Therapeutic Drug Monitoring

Variability in Drug Dosing in Special Population

Hepatic disease

- Most lipid-soluble drugs are metabolized to some degree by the liver.
- Phase I type reactions, such as oxidation, hydrolysis, and reduction, are often mediated by the cytochrome P-450 enzyme system (CYP).
- Phase II type reactions, including conjugation to form glucuronides, acetates, or sulfates, may also be mediated in the liver by cytosolic enzymes contained in hepatocytes.

Hepatic disease

- Phase I and phase II drug metabolism generally results in metabolites that are more water soluble and prone to elimination by the kidney.
- Transport proteins, such as P-glycoprotein, actively secrete drug molecules into the bile.
- Liver blood flow averages 1–1.5 L/min in adults.

Hepatic disease

- 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. So if the patient experiences a hepatic disease, 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.

Hepatic disease

- 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.
- In premature infants (<35 weeks), hepatic metabolism may take even longer to develop in the postpartum period.
- On a per kilogram basis, drug metabolism is more rapid in children until puberty.

Hepatic disease

- At that point, metabolic rate gradually decreases to adult values.
- The effect of advanced age on hepatic drug metabolism is quite variable due to effects of concurrent conditions.
- Patients over the age of 65 years may have decreased hepatic clearance of some drugs, because aging is associated with a reduction of approximately 40% in hepatic blood flow and 30% in liver mass and also first-pass metabolism decreasing by about 1%/year after age 40.

Hepatic disease

- 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.

Hepatic disease

- Liver blood flow also decreases in patients with cirrhosis because hepatocytes are replaced by nonfunctional connective tissue which increases intraorgan 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.

Hepatic disease

- The liver produces albumin and α-1-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.

- Unfortunately, there is no single laboratory test that can be used to assess liver function in the same way that 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.

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

- **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 total Child-Pugh score of 5 to 6 is considered class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease).
- If a Child-Pugh score equal to **7–9** is grounds for a moderate **decrease (~ 25%) in initial daily drug dose** for agents that are primarily (≥60%) hepatically metabolized,
- If 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 (total bilirubin 3.1 mg/dl , serum albumin 3 g/dl , prothrombin time 7 seconds ,with slight ascites and moderate encephalopathy), 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.

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.

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 by as much as 40% 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.

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

If the drug has

- *a large affinity for adipose tissue (lipophilic)*
- *a highly tissue binding*

The free fraction in adipose tissue will be small ($\downarrow f_{fat}$)

The volume of distribution in obese patients for these drugs can be dramatically larger than in normal weight patients

Obesity

- 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.
- In that sense, The volumes of distribution for digoxin, cimetidine, and ranitidine are similar in overweight- and normal-weight subjects.

Obesity

- Although the presence of excessive adipose tissue is the most obvious change that occurs in obese individuals, other physiologic changes are present;

1. ↑ *Supportive tissues*
2. ↑ *Extracellular fluid*
3. ↑ *Blood*
4. ↑ *Lean tissue (muscle)*

In the adipose tissue

Obesity

- The net result of these changes is that hydrophilic drugs with small volumes of distribution may experience distribution alterations in obese patients.
- For example, the aminoglycoside antibiotics are water-soluble molecules that have relatively small volumes of distribution.
- Since the volume of distribution is so small, the addition of just a few liters of extracellular fluid can increase the volume of distribution of these antibiotics.

Obesity

- However, if the volume of distribution for a hydrophilic drug is intermediate or large, the additional extracellular fluid contained in adipose tissue may not significantly alter the distribution of the agent.

- Examples of medications with larger and intermediate volumes of distribution are digoxin (V = 500 L) and vancomycin (V = 50 L).

Obesity

- Another change that is found in obese individuals is increased glomerular filtration rates due to increased blood volume.
- This alteration primarily affects hydrophilic drug compounds that are renally eliminated and will increase the renal clearance of the agent.
- Vancomycin, the aminoglycosides, and cimetidine all have higher clearance rates in obese patients compared to normal weight individuals.

Obesity

- Obesity has variable effects on the metabolism of drugs.
- For many agents, such as carbamazepine and cyclosporine, obesity does not significantly effect hepatic clearance.
- For other drugs, obesity increases hepatic clearance, as with diazepam due to increased rate of metabolism via CYP2C19 isoenzymes. While for other drugs such as methylprednisolone, the hepatic clearance decreased due to be an occurrence of 11-hydroxysteroid dehydrogenase type 1 in adipose tissue, and, thus, increased rate of extrahepatic metabolism in obesity.

Obesity

Half-life changes vary according to the relative alterations in clearance (Cl) and volume of distribution (V):

In the case of the aminoglycoside antibiotics, *clearance and volume of distribution* increases are about the same magnitude in obese patients, so half life dose not change.

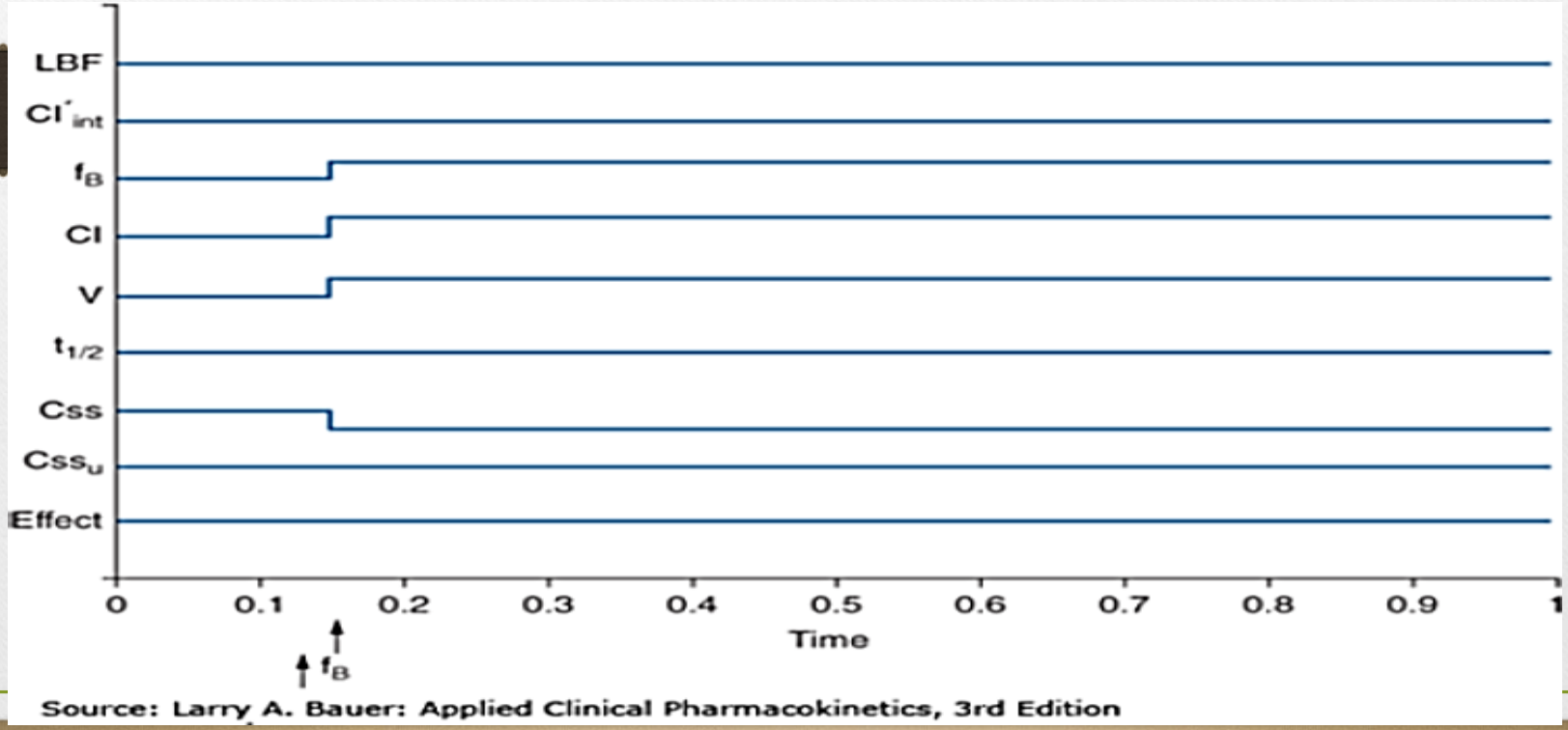
If the volume of distribution increases but clearance is unaffected , half life can increase dramatically as with carbamazepine.

Finally , if clearance changes and volume of distribution remains constant , obesity may also cause a change in the half-life of a drug as is the case for methylprednisolone.

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.



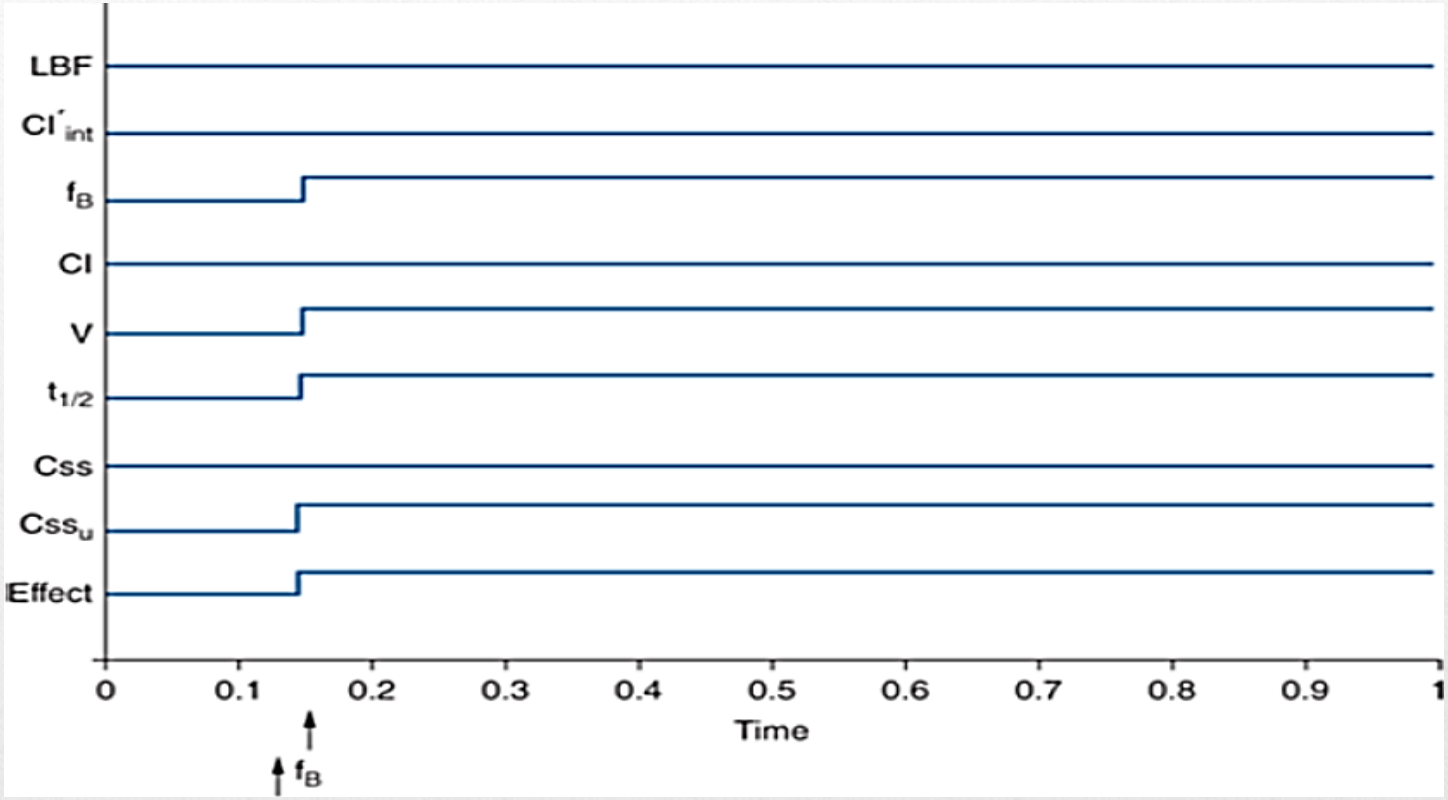
Source: Larry A. Bauer: Applied Clinical Pharmacokinetics, 3rd Edition

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 = ↑fB Cl′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 (t1/2 = [0.693 • ↑V]/↑Cl). However, it is possible that if either clearance or volume of distribution changes disproportionately, half life will change.

The total steady state concentration will decline because of the increase in clearance. The pharmacologic effect of the drug does not change because the unbound steady state concentration will remain unaltered (Cssu = ↑fB↓Css). 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.

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, total clearance does not change. However, both volume of distribution [↑V = VB + (↑fB/fT) VT] and half-life [↑t1/2 = (0.693 •↑V)/Cl] will increase. Because total clearance did not change, the total steady state concentration remains unaltered. However, the free concentration (↑Cssu = ↑fB Css) and pharmacologic effect (↑effect with ↑Cssu) of the drug will both increase.

Currently, there are no clinically significant drug interactions of this type. Most noteworthy is the fact that although total concentrations remain unchanged, the pharmacologic effect of the drug is augmented.

Route of administration plays an important role in how important plasma protein–binding displacement drug interactions are for agents with high hepatic extraction ratios.

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 (↑fB) 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 steady state drug concentrations will be lower because of decreased drug bioavailability. However, the unbound steady state drug concentration and pharmacologic effect remain unchanged because the increase in unbound fraction is offset by the decrease in the total steady state concentration.

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 (The addition of a hepatic enzyme inhibitor will decrease intrinsic clearance and total clearance for the drug (↓Cl = fB↓Cl′int). Because volume of distribution remains unaltered, the half-life of the drug will increase (↑t1/2 = [0.693 • V]/↓Cl). As a result of the total clearance decrease, total and unbound steady state drug concentrations will increase and the effect of the drug will increase in proportion to unbound concentration.

An example of this drug interaction is the addition of ciprofloxacin to a patient stabilized on theophylline therapy.

For drugs with high hepatic extraction ratios, this category of drug interaction produces variable effects depending on the route of administration for the drug. If the drug is given *intravenously* and an enzyme inhibitor is added, the decrease in intrinsic clearance is usually not substantial enough to cause major pharmacokinetic and pharmacodynamics effects because clearance is a function of liver blood flow .

However, if the drug is given *orally* and an enzyme inhibitor is added to therapy, presystemic metabolism of the medication may be greatly depressed and the first pass effect can decrease dramatically leading to improved drug bioavailability. This effective increase in administered oral dose will increase the steady state drug concentrations, and lead to an increase in the pharmacologic effect of the drug.

Induction Drug Interactions

Drugs with low hepatic extraction ratios exhibit clinically significant drug interactions that alter drug pharmacokinetics and pharmacologic response when hepatic enzyme inducers are coadministered .

Enzyme inducers increase intrinsic clearance of the drug and thereby increase the total clearance of the medication (↑Cl = fB↑Cl′int). The increase in total clearance will cause a shorter half-life as volume of distribution remains unchanged (↓t1/2 = [0.693 • V]/↑Cl). Increased total clearance will also cause decreased total steady state concentration , unbound steady state concentration (↓Cssu = fB↓Css), and pharmacologic effect (↓effect a ↓Cssu). Carbamazepine is a potent enzyme inducer that, when added to a patient's therapy, can cause this type of interaction with other medications such as warfarin.

For drugs with high hepatic extraction ratios, this type of drug interaction results in variable effects depending on the route of administration for the drug. If the drug is given *intravenously* and an enzyme inducer is added, the increase in intrinsic clearance is usually not large enough to cause major pharmacokinetic and pharmacologic effect alterations because total clearance is a function of liver blood flow.

However, if the drug is given *orally* and an enzyme inducer is added to the treatment regimen, presystemic metabolism of the medication may be increased and the first pass effect augmented leading to decreased drug bioavailability. This effective decrease in administered oral dose will decrease the total and unbound steady state drug concentrations and lead to a decrease in the pharmacologic effect of the agent.


THANK
YOU!