Drug Dosing in Special Populations

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Introduction

The dosing of most drugs will be altered by specific disease states and conditions that change the pharmacokinetics of the drug:

- **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.

Introduction

- **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

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

- The equation that describes the various routes of renal elimination is:

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

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

Renal disease

- Renal function, measured by glomerular filtration rate (GFR), varies with age.

- At birth, renal function is not yet completely developed in full-term neonates (~40 weeks gestational age).

- It is complete and stabilized 3–6 months after birth. In addition, as humans' age increase, there is a gradual decline in glomerular function so that by 65 years of age, the average GFR is ~50–60 mL/min.

Renal disease

- Additionally, in patients with renal disease, there is a functional loss of nephrons which can be reversible or irreversible depending on the aetiology of the renal disease.

- A GFR of 80–120 mL/min is usually considered the normal range by most clinical laboratories.

Estimation of glomerular filtration rate

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

$$GFR\ (\text{in mL/min/1.73 m}^2) =$$

$$186 \cdot S_{Cr}^{-1.154} \cdot Age^{-0.203} \cdot (0.742, \text{if female}) \cdot (1.21, \text{if African-American})$$

Estimation of glomerular filtration rate

- For example, the estimated GFR for a 53-year-old African-American male with a S_{Cr} = 2.7 mg/dL would be computed as follows:

$$GFR = 186 \cdot (2.7\ mg/dL)^{-1.154} \cdot (53\ y)^{-0.203} \cdot 1.21$$

$$= 32\ mL/min / 1.73\ m^2.$$

Measurement of creatinine clearance

- Creatinine clearance rates can be measured by collecting urine for a specified period and collecting a blood sample for determination of serum creatinine at the midpoint of the concurrent urine collection time:

$$CrCl\ (ml/min) = (U_{Cr} \cdot V\ urine)/(S_{Cr} \cdot T)$$

U_{Cr}: urine creatinine concentration (mg/dL)

V urine: volume of urine collected (ml)

SCr: serum creatinine collected at the midpoint of the urine collection (mg/dL)

T : time of the urine collection (minutes)

Measurement of creatinine clearance

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

Measurement of creatinine clearance

- For example, a 24-hour urine was collected for a patient with the following results:

U_{Cr} = 55 mg/dL

V urine = 1000 mL

S_{Cr} = 1.0 mg/dL

T = 24 h × 60 min/h =1440 min

CrCl (in mL/min) = $(U_{Cr} \cdot V \text{ urine})/(S_{Cr} \cdot T)$

= (55 mg/dL · 1000 mL) /(1.0 mg/dL · 1440 min)

= 38 mL/min

Measurement of creatinine clearance

- However, for the purpose of drug dosing, collection periods of 8–12 hours have been sufficient.

- In addition, if renal function is stable, the blood sample for determination of serum creatinine may not need to be collected at the precise midpoint of the urine collection.

Measurement of creatinine clearance

- Routine measurement of creatinine clearances has been associated with several problems:
    - *Incomplete urine collections*
    - *Serum creatinine concentrations obtained at incorrect times*
    - *Collection time errors*

Estimation of creatinine clearance

- The most widely used of these formulas for adults aged 18 years and older is the method suggested by ***Cockcroft and Gault:***

Estimation of creatinine clearance

- For males,

$$CrCl_{est} = [(140 - age)\ BW] / (72 \cdot S_{Cr})$$

- For females,

$$CrCl_{est} = [0.85(140 - age)BW] / (72 \cdot S_{Cr})$$

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

$CrCl_{est}$: estimated creatinine clearance (mL/min)
Age (years)
BW: body weight (kg)
S_{Cr}: serum creatinine (mg/dL)

Estimation of creatinine clearance

- The Cockcroft-Gault method should only be used in patients:
  - *≥18 years old*
  - *Actual weight within 30% of their ideal body weight*
  - *Stable serum creatinine concentrations*

- Ideal body weight

IBW males (kg) = 50 + 2.3 (Ht – 60)

IBW females (kg) = 45 + 2.3 (Ht - 60)

Ht: height in inches

Estimation of creatinine clearance

- For example, A 55-year-old, 80-kg, 5-ft 11-in male has a S_{cr} 1.9 mg/dL.

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

the Cockcroft-Gault method can be used;

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr})$$
$$= [(140 - 55\ y)80\ kg] / (72 \cdot 1.9\ mg/dL)$$
$$= 50\ mL/min$$

Estimation of creatinine clearance

- If serum creatinine values are not stable, the Cockcroft-Gault equation cannot be used to estimate creatinine clearance.

- In this case, an alternate method must be used which is ***Jelliffe and Jelliffe***

Ess male = IBW [29.3 - (0.203 · age)]

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

Ess: excretion of creatinine

IBW: ideal body weight (kg)

Age (years)

Estimation of creatinine clearance

$$Ess_{corrected} = Ess\ [1.035 - (0.0337 \cdot Scr_{ave})]$$

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

$$CrCl\ (in\ mL/min\ /\ 1.73m^2) = E/(14.4 \cdot Scr_{ave})$$

Scr_{ave}: average of the two serum creatinine determinations in mg/dL
Scr_1: first serum creatinine (mg/dL)
$Scr_{2:}$ second serum creatinine (mg/dL)
Δt: time that expired between the measurement of Scr_1 and Scr_2 (minutes)

Estimation of creatinine clearance

- If patients are not within 30% of their ideal body weight, we can use the
  - *ideal body weight*
  - *adjusted body weight* (*ideal body weight* plus *40% of obese weight*) in the Cockcroft-Gault equation for obese individuals.

Estimation of creatinine clearance

- However, a specific method (*Salazar and Corcoran*) for estimating creatinine clearance for obese patients:

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

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

Wt: weight (kg)
Ht: height (m)
S_{Cr}: serum creatinine (mg/dL)

Estimation of creatinine clearance

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

age 0–1 year,

CrCl est (in mL/min /1.73 m^2) = (0.45 · Ht)/S_{Cr}

age 1–20 years,

CrCl est (in mL/min /1.73 m^2) = (0.55 · Ht)/S_{Cr}

Ht: height (cm)

SCr: serum creatinine (mg/dL)

Estimation of drug dosing using creatinine clearance

- The initial doses of drugs that are renally eliminated are usually based on **creatinine clearance**.

- However, the suggested doses for patients with renal impairment are an initial guideline only, and doses may need to be increased in patients that exhibit suboptimal drug response and decreased in patients with adverse effects.

Estimation of drug dosing using creatinine clearance

- In order to modify doses for patients with renal impairment, it is possible;
  - **Decrease the drug dose and retain the usual dosage interval**
  - **Retain the usual dose and increase the dosage interval**
  - **Simultaneously decrease the dosage and prolong the dosage interval**

Estimation of pharmacokinetic parameters using creatinine clearance

- For drugs with **narrow therapeutic indexes**, measured or estimated creatinine clearance may be used to estimate pharmacokinetic parameters for a patient.

- These parameters are then used in dosing equations to compute initial doses for patients.

- These parameters include
  - ***Clearance***
  - ***Elimination rate constant***
  - ***Volume of distribution***

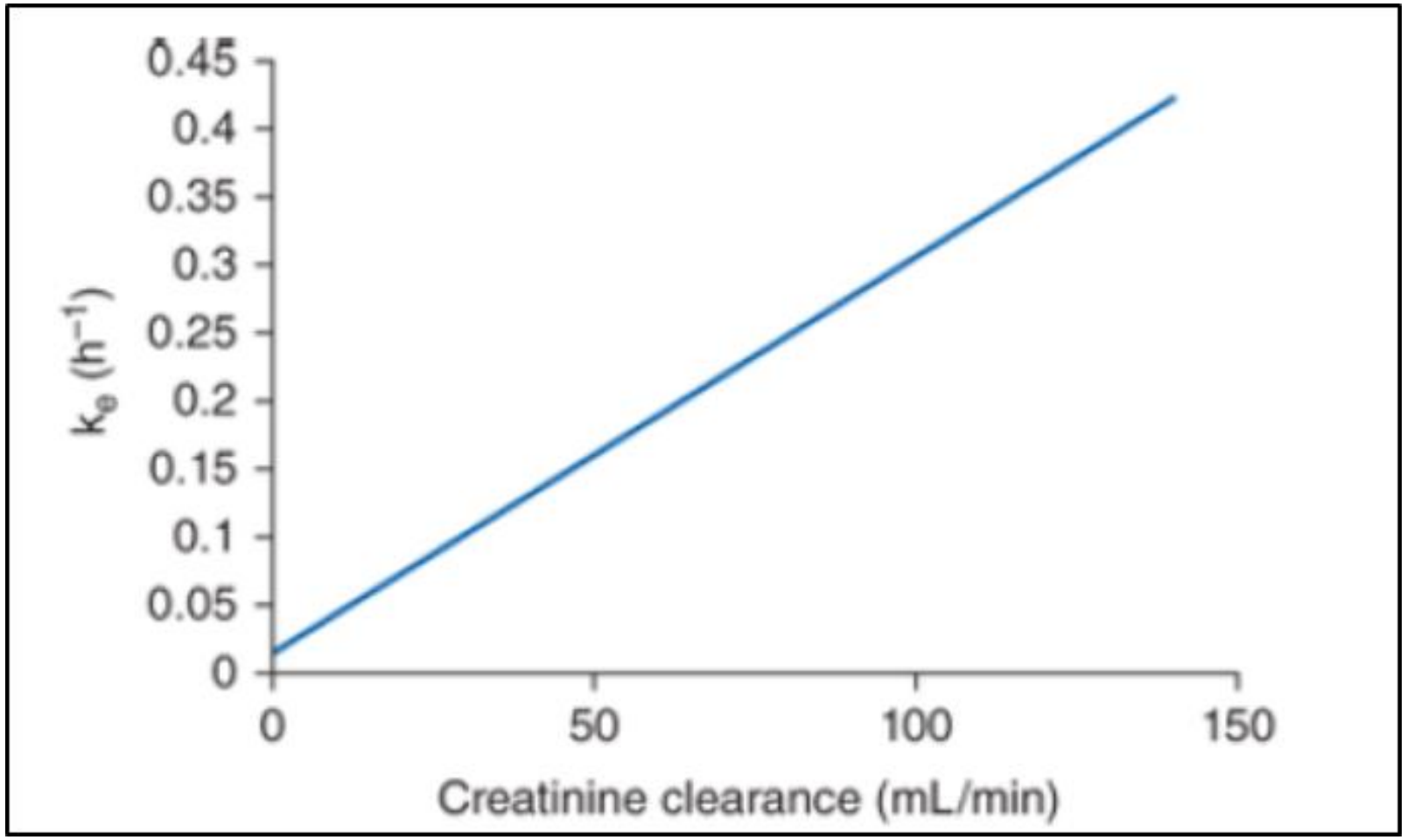
Elimination rate constant

- It can be estimated using creatinine clearance, but it is a dependent pharmacokinetic parameter and its value depends on the relative values of clearance and volume of distribution (ke = Cl/V).

- Because of this, changes in elimination rate constant may not always be due to changes in the renal elimination of the drug.

- For the aminoglycoside antibiotics, an equation that represents the relationship between aminoglycoside antibiotic elimination rate constant (ke) and creatinine clearance (CrCl in mL/min):

$$ke\ (in\ h^{-1}) = 0.00293 \cdot CrCl + 0.014$$



Relationship between creatinine clearance and aminoglycoside elimination rate constant (ke) used to estimate initial aminoglycoside elimination when no drug concentrations are available. The y-axis intercept (0.014 h^{-1}) is nonrenal elimination for aminoglycosides.

Clearance

- The relationship between drug clearance and creatinine clearance is usually approximated by a straight line with a slope that is a function of the renal clearance for the drug and an intercept that is related to the nonrenal clearance of the drug.

- For **digoxin**, an equation that describes the relationship between digoxin clearance (Cl) and creatinine clearance (CrCl in mL/min) is:

$$Cl\ (in\ mL/min) = 1.303 \cdot CrCl + Cl_{NR}$$

- Cl_{NR}: nonrenal clearance
  - ***20 mL/min in patients with moderate-severe heart failure***
  - ***40 mL/min in patients with no or mild heart failure***

Relationship between creatinine clearance and digoxin clearance used to estimate initial digoxin clearance when no drug concentrations are available.

Volume of distribution

- It can also change in patients with decreased renal function.

- Plasma protein binding displacement of drug by endogenous or exogenous substances that would normally be eliminated by the kidney but accumulate in the blood of patients with poor kidney function can ***increase the volume of distribution of drugs***.

- Conversely, the ***volume of distribution*** of a drug can **decrease** if compounds normally excreted by the kidney accumulate to the extent that *displacement* of drug from *tissue binding sites* occurs.

Volume of distribution

$$V = V_B + \frac{f_B}{f_T} V_T$$

Volume of distribution

- Digoxin volume of distribution ***decreases*** in patients with ***decreased renal function*** according to the following equation:

$$V \text{ (in L)} = 226 + [(298 \cdot CrCl)/(29.1 + CrCl)]$$

- CrCl is in mL/min.

- The decline in volume of distribution likely occurs because of displacement of tissue-bound digoxin.

Hepatic disease

- Most lipid-soluble drugs are metabolized to some degree by the liver.

- Transport proteins, such as P-glycoprotein, actively secrete drug molecules into the bile.

- 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.

Hepatic disease

- 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.

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.

Effect of liver disease on hepatic metabolism

- 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. Drug dosage schedules usually need to be modified in patients with severe cirrhosis.

Effect of liver disease on hepatic metabolism

- 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 pre-systemic 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.

Effect of liver disease on hepatic metabolism

- Liver blood flow also decreases in patients with cirrhosis because hepatocytes are replaced by non-functional 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 decreases hepatic drug clearance even further.

Effect of liver disease on hepatic metabolism

- The liver produces **albumin** and, probably, **α1-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.

Effect of liver disease on hepatic metabolism

- 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

$$V = VB + (f_B/f_T)VT$$

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

Determination of Child-Pugh scores

- There is no single laboratory test that can be used to assess liver 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***
  - ***hepatic encephalopathy***

Determination of Child-Pugh scores

- Each of these areas is given a score of 1 (**normal**) to 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.

Determination of Child-Pugh scores

- 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.

- The initial doses are used as starting points for dosage titration based on patient response and avoidance of adverse effects.

Determination of Child-Pugh scores

- 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.

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

Determination of Child-Pugh scores

- When prescribing medications that are mainly eliminated by the liver in patients with liver dysfunction, it is possible to
  - ***decrease the dose while retaining the normal dosage interval***
  - ***retain the normal dose and prolong the dosage interval***
  - ***modify both the dose and dosage interval***

- The actual method used to reduce the dose for patients with liver dysfunction will depend on the route of administration and the available dosage forms.

TABLE 3-3 Theophylline Clearance and Dosage Rates for Patients with Various Disease States and Conditions[28]

DISEASE STATE/CONDITION	MEAN CLEARANCE (mL/min/kg)	MEAN DOSE (mg/kg/h)
Children 1–9 years	1.4	0.8
Children 9–12 years or adult smokers	1.25	0.7
Adolescents 12–16 years or elderly smokers (>65 years)	0.9	0.5
Adult nonsmokers	0.7	0.4
Elderly nonsmokers (>65 years)	0.5	0.3
Decompensated CHF, cor pulmonale, cirrhosis	0.35	0.2

Mean volume of distribution = 0.5 L/kg.

Determination of Child-Pugh scores

- Table 3-3 gives values for theophylline clearance in a variety of patients, including patients with cirrhosis.

- Average theophylline clearance is about 50% less in adults with liver cirrhosis compared to adults with normal hepatic function.

- Because of this, initial theophylline doses for patients with hepatic cirrhosis are one-half the usual dose for adult patients with normal liver function.

Determination of Child-Pugh scores

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

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

- As previously discussed, hepatic drug metabolism is described by the following equation:

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

Determination of Child-Pugh scores

- For drugs with a low hepatic extraction ratio (ERH ≤ 0.3), hepatic clearance is mainly a product of the free fraction of the drug in the blood or serum and intrinsic clearance:

$$Cl_H = f_B \cdot Cl'_{int}$$

- For drugs with high hepatic extraction ratios (ERH ≥ 0.7), hepatic clearance is mainly a function of liver blood flow:

$$Cl_H = LBF$$

- 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.

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:
  1. Enzyme inhibition or induction. Enzyme inhibition decreases intrinsic clearance, and enzyme induction increases intrinsic clearance.

  2. Competition for the same metabolic pathway. If two drugs are eliminated by the same enzyme, they may compete for the **metabolic pathway** and decrease the clearance of one or both compounds.

Drug interactions

3. Competition for the elimination pathway. Two drugs eliminated by the same active renal tubular secretion mechanism can compete for the pathway and decrease the renal clearance of one or both agents.

4. Alteration of organ blood flow. Because of the pharmacologic effect, a drug may increase or decrease blood flow to an organ that eliminates or metabolizes another medication and thereby decrease the clearance of the medication.

Drug interactions

- Drug interaction mechanisms that result in altered volume of distribution:
  1. **Displacement** from **plasma protein binding** sites when the two compounds share the same binding site. Changes in plasma protein binding cause alterations in volume of distribution.

  2. **Displacement** from **tissue binding sites** if two drugs share the same tissue binding sites. Tissue-binding displacement drug interactions can occur and change the volume of distribution for one of the medications.

- To understand pharmacokinetic drug interactions, it is necessary to know if the drug has a low extraction ratio or high extraction ratio.

Plasma protein binding displacement drug interactions

1. Drugs with low hepatic extraction ratios:

- 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.

- 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 and volume of distribution.

$$\uparrow Cl = \uparrow f_B Cl'_{int}$$

$$\uparrow V = VB + (\uparrow f_B / f_T) VT$$

Plasma protein binding displacement drug interactions

- Since half-life depends on clearance and volume of distribution, it is likely that because both increase, half-life will not substantially change.

$$t_{1/2} = [0.693 \cdot \uparrow V] / \uparrow Cl$$

- 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

$$\downarrow Css = k_0 / \uparrow Cl$$

Plasma protein binding displacement drug interactions

- But, the unbound steady-state concentration will remain unaltered because the free fraction of drug in the blood is higher than it was before the drug interaction occurred

$$Cssu = \uparrow f_B \downarrow Css$$

- 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.

Plasma protein binding displacement drug interactions

2. Drugs with high hepatic extraction ratios:

- For agents with high hepatic extraction ratios, route of administration plays an important role in plasma protein binding displacement drug interactions.

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

Plasma protein binding displacement drug interactions

- Because the *clearance* of the drug is dependent only on *liver blood flow*, total clearance does not change.

- However, both volume of distribution and half-life will increase because of plasma protein binding displacement of the drug.

$$\uparrow V = VB + (\uparrow f_B / f_T) VT$$

$$\uparrow t_{1/2} = (0.693 \cdot \uparrow V) / Cl$$

Plasma protein binding displacement drug interactions

- Since total clearance did not change, the total steady-state concentration remains unaltered.

$$Css = k_0 / Cl$$

- However, the free concentration and pharmacologic effect of the drug will both increase.

$$\uparrow Cssu = \uparrow f_B \, Css$$

$$\uparrow effect \propto \uparrow Cssu$$

- Currently, there are no clinically significant drug interactions of this type.

Plasma protein binding displacement drug interactions

- 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 ($\uparrow f_B$) and the hepatic pre-systemic metabolism of the drug.

- Hepatic pre-systemic 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.

Plasma protein binding displacement drug interactions

- The increase in hepatic pre-systemic 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

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

- 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

$$C_{ssu} = \uparrow f_B \downarrow Css$$

Inhibition drug interactions

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

1. Drugs with low hepatic extraction ratios:

- 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

$$\downarrow Cl = f_B \downarrow Cl'_{int}$$

- Since volume of distribution remains unaltered, the half-life of the drug will increase

$$\uparrow t_{1/2} = [0.693 \cdot V] / \downarrow Cl$$

Inhibition drug interactions

- As a result of the total clearance decrease, total steady-state drug concentrations will increase.

$$\uparrow Css = k_0 / \downarrow Cl$$

- Both unbound steady-state drug concentration and the total drug concentration will increase, and the effect of the drug will increase in proportion to unbound concentration.

$$\uparrow Cssu = f_B \uparrow Css$$

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

Inhibition drug interactions

2. Drugs with high hepatic extraction ratios:

- 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 pharmacodynamic effects because clearance is a function of liver blood flow.

$$Cl = LBF$$

Inhibition drug interactions

- However, if the drug is given orally and an enzyme inhibitor is added to therapy, pre-systemic metabolism of the medication may be greatly decreased, and the first-pass effect can decrease dramatically leading to improved drug bioavailability.

- This effective increase in administered oral dose will increase the total and unbound steady-state drug concentrations and lead to an increase in the pharmacologic effect of the drug.

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

$$\uparrow Cssu = f_B \uparrow Css$$

Induction drug interactions

1. Drugs with low hepatic extraction ratios:

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

- Enzyme inducers increase intrinsic clearance of the drug and thereby increase the total clearance of the medication

$$\uparrow Cl = f_B \uparrow Cl'_{int}$$

- The increase in total clearance will cause a shorter half-life since volume of distribution remains unchanged

$$\downarrow t_{1/2} = [0.693 \cdot V] / \uparrow Cl$$

Induction drug interactions

- Increased total clearance will also cause decreased total steady-state concentration, unbound steady-state concentration, and pharmacologic effect.

$$\downarrow Css = k_0 / \uparrow Cl$$

$$\downarrow Cssu = f_B \downarrow Css$$

$$\downarrow effect \propto \downarrow Cssu$$

- Carbamazepine is a potent enzyme inducer that, when added to a patient's therapy, can cause this type of drug interaction with many other medications such as warfarin.

Drugs with high hepatic extraction ratios

- 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

$$Cl = LBF$$

Drugs with high hepatic extraction ratios

- However, if the drug is given orally and an enzyme inducer is added to the treatment regimen, pre-systemic metabolism of the medication may be increased, and the first-pass effect increased 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

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

$$\downarrow Cssu = f_B \downarrow Css$$

$$\downarrow effect \propto \downarrow Cssu$$

Alteration in organ blood flow

- By virtue of the pharmacologic effect for a drug, it may be possible for an agent to change liver blood flow.

- For example, β-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. β-blockers decrease lidocaine clearance by decreasing liver blood flow.

Alteration in organ 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.

- Since volume of distribution remains unaltered, the half-life of the drug will increase

$$\uparrow t_{1/2} = [0.693 \cdot V] / \downarrow Cl$$

- As a result of the total clearance decrease, total steady-state drug concentrations will increase

$$\uparrow Css = k_0 / \downarrow Cl$$

Alteration in organ blood flow

- The unbound steady-state drug concentration will also increase, and the effect of the drug will increase in proportion to unbound concentration

$$\uparrow Cssu = f_B \uparrow Css$$

- If the co-administered drug increases liver blood flow (e.g. vasodilators like the calcium channel blockers), all of the above-mentioned changes will occur in the opposite direction, and the decline in unbound steady-state concentration will cause a decrease in pharmacologic effect of the drug.

$$\uparrow Cl = \uparrow LBF$$

$$\downarrow t_{1/2} = [0.693 \cdot V] / \uparrow Cl$$

$$\downarrow Css = k_0 / \uparrow Cl$$

$$\downarrow Cssu = f_B \downarrow Css$$

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 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:

$$V = V_B + \frac{f_B}{f_T} V_T = V_B + \frac{f_B}{f_{heart}} V_{heart} + \frac{f_B}{f_{muscle}} V_{muscle} + \frac{f_B}{f_{fat}} V_{fat} + \cdots + \frac{f_B}{f_n} V_n$$

Obesity

- Because of this, the sheer amount of adipose tissue will be a primary determinant of how much obesity will effect the volume of distribution of the drug.

- Also, 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.

Obesity

- 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.

Obesity

- 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.

Any questions?