PHARM D - V Pd - 5.3. unit - 5

Dosage Adjustment in Renal and Hepatic Disease

Renal impairment :

- the kidney is an important organ in regulating body fluids. Electrolyte balance, removal of metabolic waste, and drug excretion from the body. Impairment or degeneration of kidney function affects the pharmacokinetics of drugs.

- Various more common cause of kidney failure include disease, injury, & drug-toxication.

- List some of the conditions that may lead to chronic or acute renal failure.

- Acute disease 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.

- Uremia generally reduces glomerular filtration and/or active secretion, which leads to a ↓ in renal drug excretion resulting in a longer elimination Half-Life of the administered drug.

. To changing renal elimination directly, uremia can affect drug pharmacokinetics in unexpected ways.

eg: Declining renal function leads to disturbances in Electrolyte and fluid balance, resulting in physiologic and metabolic changes that may alter the Pharmacokinetics and Pharmacodynamics of a drug.

pharmacokinetic processes :

- Drug distribution
  - Vd
  - protein binding.
- Elimination
  - Biotransformation
  - Renal Excretion.

- Both therapeutic and toxic responses may be attend as a result of changes in drug Sensitivity at the receptor site.

* Note : uremic patients have care take special dosing consideration to account for p'k & p'd alterations.

Pharmacokinetic Consideration.

Renal impairment patients may exhibit pharmacokinetic changes in bioavailability, volume of distribution and clearance.

The oral bioavailability of a drug in Severe uremia maybe decreased as a result of disease-related changes in GIT motility and PH caused by Nausea, Vomiting and diarrhea. Measenteric blood flow may also be altered.

However, the oral bioavailability of a drug such as propranolol (which has a high first-pass effect)

may be increased in patients with renal impairment as a result of the decrease in first-pass Hepatic metabolism.

The apparent volume of distribution depends largely on drug protein binding in plasma tissue and total body water.

Renal impairment may alter the distribution of the drug as a result of changes in fluid balance, drug protein binding, or other factors that may cause changes in the apparent volume of distribution.

- Plasma protein binding of weak acidic drugs

↓

↓ the uremic patient.

- protein binding of weak basic drugs

↓

Less affected

- The decrease in drug protein binding results in a larger fraction of free drug and an increase in the Vd.
- However, $E_{1/2}$ increased results of ↓ the glomerular filteration.

Total body clearance of drug in uremic patients is also reduced by either a decrease in the glomerular filtration rate and possibly active tubular secretion or reduced hepatic clearance resulting from a decrease in intrinsic hepatic clearance.

In clinical practice

- Estimation of the appropriate drug dosage regimen in patient with impaired renal function is based on an estimate of the remaining renal function of the patient & a prediction of total body clearance.

- A complete p'k analysis of the drug in the uremic patient is not possible.

Note :- patient's uremic condition may not be stable and may be rapidly too changing for Pharmacokinetic analysis.

- Dosing guidelines for individual drugs in patient with renal impairment may be found in various case studies & reference book. medical literature also support.

physicians' Desk reference.

General Approaches for dose adjustment in Renal disease.

Several approaches are available for estimating the appropriate dosage regimen for a patient with renal impairment.

Each of the method assume that the required therapeutic plasma drug concentration in uremic patients is similar to that required in patients with normal renal function.

Uremic patients are maintained on the same Cav after multiple oral doses. or multiple IV bolus injections

For IV infusions, the same C_{ss} is maintained. (C_{ss} is the same as C_{av} after the plasma drug concentration reaches steady state).

Common Assumptions in Dosing Renal-Impaired patients:

Assumption	Comment
Creatinine clearance diagnostic test	→ C_{cr} may be biased. Should be physical diagnosis and other clinical test.
Drug follows dose-independent p'k	→ p'k should not be dose-dependent (nonlinear)

Renal disease may also affect the liver and changes drug metabolism.

Non renal drug elimination remains → constant

Drug absorption remains constant → uncharged drug abs from GIT.

Drug clearance ~~Cl~~ Cl_cr declines linearly with → Creatine clearance Cl_cr.

Normal drug clearance may include active secretion & passive filtration & may not decline linearly

unaltered drug protein binding (PB) → Drug Pb may be altered due to accumulation of urea, nitrogenous waste & drug metabolites.

Target drug conc remains constant → Changes in electrolyte composition such as may affect sensitivity to the effect of digoxin

→ Accumulation of active metabolites may cause more intense pharmacodynamic response compared to parent drug alone.

- Uremic patients is based on the P'K changes that have occurred as a result of the uremic condition.
- Uremic patients are based on an accurate estimation of the drug clearance in these patients.

• kidney impairment	Less severe uremic cond^{n}
① prolong $E_{1/2}$ & changes apparent Vd	① edema significant changes in apparent volume of distribution

▲ Several specific clinical approaches for the calculation of drug clearance based on monitoring kidney function.

Two general pharmacokinetic approaches for dose adjustment include ⊛ methods based on drug clearance and ⊛ method based on the elimination half-life.

- Clearance
- Elimination half-life

MEASUREMENT OF GLOMERULAR FILTRATION RATE [GFR]

Number of drug substances have been endogenous used as markers to measure GFR. These markers are carried to the kidney by the blood via the renal artery and are filtered at the glomerulus.

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

i) The drug must be freely filtered at the glomerulus.

ii) The drug must not be reabsorbed nor actively secreted by the renal tubules.

iii) The drug should not be metabolized.

iv) The drug should not bind significantly to plasmaproteins

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

vi) The drug should be nontoxic

vii) The drug may be infused in a sufficient dose to permit simple & accurate quantity in plasma and in urine.

Therefore, the rate at which these drug markers are filtered from the blood into the urine

per unit of time reflects the glomerular filtration rate of the ~~urine~~ & kidney.

change in GFR reflect changes in kidney function that may be diminished in uremic conditions.

clearance of inlin may then be measured by the rate of infusion divided by the steady-state plasma inulin concentration. Although this procedure gives an accurate value for GFR, inulin clearance is not used frequently in clinical practice.

SERUM CREATININE CONCENTRATION AND CREATININE CLEARANCE

Creatinine production is roughly equal to creatinine excretion. so the serum creatinine level remains constant. In a patient with reduced glomerular filtration, serum conc will accumulate in accordance with the degree of loss of glomerular filtration in the kidney.

The serum creatinine concentration alone is frequently used to determine creatinine clearance, C_{Cr}.

Creatinine clearance from the serum creatinine conc is a rapid and

Convenient way to monitor kidney function.

Creatinine clearance defined as the rate of urinary excretion of creatinine.

C_{Cr} can be calculated directly by determining the patient's serum creatinine concentration and the rate of urinary excretion of creatinine.

The approach is similar to that used in the determination of drug clearance.

Eg In practice, the serum creatinine conc. is determined at the mid point of the urinary collection period & the

and the rate of urinary excreation of creatinine is rate.

- Ccl is expressed in ml/min and serum creatinine conc in mg/dL or mg %.

- other Ccl methods based on serum ~~conc~~ creatinine are generally compared to the Ccl obtained from the 24 hrs urinary creatinine excreation.

The below equation is used to calculate creatinine clearance in ml/min when the serum creatinine conc is known:

$$Cl_{cr} = \frac{\text{rate of urinary excreation of } C_r}{\text{serum conc of } C_r}$$

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

where, C_{Cr} = Creatinine conc (mg/dL) of the serum at the 12th hr. (or) at the midpoint of the urine-collection period.

V = volume of urine excreted (mL) in 24 hrs.

C_u = Concentration of Creatinine in urine (mg/mL)

and

Cl_{cr} = Creatinine clearance in mL/min

Creatinine is eliminated primarily by glomerular filtration. A small fraction of Creatinine also is eliminated by active secreation and some non renal elimination.

∴ Cl_{cr} values obtained from creatinine measurements overestimate the actual glomerular filtration rate.

Several empirical equations have been used to estimate lean body weight, LBW, based on the patient's height and actual (total) body weight. The following eqn have been used to estimate LBW in renally impaired patients:

LBM (males) = 50 kg + 2.3 kg for each inch over 5 ft

LBM (females) = 45.5 kg + 2.3 kg for each inch over 5 ft.

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.

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

Various method for drug removal:

1. Hemodialysis:
2. Peritoneal dialysis

- utilized counter current flow, i.e. dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit.
- Counter-current flow maintains the conc. gradient across the membrane at a maximum and increases the efficiency of the dialysis.
- pressure in the dialysate compartment is lower than blood compartment.

3. Hemofiltration
4. Hemodiafiltration
5. Hemoperfusion

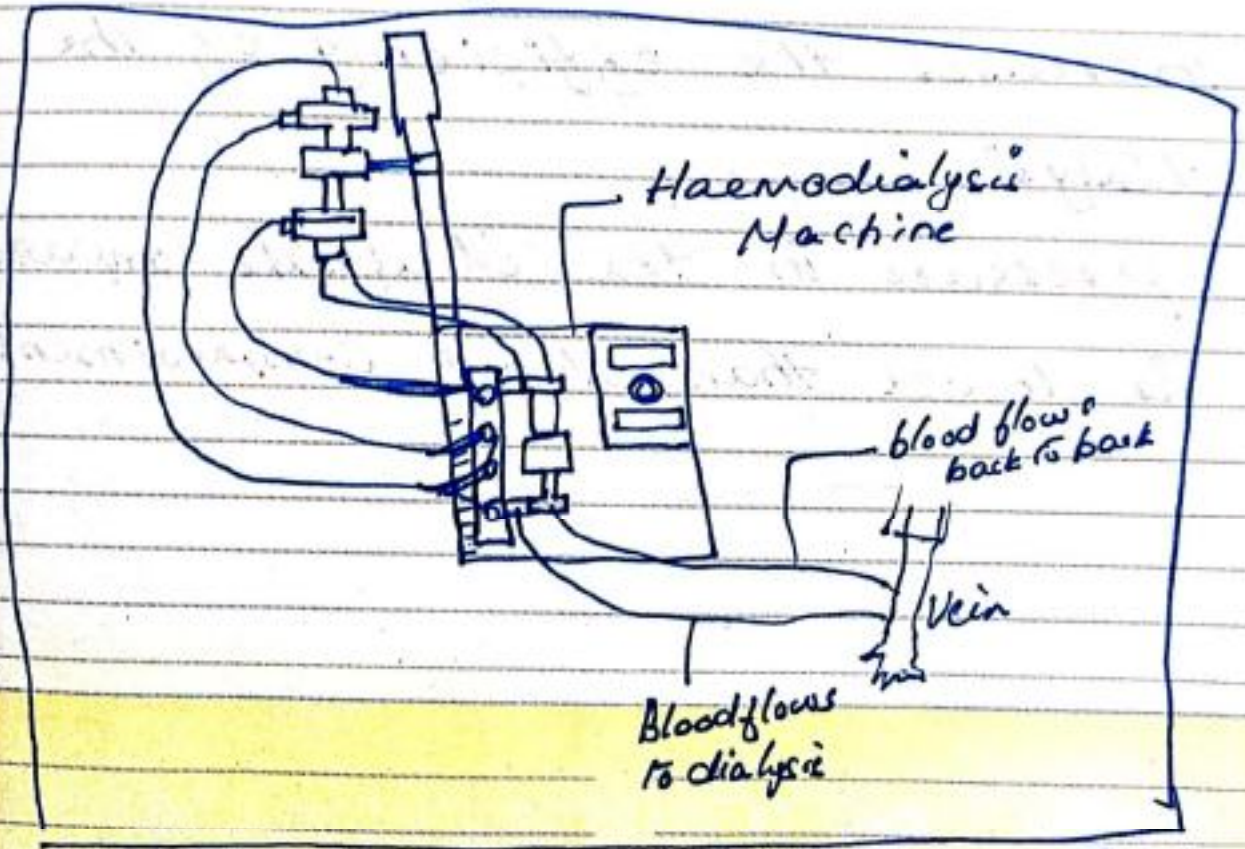
1. Hemodialysis :

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

principles :

Diffusion of solute across a semipermeable membran

- Inside the dialyzer, a porous artificial membrane separates blood from the dialysis fluid (dialysate)
- Diffusion of extra fluid and wastes from the blood into the dialysate.
- purified blood is then pumped back into the body.



- Membrane is permeable to water & small ions but is impermeable to blood cells, lipids or plasma proteins.