Therapeutic Drug Monitoring(TDM)

Drug dosing in special population

• Renal or hepatic disease will decrease the elimination or metabolism of the majority drugs and change the clearance of the agent.

•Dialysis procedures, conducted using artificial kidneys in patients with renal failure, remove 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.

• 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

The equation that describes these various routes of renal elimination is:

$$Cl_R = \left[(f_B \cdot GFR) + \frac{RBF \cdot (f_B Cl'_{sec})}{RBF + (f_B Cl'_{sec})} \right] (1 - FR)$$

where f_B , is the free fraction of drug in the blood, GER is glomerular filtration rate, RBF is renal blood flow, Cl'_{sec} is the intrinsic clearance for tubular secretion of unbound drug, and FR is the fraction reabsorbed .

1- Measurement of glomerular filtration rate:

Glomerular filtration rate (GFR) can be estimated using the modified Modification of Diet in Renal Disease (MDRD) equation:

GFR (in mL/min/ 1.73 m^2) = 186. $SCr^{-1.154}$. $Age^{-0.203}$. (0.742, if female) . (1.21, if African-American).

For example, the estimated GFR for a 53-year-old African-American male with a SCr = 2.7 mg/dL would be computed as follows: GFR= 186· $(2.7\ mg/dL)^{-l.154}$. $(53\ y)^{-0.203}$. 1.21 = 32 mL/min/1.73 m^2.

Measurement and Estimation of Creatinine Clearance

Method 1:-

CrCl (in mL/min) = (Ucr. Vurine) /(SCr .T)

* Where Ucr is the urine creatinine concentration in mg/dL, Vurine is the volume of urine collected in mL, SCr is the serum creatinine collected at the midpoint of the urine collection in mg/dL, and T is the time in minutes of the urine collection.

* Because creatinine renal secretion exhibits diurnal variation, most nephrologists use a 24- hour urine collection period for the determination of creatinine clearance.

* For example, a 24-hour urine was collected for a patient with the following results: UCr= 55mg/dL, Vurine = 1000 mL, SCr = 1.0 mg/dL, T = 24 h x 60 min/h= 1440 min, and CrCl (in mL/min) = (Ugr Vurine) / (SCr T= (55)mg/dL · 1000 mL) / (1.0 mg/dL 1440 min)= 38 mL/min.

Method 2:-

Cockcroft and Gault: The Cockcroft-Gault method should only be used in patients:

A- ≥18 years old

B-Actual weight within 30% of their ideal body weight.

C- Stable serum creatinine concentrations.

For male ...CrCl= [(140 - age) BW/ (72 SCr)

*For females... CrCl [0.85(140 - age) BW] / (72 * SCr)

Where CrCl 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 0.85 correction factor for females is present because women have smaller muscle mass than men and, therefore, produce less creatinine per day.

IBW (in kg) = 50 + 2.3(Ht - 60) for male or

IBW (in kg) = 45 + 2.3(Ht - 60), for female

•Where Ht is height in inches‹

•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= (140 -age) BW] / (72 * S.Cr) = (140 - 55 y) 80 kg] / (72· 1.9 mg/dL) = 50 mL/min.

Method 2:- Salazar and Corcoran

A-If patients are not within 30% of their ideal body weight (obese)

B - ≥ 18 years old

C- Stable serum creatinine concentrations

$$CrCl_{est(male)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(female)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

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

Method 3: Jelliffe and Jelliffe method

Used if serum creatinine values are not stable

1- 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:

Ess male = IBW [29.3 - (0.203- age)]

Ess female = IBW [25.1 - (0.175· age)]

Where Ess is the excretion of creatinine, IBW is ideal body weight in kilograms, and age is in years.

2-Step2: correct creatinine production for renal function

Ess corrected = Ess [1.035 - (0.0337· Scr_{ave})]

3- Step3: adjust the estimated creatinine clearance value according to whether the renal function is getting better or worse

$$E = Ess_{corrected} - \frac{[4IBW(Scr_2 - Scr_1)]}{\Delta t}$$

4- Step4: calculate CrCl

CrCI (in mL/min / 1.73m2) = E/ (14.4 · Scr_{ave})

Where $S.cr_{ave}$ is the average of the two serum creatinine determinations in mg/dL, Scr1 is the first serum creatinine and Scr2 is the second serum creatinine both in mg/dL, and Δt is the time that expired between the measurement of Scr_1 and Scr_2 in minutes.

Method 4: Methods to estimate creatinine clearance for children and young adults or children:

1- Age 0-l year

$CrCl_{est}$ (in mL/min / 1.73 m2) = (0.45• Ht) / SCr

2- Age 1-20 years

$CrCl_{est}$ (in mL/min / 1.73 m2) = (0.55 Ht)/SCr

* Where Ht is in cm and SCr is in mg/dL.

Q/What are the best way to correct the dose of a drug eliminated mainly by kidney if renal impairment occurred

A-decrease the dose without any change in time interval or

B- increase the time interval without any change in a dose?

Answer:

B- Increase the time interval without any change in a dose since this way produce concentration time profile similar to that of healthy patient

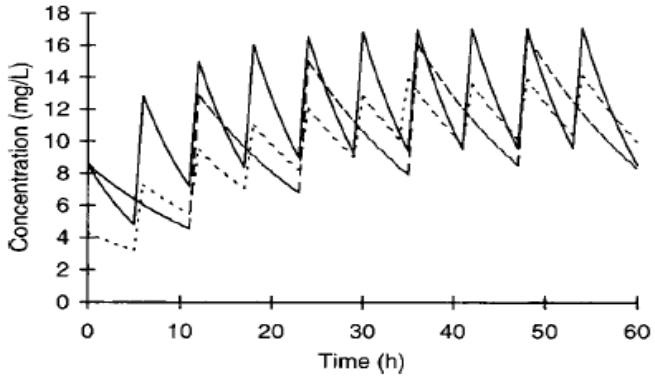


FIGURE:-Serum concentration versus time profile for a patient with normal kidney function receiving a renally eliminated drug at the dose of 300 mg every 6 hours (solid line). In a patient with renal dysfunction, it very is possible to give the same dose and prolong the dosage interval (300 mg every 12 hours, dashed line), or a reduced dose at the same dosage interval (150 mg every6 hours, dotted line). Giving the same dose at a longer dosage interval in the patient with renal disease usually results in a concentration/time profile similar to that seen in a normal patient receiving the normal dose. However, giving a smaller dose and keeping the dosage interval the same usually produces a concentration/time profile with a lower peak steady-state concentration and a higher trough steady-state concentration.

HEPATIC DISEASE

☻ 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.

Determination of Child-Pugh Scores

☺ 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.

TABLE 3-2 Child-Pugh Scores for Patients with Liver Disease[27]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

Φ If 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

ΦIf 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.

Hepatic Clearance-:

Liver blood flow averages 1-1.5 L/min in adults with about one-third coming from the hepatic artery and about two-thirds coming from the portal vein. Orally administered medications must pass through the liver before entering the systemic circulation, so if the drug is metabolized by the liver, a portion of the dose may be inactivated by the hepatic first-pass effect before having a chance to exert a pharmacologic effect .In addition to hepatic metabolism, drugs can be eliminated unchanged by liver in the bile. The equation that describes hepatic drug metabolism is

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

Where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance.

☺There are two major types of liver disease: hepatitis and cirrhosis.

☺ Patients with acute hepatitis usually experience mild, transient decreases in drug metabolism that require no or minor changes in drug dosing.

☺ If the patient develops chronic hepatitis, it is likely that irreversible hepatocyte damage will be more widespread, and drug dosage changes will be required at some point.

☺ In patients with hepatic cirrhosis, there is a permanent loss of functional hepatocytes so drug dosage schedules usually need to be modified.

☺ 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 because hepatocytes are replaced by nonfunctional connective tissue which increases intra-organ pressure causing portal vein hypertension and shunting of blood flow around the liver.

☺ The decrease in liver blood flow results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further.

☺ The liver produces albumin and, probably, αl-acid 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

$$\mathbf{V = V_B + (f_B/f_T)\, V_T}$$

☺Since clearance typically decreases and volume of distribution usually increases or does not appreciably change for a drug in patients with liver disease, the elimination rate constant (k_e) almost always decrease in patients with decreased liver function

$$Ke = Cl / V$$

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 total and unbound steady-state concentrations and drug response.

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

1- For drugs with a low hepatic extraction ratio (≤ 30%)

The numeric value of liver blood flow is much greater than the product of unbound fraction of drug in the blood and the intrinsic clearance of the compound (LBF >>$f_B.Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [LBF =~ LBF + (f_B · Cl'_{int})]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug for a drug with a low hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF} = f_B \cdot Cl'_{int}$$

2- For drugs with a high hepatic extraction ratio (≥70%)

Similarly, for drugs with a high hepatic extraction ratio (270%), the numeric value of liver blood fow is much less than the product of unbound fraction of drug in the blood and the intrinsic clearance of the agent (LBF<< $f_B.Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to the product of free fraction of drug in the blood and intrinsic clearance [$f_B.Cl'_{int}$ =~ LBF + ($f_B.Cl'_{int}$). When this substitution is made into the hepatic clearance equation, hepatic

clearance is equal to liver blood flow for a drug with a high hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{f_B \cdot Cl'_{int}} = LBF$$

3- For drugs with intermediate hepatic extraction ratios

For drugs with intermediate hepatic extraction ratios, the entire liver clearance equation must be used and all three factors, liver blood flow, free fraction of drug in the blood, and intrinsic clearance are important parameters that must be taken into account. An extremely important point for clinicians to understand is that the factors which are important determinants of hepatic clearance are different depending on the liver extraction ratio for the drug.

Answering the question of drug interaction

Equation used to answer the questions

1- The hepatic clearance

The hepatic clearance of drugs with low hepatic extraction ratios equals to the product of free fraction in the blood and intrinsic clearance

$$Cl_H = f_B.C1'$$

While hepatic clearance of drugs with high hepatic extraction ratios equals to liver blood flow only

$$Cl_H = LBF\ .$$

2- Volume of distribution

$$V = V_B + [f_B/f_T]V_T$$

3- Half-life:

$$T1/2 = [0.693\ .\ V]/Cl$$

4- steady state concentration

Affected by bioavailability (F) and clearance (CL)

$$Css = [F(D/\tau)]/CI$$

5- **The unbound steady-state concentration** of drug in the blood equals the product of the total steady-state concentration and the unbound fraction of drug in the blood $Css_u, = f_B.Css$

6- **The effect of the drug**

increases when the unbound steady-state concentration increases and

decreases when Css_u declines.

7- Bioavailability (F)

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.

So bioavailability used only for oral drugs and inversely proportional with LBF ,F_B ,CL_{int}

* For answering any question

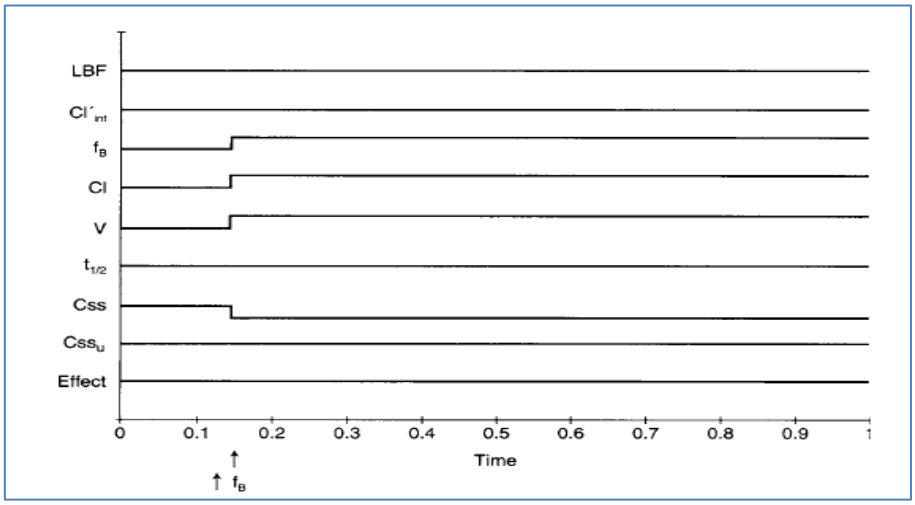
1- You have to know if the drug is low or high extraction ratio in order determine what the factors that effect on CL.

2- You have to know what is/are the parameter(s) that changed according to the given question and what are the effect of this change in the factors according to the equations from 1 to 7.

DRUG INTERACTIONS

***Plasma Protein-Binding Displacement Drug Interactions**

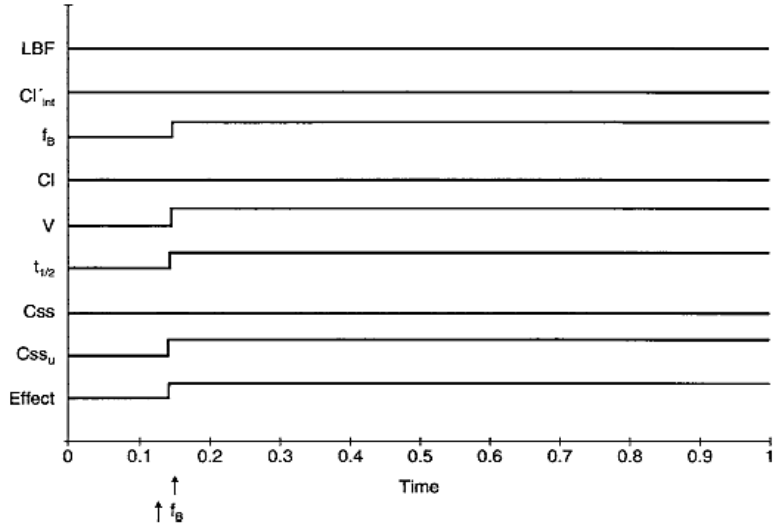
A-For a drug with a low hepatic extraction ratio, plasma protein-binding displacement drug interactions cause major pharmacokinetic alterations, but these interactions are not clinically significant because the pharmacologic effect of the drug does not change.



Because the clearance of the drug is dependent on the fraction of unbound drug in the blood and intrinsic clearance for a low hepatic extraction ratio agent, addition of a plasma protein--binding displacing compound will increase clearance (↑Cl = f_BCl'int) and volume of distribution (↑V= VB +[↑fB/fT]VT). Because half life depends on clearance and volume of distribution, it is likely that because both increase, half-life will not substantially change ($t_{1/2}$ = [0.693. ↑V/↑CI). However, it is possible that if either clearance or volume of distribution changes disproportionately, half-life will change. The total SteadyState concentration will decline because of the increase in clearance (↓Css= k0/↑CI, where k0 is the infusion rate of drug). However, the unbound SteadyState concentration will remain unaltered because the free fraction of drug in the blood is higher than it was before the drug interaction occurred (Cssu = ↑fB↓Css). The pharmacologic effect of the drug does not change because the free concentration of drug in the blood is unchanged. An example of this drug interaction is the addition of diflunisal to patients stabilized on warfarin therapy.

Diflunisal displaces warfarin from plasma protein-binding sites but does not augment the anticoagulant effect of warfarin. If drug concentrations are available for the medication, it can be difficult to convince clinicians that a drug dosage increase is not needed even though total concentrations decline as a result of this interaction. When available, unbound drug concentrations can be used to document that no change in drug dosing is needed.

B- For drugs with high hepatic extraction ratios given intravenously, plasma protein-binding displacement drug interactions cause both major pharmacokinetic and pharmacodynamics changes.



Because the clearance of the drug is dependent solely on liver blood flow for an agent of this type, total clearance does not change. However, both volume of distribution [↑V =VB + (↑fB/fT) VT] and half-life [↑$t_{l/2}$ = (0.693 . ↑V)/Cl] will increase because of plasma protein-binding displacement of the drug. Because total clearance did not change, the total SteadyState concentration remains unaltered. However, the free concentration (↑Cssu = ↑fB. Css) and pharmacologic effect (↑effect α ↑Cssu) of the drug will both increase.

Currently, there are no clinically significant drug interactions of this type. However, clinicians should be on the outlook for this profile for highly protein bound drugs with high hepatic extraction ratios given intravenously because the interaction is very subtle. Most noteworthy is the fact that although total concentrations remain unchanged, the pharmacologic effect of the drug is augmented. If available, unbound drug concentration could be used to document the drug interaction. If a drug with a high hepatic extraction ratio is given orally. a plasma protein-binding displacement drug interaction will cause a simultaneous increase in the unbound fraction of drug in the blood (↑f_B) and the hepatic presystemic metabolism of the drug. Hepatic presystemic metabolism increases because the higher unbound fraction of drug in the blood allows more drug molecules to enter the liver where they are ultimately metabolized. The increase in hepatic presystemic metabolism leads to an increased first pass effect and decreased drug bioavailability (↓F) .

Total SteadyState drug concentrations will be lower because of decreased drug bioavailability [↓ Css =(↓F (D/t)/Cl]. However, the unbound Steady State drug concentration and pharmacologic effect remain unchanged due to this type of drug interaction because the increase in unbound fraction is offset by the decrease in the total Steady State concentration (~Cssu = ↑fB↓Css). Route of administration plays an important role in how important plasma protein-binding displacement drug interactions are for agents with high hepatic extraction ratios.

Inhibition Drug Interactions

Inhibition of hepatic drug metabolism is probably the most common drug interaction encountered in patients.

For drugs with low hepatic extraction ratios, this type of drug interaction produces clinically significant changes in drug pharmacokinetics and effect .

Induction Drug Interactions

Drugs with low hepatic extraction ratios exhibit clinically significant drug interactions that alter drug pharmacokinctics and pharmacologic response when hepatic enzyme inducers are coadministered. (see Figure 3-17 , 3-18)

Effect of age on hepatic metabolism

•Hepatic metabolism of drugs is not completely developed in neonates (~ 40-weeks gestational age) and continues to increase so that by age 3-6 months it is stable. Drug metabolism is more rapid in children until puberty (when measured on per kilogram basis). At that point, metabolic rate gradually decreases to adult values.

•Patients over the age of 65 years may have decreased hepatic clearance of some drugs, but often, concurrent disease states and conditions that effect drug pharmacokinetics obscure the influence of age in these older individuals. Elderly individuals have decreased liver mass, and it appears that hepatocytes which are still present have decreased ability to metabolize drugs.

HEART FAILURE

Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow.

Changes in drug pharmacokinetics due to decreased renal blood flow are not widely reported. However.

declines in hepatic clearance, especially for compounds with moderate to high hepatic extraction ratios, are reported for many drugs. Additionally, decreased drug bioavailability has been reported in patients with heart failure. The proposed mechanisms for decreased bioavailability are collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult and decreased blood flow to the gastrointestinal tract. The volume of distribution for some drugs decreases in patients with heart failure. Because clearance and volume of distribution may or may not simultaneously change, the alteration in half life, if any, is difficult to predict in patients with heart failure.

OBESITY

The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution, The general physiologic equation for volume of distribution can be broken down into separate parameters for individual tissue types:

•If the drug has a large affinity for adipose tissue and is highly bound there, the free fraction in adipose tissue will be small (↓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, and trazodone.

•However, 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.