necessary use them with great care.

- The dose required in patients with renal impairment can be calculated by simple formula

$$\text{Normal dose} \times \text{Renal function}$$

- The dosing interval in hours can be calculated from

$$\frac{\text{Normal interval (in hours)}}{\text{Renal function}}$$

- When the drug is eliminated both by renal and nonrenal mechanism the dose to be administered in patients with renal impairment is calculated from

Normal dose [RF ×Fraction excreted in urine +Fraction eliminated nonrenally]

CONCLUSION

- Once a potential renal problem necessitating dose modification has been identified, there are number of accepted reference sources that provide guidance for dosage adjustment.
- The patient must be monitored and treatment modified in light of individual response