5th.lec.

TDM

Lect.Dr.

Shaimaa Saleh

Drug Dosing in Special Populations

All medications have specific disease states and conditions that change the pharmacokinetics of the drug and need dosage modification.

- Renal or hepatic disease will decrease the elimination or metabolism of the majority drugs and change the clearance of the agent.
- Dialysis procedures removes some medications from the body while the pharmacokinetics of other drugs are not changed.
- Heart failure results in low cardiac output which decreases blood flow to eliminating organs, and the clearance rate of drugs with moderate-to-high extraction ratios are particularly sensitive to alterations in organ blood flow.
- Obesity adds excessive adipose tissue to the body which may change the way drugs distribute in the body and alter the volume of distribution for the medication
- Finally, drug interactions can inhibit or induce drug metabolism, alter drug protein binding, or change blood flow to organs that eliminate or metabolize the drug.

RENAL DISEASE

- Most water-soluble drugs are eliminated unchanged to some extent by the kidney. In addition to this, drug metabolites that were made more water soluble via oxidation or conjugation are typically removed by renal elimination.

- Unbound drug molecules that are relatively small are filtered at the glomerulus. Glomerular filtration is the primary elimination route for many medications.

- Drugs can be actively secreted into the urine, and this process usually takes place in the proximal tubules. Tubular secretion is an active process conducted by relatively specific carriers or pumps that move the drug from blood vessels in close proximity to the nephron into the proximal tubule.

- Additionally, some medications may be reabsorbed from the urine back into the blood by the kidney. Reabsorption is usually a passive process and requires a degree of lipid solubility for the drug molecule.

Dosage Adjustment In Renal failure

A. Estimation of Kidney Function Through Glomerular Filtration Rate (GFR) and Creatinine Clearance

1-MDRD study equation

GFR (mL/minute/1.73 m^2) = 186 * $(Scr)^{-1.154}$ * $(age\ in\ year)^{-0.203}$ * 1.212 (if patient is African American) * 0.742 (if patient is a woman)

2- CrCl calculation to measure GFR

- CrCl is calculated from a 24-hour urine collection and the following equation :

$$CrCl\ (mL/minute/1.73\ m^2) = \frac{volume\ of\ urine/1440\ minutes \times urine\ creatinine\ concentration}{serum\ creatinine\ concentration}$$

Healthy young men = 125 mL/minute/1.73 m^2

Healthy young women = 115 mL/minute/1.73 m^2

- After age 30, 1% of GFR is lost per year.

❖ **Problems associated with routine measurement of creatinine clearances**

1. Incomplete urine collections,
2. serum creatinine concentrations obtained at incorrect times,
3. and collection time errors can produce erroneous measured creatinine clearance values.

❖ **methods which estimate creatinine clearance from serum creatinine values and other patient characteristics in various populations**

I. Cockcroft and Gault

for males, $CrCl_{est} = [(140 - age)\ BW]/ (72 \cdot SCr)$;

for females, $CrCl_{est} = [0.85(140 - age)BW] / (72 \cdot SCr)$;

where $CrCl_{est}$ is estimated creatinine clearance in mL/min, age is in years, BW is body weight in kg, and SCr is serum creatinine in mg/dL.

The Cockcroft-Gault method should only be used in

- patients >18 years old,

- actual weight within 30% of their ideal body weight
  IBW males (in kg) = 50 + 2.3(Ht − 60)
  IBW females (in kg) = 45 + 2.3(Ht − 60)
  where Ht is height in inches

- and stable serum creatinine concentrations.

For example :- a 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be:

IBW males = 50 + 2.3 (Ht − 60)

= 50 + 2.3(71 − 60) = 75 kg,

so the patient is within 30% of his ideal body weight and the Cockcroft-Gault method can be used;

$CrCl_{est}$ = [(140 − age)BW] / (72 · SCr) = [(140 − 55 y)80 kg] / (72 · 1.9 mg/dL) = 50 mL/min.

II. Jelliffe and Jelliffe

If serum creatinine values are not stable, but increasing or decreasing in a patient, the **Jelliffe and Jelliffe** equation can be used to estimate creatinine clearance The first step in this method is to estimate creatinine production. The formula for this is different for males and females due to gender-dependent differences in muscle mass:

$$\mathbf{E_{ss}male = IBW[29.3 - (0.203 \cdot age)];}$$

$$\mathbf{E_{ss}female = IBW[25.1 - (0.175 \cdot age)],}$$

where Ess is the excretion of creatinine, IBW is ideal body weight in kilograms, and age is in years. The remainder of the equations correct creatinine production for renal function, and adjust the estimated creatinine clearance value according to whether the renal function is getting better or worse:

$$\mathbf{E_{ss}corrected = E_{ss}[1.035 - (0.0337 \cdot Scr._{ave})]}$$

$$\boldsymbol{E = \text{Ess } corrected - \frac{4\ \text{IBW}(Scr2 - \text{Scr1})}{\nabla t}}$$

$$\mathbf{CrCl\ (in\ mL/min\ /\ 1.73m2) = E/(14.4 \cdot Scr._{ave})}$$

III- Salazar and Corcoran

- If patients are not within 30% of their ideal body weight, Salazar and Corcoran method should be used to estimate creatinine clearance for obese patients.

$$\mathbf{CrClest(male)} = \frac{\mathbf{(137-Age)[(0.285*Wt)+(12.1*Ht2)]}}{\mathbf{51*Scr}}$$

CrClest(female)= (146-Age)[(0.287*Wt)+(9.74 *Ht2)])/(60*Scr)

where age is in years, Wt is weight in kg, Ht is height in m, and SCr is serum creatinine in mg/dL

Methods to estimate creatinine clearance for children and young adults are also available according to their age:

- age 0–1 year,

CrClest (in mL/min / 1.73 m2) = (0.45 · Ht) / SCr

- age 1–18 years,

CrClest (in mL/min / 1.73 m2) = (0.55 · Ht)/SCr

where Ht is in cm and SCr is in mg/dL.

Estimation of Drug Dosing and Pharmacokinetic Parameters Using Creatinine Clearance

- modest decrease in drug doses when creatinine clearance is <50–60 mL/min,
- a moderate decrease in drug doses when creatinine clearance is <25–30 mL/min, and
- a substantial decrease in drug doses when creatinine clearance is ≤15 mL/min.

❖ In order to modify doses for patients with renal impairment, it is possible to decrease the drug dose and retain the usual dosage interval, retain the usual dose and increase the dosage interval, or simultaneously decrease the dosage and prolong the dosage interval. The approach used depends on the **route of administration**, **the dosage forms available**, and the **pharmacodynamic response to the drug**.

HEPATIC DISEASE

- Most lipid-soluble drugs are metabolized to some degree by the liver.
- When hepatocytes are damaged they are no longer able to metabolize drugs efficiently, and intrinsic clearance decreases which reduces the hepatic clearance of the drug. If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and bioavailability will increase. A simultaneous decrease in hepatic clearance and liver first-pass effect results in extremely large increases in steady-state concentrations for orally administered drugs.
- Liver blood flow also decreases in patients with cirrhosis. The decrease in liver blood flow results in less drug delivery to hepatocytes and decreases hepatic drug clearance even further.
- The liver produces albumin and,glycoprotein, the two major proteins that bind acidic and basic drugs, respectively, in the blood. In patients with cirrhosis, the production of these proteins decline. When this is the case, the free fraction of drugs in the blood increases because of a lack of binding proteins. Additionally, high concentrations of endogenous substances in the blood that are normally eliminated by the liver, such as bilirubin, can displace drugs from plasma protein binding sites. The increased free fraction in the blood will alter hepatic and renal drug clearance as well as the volume of distribution for drugs that are highly protein bound

Determination of Child-Pugh Scores

Unfortunately, there is no single laboratory test that can be used to assess liver function in the same way that measured or estimated creatinine clearance is used to measure renal function.

The most common way to estimate the ability of the liver to metabolize drug is to determine the **Child-Pugh score** for a patient. The Child-Pugh score consists of five laboratory tests or clinical symptoms. The five areas are serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal)–3 (severely abnormal) and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score equal to 8–9 is grounds for a moderate decrease (~ 25%) in initial daily drug dose for agents that are primarily (≥60%) hepatically metabolized, and a score of 10 or greater indicates that a significant decrease in initial daily dose (~ 50%) is required for drugs that are mostly liver metabolized .

For example, the usual dose of a medication that is 95% liver metabolized is 500 mg every 6 hours, and the total daily dose is 2000 mg/d. For a hepatic cirrhosis patient with a Child-Pugh score of 12, an appropriate initial dose would be 50% of the usual dose or 1000 mg/d. The drug could be prescribed to the patient as 250 mg every 6 hours or 500 mg every 12 hours. The patient would be closely monitored for pharmacologic and toxic effects due to the medication, and the dose would be modified as needed.

Implications of Hepatic Disease on Serum Drug Concentration Monitoring and Drug Effects

The pharmacokinetic alterations that occur with hepatic disease result in complex changes for steady-state concentrations and drug response.

The changes that occur depend on whether the drug has a low or high hepatic extraction ratio.

- for drugs with a high hepatic extraction ratio ($\geq$70), hepatic clearance is equal to liver blood flow.

$$Cl_H = LBF$$

- For drugs with intermediate hepatic extraction ratios, liver blood flow, free fraction of drug in the blood, and intrinsic clearance are important parameters that must be taken into account.

- For drugs with a low hepatic extraction ratio (≤30%), hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug.

$$Cl_H = f_B . Cl_{int}$$

HEART FAILURE

- Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow. declines in hepatic clearance, especially for compounds with moderate-to-high hepatic extraction ratios, are reported for many drugs.
- decreased drug bioavailability has been reported in patients with heart failure.

The proposed mechanisms for decreased bioavailability are:-

1. collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult
2. decreased blood flow to the gastrointestinal tract.

OBESITY

The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution.

the magnitude of effect that adipose tissue has on the volume of distribution for a drug is dependent on the binding of drug in the tissue itself.

- If the drug has a large affinity for adipose tissue and is highly bound there, the free fraction in adipose tissue will be small ($\Downarrow f_{fat}$), and a large amount of drug will accumulate in that tissue. Medications that have high lipid solubility tend to partition into adipose tissue, and the volume of distribution in obese patients for these drugs can be dramatically larger than in normal weight patients. Examples of lipophilic drugs with larger volume of distribution values in obese individuals are Diazepam , carbamazepine
- hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution for many water-soluble drugs is not significantly different in obese and normal weight patients. The volumes of distribution for digoxin, cimetidine, and ranitidine are similar in overweight- and normal-weight subjects
- Half-life changes vary according to the relative alterations in clearance (Cl) and volume of distribution (V): $t_{1/2} = (0.693 * V) / Cl$, where $t_{1/2}$ is half-life. In the case of the aminoglycoside antibiotics, clearance and volume of distribution increases are about the same magnitude in obese patients, so half-life does not change

DRUG INTERACTIONS

Pharmacokinetic drug interactions occur between drugs when one agent changes the clearance or volume of distribution of another medication. There are several drug interaction mechanisms that result in altered drug clearance.

- A drug can inhibit or induce the enzymes responsible for the metabolism of other drugs. Enzyme inhibition decreases intrinsic clearance, and enzyme induction increases intrinsic clearance
- Another type of drug interaction displaces a drug from plasma protein binding sites because the two compounds share the same binding site, and the two compete for the same area on plasma proteins.
- For a drug with a low hepatic extraction ratio, plasma protein binding displacement drug interactions cause major pharmacokinetic alterations but are not clinically significant because the pharmacologic effect of the drug does not change
- For drugs with high hepatic extraction ratios given intravenously, plasma protein binding displacement drug interactions cause both major pharmacokinetic and pharmacodynamic changes

By virtue of the pharmacologic effect for a drug, it may be possible for an agent to change liver blood flow. For instance, B-blockers can decrease heart rate and cardiac output which decreases liver blood flow. Since liver blood flow is the predominate factor that determines clearance for high hepatic extraction ratio drugs, this type of interaction is only important for this category of medication. B-blockers decrease lidocaine clearance by decreasing liver blood flow. If a drug with a high hepatic extraction ratio is administered to a patient, and another agent that decreases liver blood flow is then added to the patient's therapy, total clearance will decrease.