Dose Adjustment in Renal and Hepatic Disease

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DOSE V/S DOSAGE

- **DOSE:** it refers to a specified amount of medication taken at one time.

- **DOSAGE:** it refers to the prescribed administration of a specific amount , number, and frequency of doses over a specific period of time.

Function of Kidney

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.

Renal failure or kidney failure

- Formerly called renal insufficiency describes a medical condition in which the kidneys fail to filter adequate toxins and waste products from the blood.

- • Renal failure is described as a decrease in glomerular filtration rate (GFR).

Causes of kidney failure

- Some of the more common causes of kidney failure include

- **Disease:** Diabetes, High Blood Pressure, Autoimmune diseases, such as lupus and IgA nephropathy
- Genetic diseases such as polycystic kidney disease, Nephrotic syndrome, Urinary tract problems

- **Injury:** Not enough blood flow, An injury directly to your kidneys, A blockage in your ureters

- **Drug intoxication:** Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like aspirin, ibuprofen, or naproxen, some chemotherapy drugs, some antibiotics

Causes of Renal Failure

condition	comment
Pyelonephritis	Inflammation of pyelonephrons due to infection
Hypertension	Chronic overloading of kidney with fluid and electrolytes lead to kidney insufficiency
Diabetes mellitus	The disturbance of sugar metabolism may lead to degenerative renal disease
Nephrotoxic drugs/metals	certain drugs like aminoglycosides, Phenacetin cause irreversible kidney disease
Hypovolemia	Any condition that causes a reduction in renal blood flow leads to renal damage.

RENAL DISEASE: EFFECTS

- Patients are more vulnerable to given drug.
- Drug effect may increase or decrease.
- Higher steady state concentration when given in usual doses.

Cause of Kidney Disease

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative glomerulonephritis; focal and segmental glomerulosclerosis; membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary-tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis; fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport's syndrome, Fabry's disease	Renal dysplasia, medullary cystic disease, podocytopathies

Genetic diseases are not considered separately because some diseases in each category are now recognized as having genetic determinants.

What is Uremia?

- 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.

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

Pharmacokinetic Considerations /Effects of uremia

Uremic patients may exhibit pharmacokinetic changes in

- 1. decrease in GFR
- 2. volume of distribution
- 3.clearance
- 4.drug accumulation
- 5. in bioavailability
- 6. Mesenteric blood flow may also be altered due to disease related change

- 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.

How VD is Changed in Uremia?

- The apparent volume of distribution depends largely on drug protein binding in plasma or tissues and total body water. Renal impairment may alter the distribution of the drug as a result of changes in fluid balance, drug protein binding, or other factors that may cause changes in the apparent volume of distribution. The decrease in drug protein binding results in a larger fraction of free drug and an increase in the volume of distribution.

Uremia causes change in total clearance

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

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 these approaches has similar assumptions. Most of these methods 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 **C_{∞} av** after multiple oral doses or multiple IV bolus injections. For IV infusions, the same CSS is maintained. (CSS is the same as C_{∞} av after the plasma drug concentration reaches steady state.)

- In clinical practice, estimation of the appropriate drug dosage regimen in patients with impaired renal function is based on an estimate of the remaining renal function of the patient and a prediction of the total body clearance.

Measurement of Glomerular Filtration Rate

- Several drugs and endogenous substances have been used as markers to measure GFR. These markers are carried to the kidney by the blood via the renal artery and are filtered at the glomerulus. Several criteria are necessary to use a drug to measure GFR

Criteria 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 proteins.
- 5. The drug should not have an effect on the filtration rate nor alter renal function.
- 6. The drug should be nontoxic.
- 7. The drug may be infused in a sufficient dose to permit si and accurate quantitation 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 kidney. Changes in GFR reflect changes in kidney function that may be diminished in uremic conditions.

Example of Markers

- **1.Inulin**, a fructose polysaccharide, fulfils most of the criteria listed above and is therefore used as a standard reference for the measurement of GFR.

- **2. The clearance of creatinine** is used most extensively as a measurement of GFR. Creatinine is an endogenous substance formed from creatine phosphate during muscle metabolism.
  Creatinine production varies with the age, weight, and gender of the individual. In humans, creatinine is filtered mainly at the glomerulus, with no tubular reabsorption. Normal range: 0.6-1.1 mg/dl {male}
- 0.7-1.3 mg/dl {female}
- **3. Blood urea nitrogen (BUN)** is a commonly used clinical diagnostic laboratory test for renal disease. Urea is the end product of protein catabolism and is excreted through the kidney.

- Normal BUN levels range from 10 to 20 mg/dL. Higher BUN levels generally indicate the presence of renal disease.

Serum Creatinine Concentration and Creatinine Clearance

- Under normal circumstances, creatinine production is roughly equal to creatinine excretion, so the serum creatinine level remains constant. In a patient with reduced glomerular filtration, serum creatinine 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, ClCr. Creatinine clearance from the serum creatinine concentration is a rapid and convenient way to monitor kidney function.

- Creatinine clearance may be defined as the rate of urinary excretion of creatinine/serum creatinine. Creatinine clearance can be calculated directly by determining the patient's serum creatinine concentration and the rate of urinary excretion of creatinine.

Calculation of Creatinine Clearance from Serum Creatinine Concentration

- The problems of obtaining a complete 24-hour urine collection from a patient, the time necessary for urine collection, and the analysis time preclude a direct estimation of creatinine clearance. Serum creatinine concentration, CCr, is related to creatinine clearance and is measured routinely in the clinical laboratory. Therefore, creatinine clearance, ClCr, is most often estimated from the patient's CCr. Several methods are available for the calculation of creatinine clearance from the serum creatinine concentration.

- The more accurate methods are based on the patient's **age, height, weight, and gender**. These methods should be used only for patients with intact liver function and no abnormal muscle disease, such as hypertrophy or dystrophy. Moreover, most of the methods assume a stable creatinine clearance. The units for ClCr are mL/min.

- GFR can be estimated with Cockcroft & Gault equation or, if GFR less than 60 mL/minute per 1.73 m ^{2} or patient older with GFR less than 90 mL/minute per 1.73 m ^{2}, with MDRD **(Modification of Diet in Renal Disease)** equation.
  - For males, $clcr = 140 - age\ years \times bodyweigh(kg)\ /72 \times ccr$
  - For females multiply with 0.85.

- Loading doses do not generally need adjustment.

- Dosing adjustment methods include dose reduction, lengthening of dosing interval, or both.

- Dose reduction allows more constant drug level, but higher risk for toxicity.

- Lengthening of dosing interval has lower risk for toxicity but higher risk for sub therapeutic level.

Common Medications Requiring Dose Reduction in CKD

- **Allopurinol**
- **Gabapentin**
  - CKD 4- Max dose 300mg qd
  - CKD 5- Max dose 300mg qod
- **Reglan**
  - Reduce 50% for eGFR< 40
  - Can cause irreversible EPS with chronic use
- **Narcotics**
  - Methadone and fentanyl best for ESRD patients
    - Lowest risk of toxic metabolites

Renally cleared beta blockers
Atenolol, bisoprolol, nadolol

Digoxin

Some Statins
Lovastatin, pravastatin, simvastatin. Fluvastatin, rosuvastatin

Antimicrobials
Antifungals, aminoglycosides, Bactrim, Macrobid

Enoxaparin

Methotrexate

Colchicine

DRUGS THAT DO NOT REQUIRE RENAL ADJUSTMENTS

- Moxifloxacin
- Azithromycin
- Ceftriaxone
- Clindamycin
- Metrogyl Clavulate
- Doxicyclin

Linezolid

Tigecyclin

Ambisome

Voriconazole

Why doesn't it matters for some antibiotics

- Risk of toxicity is low
- Patient can tolerate higher concentration
- Eg: beta-lactams , carbapenam

Antihypertensive Agents:

- Thiazide diuretics not recommended if serum creatinine greater than 2.5 mg/dL or creatinine clearance less than 30 mL/minute.
- Loop diuretics are most common drugs for uncomplicated hypertension in chronic kidney disease.
- Potassium-sparing diuretics and aldosterone blockers can increase serum potassium.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are first line for patients with diabetes mellitus and early kidney disease.
- ACE inhibitors and ARBs can cause GFR decrease and creatinine increase, especially if congestive heart failure, diuretic or NSAID use, or at high dose; discontinuation recommended if serum creatinine increases more than 30% or serum potassium at least 5.6 mEq/L.
- Hydrophilic β-blockers need adjustment.
- No adjustment needed for metoprolol tartrate, metoprolol succinate, propranolol, labetalol, calcium channel blockers, clonidine, an[illegible] blockers.

Hypoglycemic Agents:

- Metformin increases risk for lactic acidosis and not recommended if serum creatinine is greater than 1.5 mg/dL in men or 1.4 mg/dL in women, age is older than 80 years, or there is chronic heart failure.
- Sulfonylureas can cause severe hypoglycemia and should not be used in stages 3 to 5 chronic kidney disease.
- No adjustment needed for glipizide.

Antimicrobial agents:

- Penicillin G or carbenicillin can cause neuromuscular toxicity, myoclonus, seizures, or coma.
- Imipenem/cilastatin can cause seizures.
- Tetracyclines, except doxycycline, can exacerbate uremia.
- Nitrofurantoin metabolite can cause peripheral neuritis.
- Aminoglycosides should not be used if possible.

Analgesic agents:

- Meperidine, dextro propoxyphene, morphine, tramadol, and codeine metabolites can affect central nervous and respiratory systems and are not recommended in stage 4 or 5 disease.

- No adjustment needed for acetaminophen.

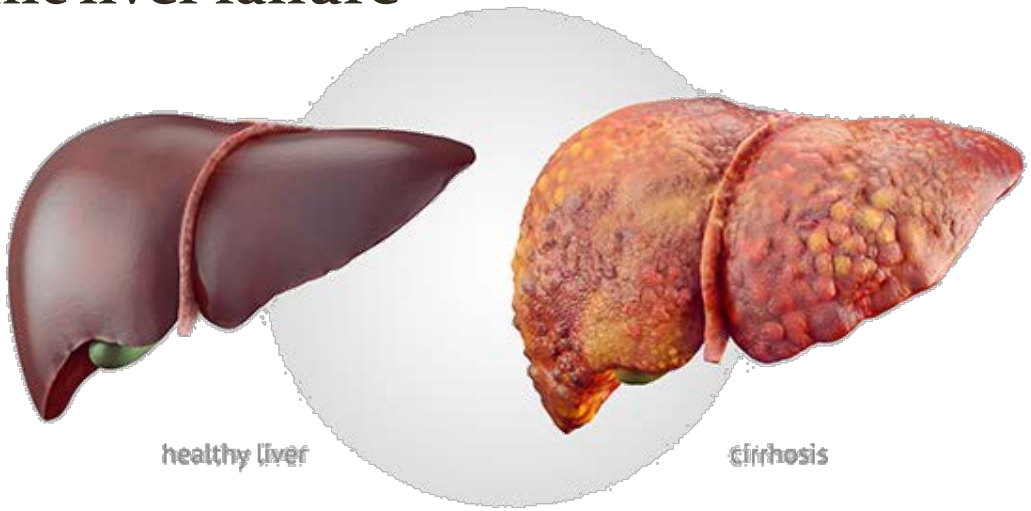
NSAIDs:

- Use is linked to 3-times-higher risk for acute renal failure.
- Use can cause nephrotic syndrome with interstitial nephritis and chronic renal failure.
- Decreased potassium excretion can lead to hyperkalemia.
- Decreased sodium excretion can lead to peripheral edema, elevated blood pressure, and exacerbation of heart failure.
- Antihypertensive effects of β-blockers, ACE inhibitors, or ARBs can be decreased.
- Short-term NSAID use is well tolerated if patient is well hydrated and has good renal function and absence of heart failure, diabetes, or hypertension.
- Long-term use not recommended.
- Serum creatinine should be checked every 2 to 4 weeks in early treatment.

- **Statins:**
  - Dosing adjustment is recommended except for atorvastatin.
- **Herbal products:**
  - St. John's wort and ginkgo can increase metabolism of other medications.
  - Ginkgo increases bleeding risk if taking aspirin, ibuprofen, or warfarin.
  - Alfalfa, dandelion, and noni juice contain potassium.
  - Products with heavy metals and Chinese herbal products with aristolochic acid are nephrotoxic.
  - Vaso-constrictive ingredients can cause hypertension.

LIVER FAILURE

- • Liver failure or hepatic insufficiency is the inability of the liver to perform its normal synthetic and metabolic function as part of normal physiology.
- Two forms are recognized;
- ¬ **Acute liver failure**
- ¬ **Chronic liver failure**



Types of Liver Failure

- **ACUTE LIVER FAILURE**

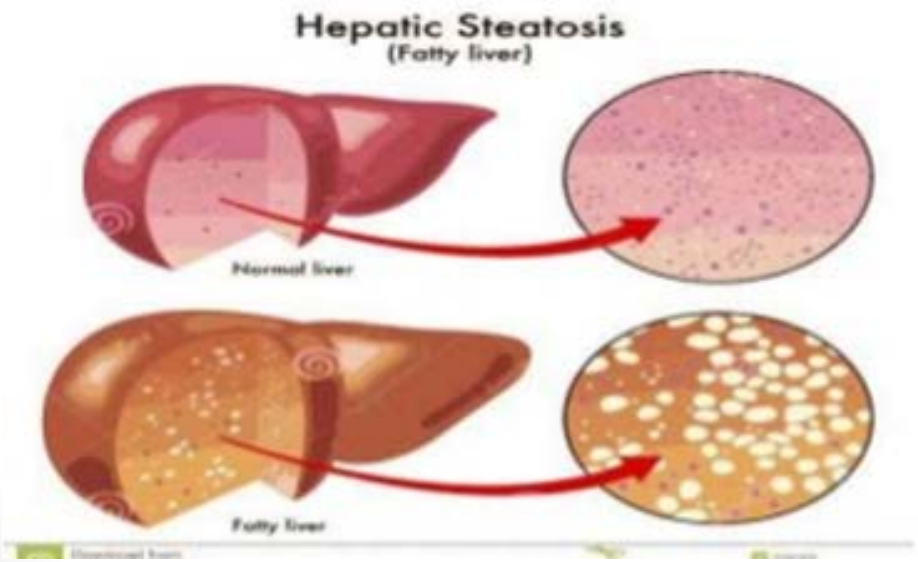
• It is defined as the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) in a patient without known prior liver disease.

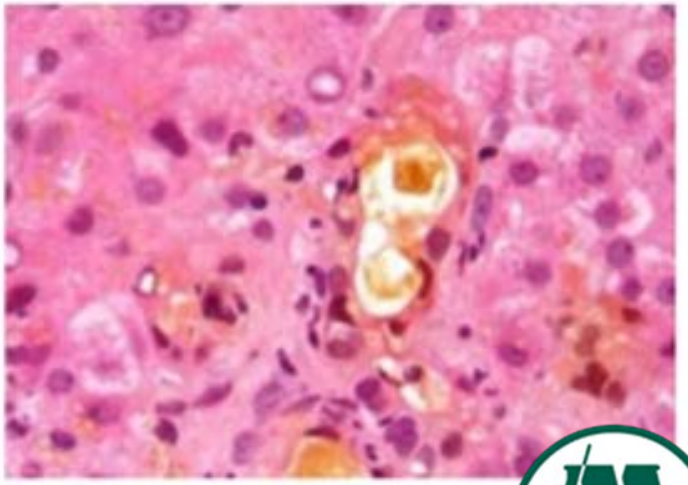
- **CHRONIC LIVER FAILURE**

• It usually occurs in the context of cirrhosis , itself potentially the result of many possible causes, such as excessive alcohol intake, hepatitis B or C , auto immune , hereditary and metabolic causes.

ETIOLOGY

- • **The liver can be damaged in a variety of ways:**
- ⎫ Cells can become inflamed(such as hepatitis).
- ⎫ Bile flow can be obstructed (such as cholestasis).
- ⎫ Cholesterol or triglycerides can accumulate (steatosis).



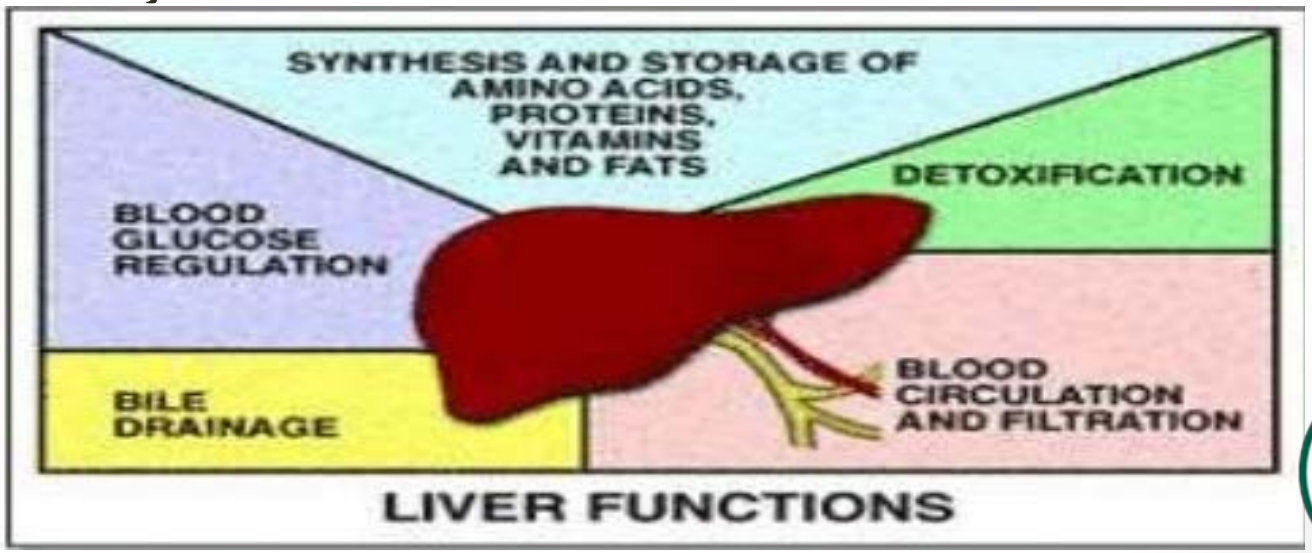


Considerations in Dosing Patients with Hepatic Impairment

ITEM	COMMENTS
Drug elimination	Drugs eliminated by the liver >20% are less likely to be affected by liver disease.
Protein binding	Drug protein binding may be altered due to alteration in hepatic synthesis of albumin.
Therapeutic range	Drugs with a wide therapeutic range will be less affected by moderate hepatic impairment.

Liver Function Tests and Hepatic Metabolic Markers

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



Useful Hepatic Marker Compounds

- **1.Asparatate Aminotransferase (AST):** Normal AST value for males is 10-55 U/L; and for females is 7-30 U/L.

- **2.Alkaline phosphatase (AP):**Normal AP values for males is 45-115 U/L and for females is 30-100 U/L ,

❖Marked AP elevations may indicate hepatic tumors or biliary obstruction in the liver.

- **3. Bilirubin :** Normal value is 0-1 mg/dl

❖Unconjugated hyperbilirubinemia results from increased bilirubin production.

❖Conjugated hyperbilirubinemia results from defects in hepatic excretion.

- **4. Prothrombin time :** Normal value is 11.2-13.2 sec , with the exception of factor 8 , all coagulation factors are synthesized by the liver ; therefore hepatic disease can alter the coagulation.

Effect of hepatic disease on pharmacokinetics

- • Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver.
- • Drugs and metabolites may also be excreted by biliary secretion.
- • Liver disease may also alter kidney function, which can lead to accumulation of a drug and its metabolite's even when the liver is not primarily responsible your elimination.
- • Hepatic disease can alter the pharmacokinetics of a drug including the absorption and disposition and the pharmacodynamics including efficacy and safety.

Hepatic blood flow and intrinsic clearance:

- • Blood flow changes can occur in patients with chronic liver disease.
- • Hepatic arterial venous shunts may lead to reduced drug fraction of drug excreted and an increase in the bioavilability of drug.
- • In other patients , resistance to blood flow may be increased as a result of tissue damage and fibrosis , causing a reduction in intrinsic hepatic clearance.
- The following equation may be applied to estimate hepatic clearance (*clh*) of a drug after assessing changes in blood flow and intrinsic clearance (*clint*): $clh = Q.clint/Q+clint$
- •Alternatively, when both Amount of blood flows to liver Q and the extraction ratio ER, are known in the patient , clearance(cl) may also be estimated : cl=Q(ER).

Drugs with Significantly Decreased Metabolism in Chronic Liver Failure

DRUGS	DRUGS
Chloramphenicol	Diazepam
Antipyrine	Hexobarbitol
Erythromycin	Theophylline
Verapamil	Promazine
Caffeine	Metronidazole

Hepatic impairment and dose adjustment

- • The drug is metabolized in the liver to a small extent (<20%) and the therapeutic range of the drug is wide so that modest impairment of the drug directly or by increasing its interaction with other drugs.
- • The drug is gaseous or volatile , and the drug and its active metabolites are primarily eliminated via the lungs.
- • For each drug case , the physician needs to assesses the degree of hepatic impairment and consider the known pharmacokinetics and pharmacodynamics of the drug.
- • Starting therapy with low doses and monitoring response or plasma levels provides the best opportunity for safe, efficacious treatment

Dosage considerations in hepatic failure:

- • Several physiologic and pharmacokinetic factors are relevant in considering dosing of a drug in patients with hepatic disease.
- • Chronic disease and tissue injury may change the accessibility of some enzymes as a result of re-direction of hepatic blood circulation.
- • Drugs with flow dependent clearance are avoided otherwise the dose of those drugs need to be reduced to as low as one- tenth of 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.

Dosing in Liver Disease

- • For severe liver dysfunction (albumin<30g/L, INR > 1.2):
- INR=International normalized ratio

(a) If the drug is a high clearance drug (liver blood flow dependent) reduce dose by 50%:

High Clearance Drugs	Example
Antipsychotics	Opioids (most)
Beta-blockers (most)	Tricyclic antidepressants
Lignocaine	statins
Nitrates	SSRIs

Dosing in Liver Disease

- (b) If the drug is low clearance (flow-independent - includes all other metabolised drugs) reduce dose by 25%:

Low clearance drugs	Examples
Anticonvulsants (most)	Sulphonylureas
Spironolactone	Theophylline
Paracetmol	Warfarin
NSAID's	Steroids

Formulas:

- **• Model for end stage liver disease(MELD):**

- **MELD**=3.78× *serum bilirubin*(*mg*/*dl*)+ 11.20× *INR* + 9.57 × serum creatinine (mg/dl)+ 6.43(constant for liver disease etiology).

- Where INR=International normalized ratio.

- **NOTE :** If the patient has been dialyzed twice with in the last 7 days , then the value for serum creatinine used should be 4.0.

- **Paediatric end stage liver disease(PELD):**

- It is a disease severity scoring system for children under 12 years of age .

PELD= 4.80× [*serum bilirubi*(*mg*/*dl*]+ 18.57[INR]-6.87 albumin(g/dl)+ 4.36(<1 year old)+ 6.67(growth failure)

- • A higher score correlates with a more critical condition . Thus , liver donations are allocated by UNOS(United network for organ sharing) according to the PELD score to maximize the life saving capability of each donated liver.

Hepatic vs Renal Failure:

- • Dose adaptation for patients with liver disease is more difficult than for patients with impaired renal function.

- • Unlike creatinine clearance for the kidney ,for liver there is no *in-vivo* surrogate to predict the drug clearance.

CONCLUSION

- • The liver and kidneys are important for the body's ability to break down and excrete medication.
- • Diseases of the liver or the kidneys, in addition to aging , often require doses to be lowered in order to avoid adverse drug reactions.
- • Patients with markedly reduced liver function should avoid certain medications and dietary supplements.
- • Moderately impaired kidney function may require lower medication doses; severely impaired function requires avoidance of certain medications.

THANK YOU