Chapter 3

REFERENCE: APPLIED CLINICAL PHARMACOKINETICS

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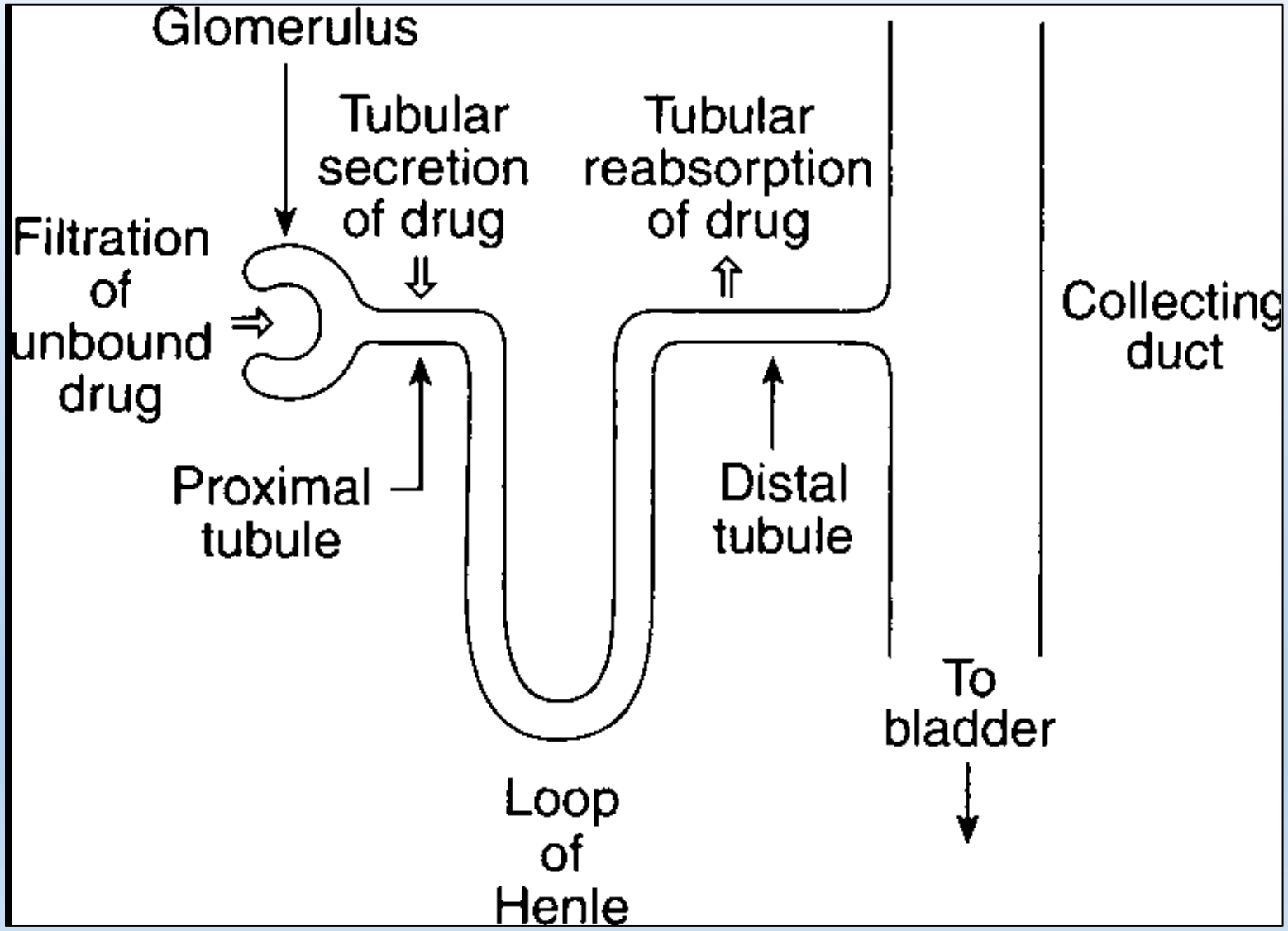
DRUG DOSING IN SPECIAL POPULATIONS

DRUG DOSING IN SPECIAL POPULATIONS

- RENAL DISEASE,
- HEPATIC DISEASE,
- HEART FAILURE,
- OBESITY,
- DRUG INTERACTIONS

✓ RENAL DISEASE



Glomerular Filtration Rate (GFR)

Groups need to follow renal function and GFR:

- Neonates
- Elderly
- Acute and chronic renal failure

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

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

- fB is the free fraction of drug in the blood,
- GFR is glomerular filtration rate,
- RBF is renal blood flow,
- Cl′sec is the intrinsic clearance for tubular secretion of unbound drug,
- FR is the fraction reabsorbed

➢ Normal glomerular filtration rate of 80–120 mL/min

Determination of Glomerular filtration rate

Glomerular filtration rate can be determined practically by administration of special test compounds such as inulin or 125I-iothalamate.

Measurement of Glomerular filtration rate

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

$$GFR\ (\text{in mL/min / 1.73 m2}) = 186 \cdot SCr^{-1.154} \cdot Age^{-0.203}$$

- Multiply by (0.742) if female, and (1.21) if African-American

Example, the estimated GFR for a 53-year-old African-American male with a SCr = 2.7 mg/dL

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

  $= 32\ mL/min / 1.73\ m2$

Measurement of Creatinine Clearance

- Creatinine is a by-product of muscle metabolism that is primarily eliminated by glomerular filtration
- 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

Method 1: CrCl measured from serum and urine

$$\text{CrCl (in mL/min)} = (\text{UCr} \cdot \text{Vurine}) / (\text{SCr} \cdot \text{T})$$

- 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,
- T is the time in minutes of the urine collection

➢ most nephrologists use a 24-hour urine collection period

Example, a 24-hour urine was collected for a patient with the following results: UCr = 55 mg/dL, Vurine = 1000 mL, SCr = 1.0 mg/dL, T = 24 h. measure CrCl.

- $T = 24\ h \times 60\ min/h = 1440\ min$
- $CrCl\ (in\ mL/min) = (UCr \cdot Vurine) / (SCr \cdot T)$

$= (55\ mg/dL \cdot 1000\ mL) / (1.0\ mg/dL \cdot 1440\ min)$

$= 38\ mL/min.$

Routine measurement of creatinine clearances in patients has been fraught with problems:

1- Incomplete urine collections,

2- serum creatinine concentrations obtained at incorrect times, and

3- collection time errors can produce erroneous measured creatinine clearance values.

Method 2: Estimate CrCl from serum creatinine

- Cockcroft and Gault method
- Jelliffe and Jelliffe method
- Salazar and Corcoran method

A/ Cockcroft and Gault method

For males, $CrCl_{est}$ = [(140 − age) BW]/ (72 · SCr)

For females, $CrCl_{est}$ = [0.85(140 − age)BW] / (72 · SCr)

- CrClest is estimated creatinine clearance in mL/min,
- age is in years,
- BW is body weight in kg,
- SCr is serum creatinine in mg/dL.

When serum creatinine values are stable

- patients ≥18 years old,
- actual weight within 30% of their ideal body weight
- stable serum creatinine concentrations

IBW measures

- IBW males (in kg) = 50 + 2.3(Ht – 60)
- IBW females (in kg) = 45 + 2.3(Ht – 60),
- where Ht is height in inches

Example, a 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dL. Calculate the estimated creatinine clearance.

- $IBW_{males} = 50 + 2.3\,(Ht - 60)$

  $= 50 + 2.3(71 - 60)$

  $= 75$ kg (so the patient is within 30% of his ideal body weight
- $CrCl_{est} = [(140 - age)BW] / (72 \cdot SCr)$

  $= [(140 - 55\ y)80\ kg] / (72 \cdot 1.9\ mg/dL)$

  $= 50$ mL/min.

If serum creatinine values are not stable, but increasing or decreasing in a patient, the Cockcroft-Gault equation cannot be used to estimate creatinine clearance. In this case, an alternate method must be used:

B/ Jelliffe and Jelliffe method

First step: estimate creatinine production

$$\text{Ess male} = \text{IBW}\,[29.3 - (0.203 \cdot \text{age})]$$
$$\text{Ess female} = \text{IBW}\,[25.1 - (0.175 \cdot \text{age})]$$

- Ess is the excretion of creatinine,
- IBW is ideal body weight in kilograms,
- age is in years

Second step

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

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

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

- Scr_{ave} is the average of the two serum creatinine determinations in mg/dL,
- Δt is the time that expired between the measurement of Scr1 and Scr2 in minutes

If patients are not within 30% of their ideal body weight (obese), other methods to estimate creatinine clearance should be used:

C/ Salazar and Corcoran method

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

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

- Age in years,
- Wt, weight in kg,
- Ht, height in m,
- SCr, serum creatinine in mg/dL

Methods to estimate creatinine clearance for children and young adults

- Age 0–1 year,

➢ CrClest (in mL/min / 1.73 m^2) = (0.45 · Ht) / SCr

- Age 1–20 years,

➢ CrClest (in mL/min / 1.73 m^2) = (0.55 · Ht)/SCr

- Ht is height in cm,
- SCr is serum creatinine 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,
- A substantial decrease in drug doses when creatinine clearance is $\leq$ 15 mL/min.

In order to modify doses for patients with renal impairment:

- Decrease the drug dose and retain the usual dosage interval,
- Retain the usual dose and increase the dosage interval, or
- Decrease the dosage and prolong the dosage interval.

➢ Depends on the route of administration, the dosage forms available, and the pharmacodynamic response to the drug.

A) if the drug is orally and only a limited number of solid dosage forms are available:

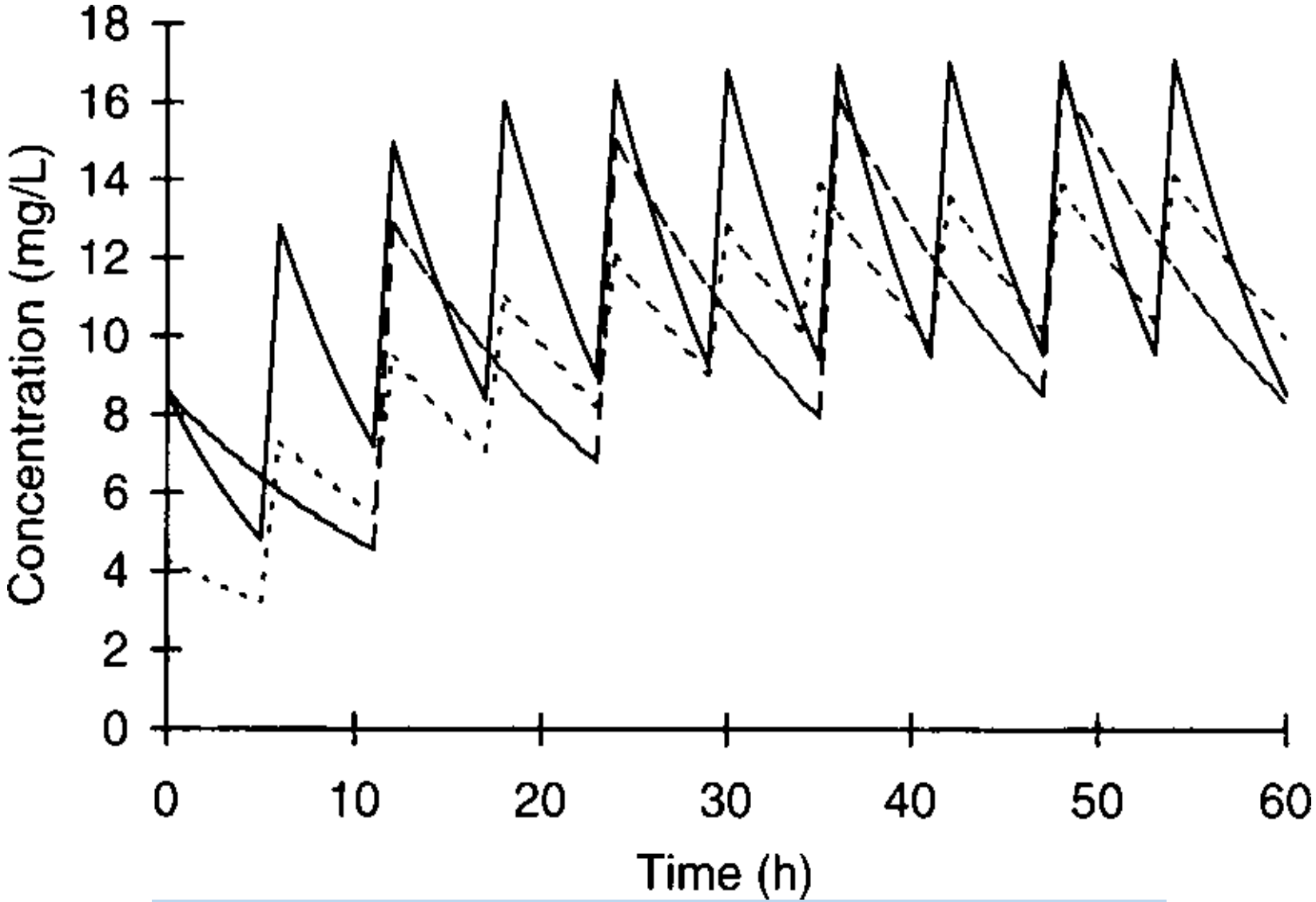
administer the usual dose and increase the dosage interval

B) If the drug is given parenterally:

a smaller dose can be administered, and the usual dosage interval will be retained

C) for drugs with narrow therapeutic ranges like aminoglycoside antibiotics and vancomycin

both the dose and dosage interval can be manipulated to achieve the targeted drug levels.



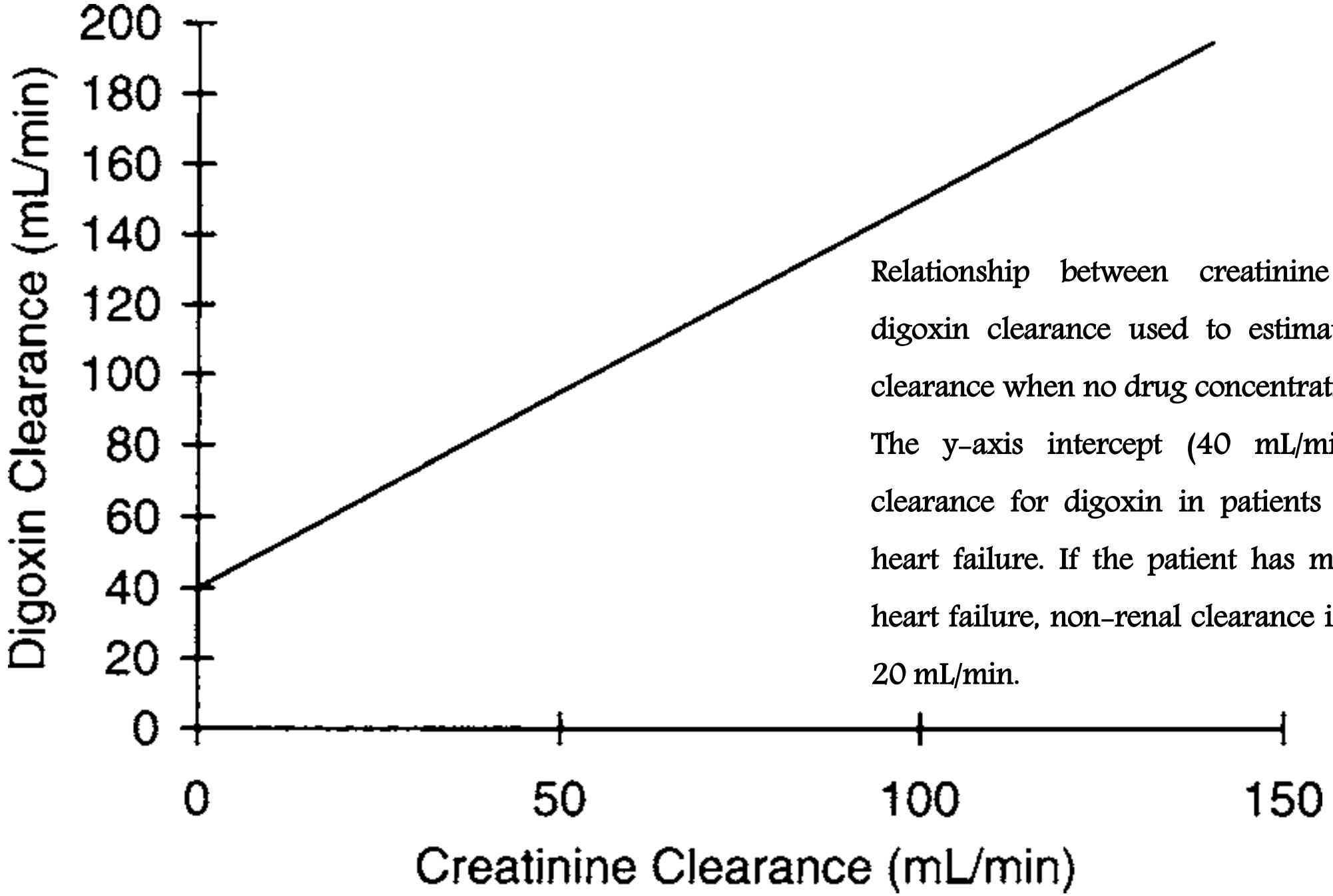
Solid line--- 300 mg every 6 hours
Dashed line--- 300 mg every 12 hours,
Dotted line--- 150 mg every 6 hours,

DRUG CLEARANCE

- Drug Clearance is dependent on renal clearance and non-renal clearance.

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

- where Cl_{NR} is non-renal clearance and equals 20 mL/min in patients with moderate-severe heart failure and 40 mL/min in patients with no or mild heart failure



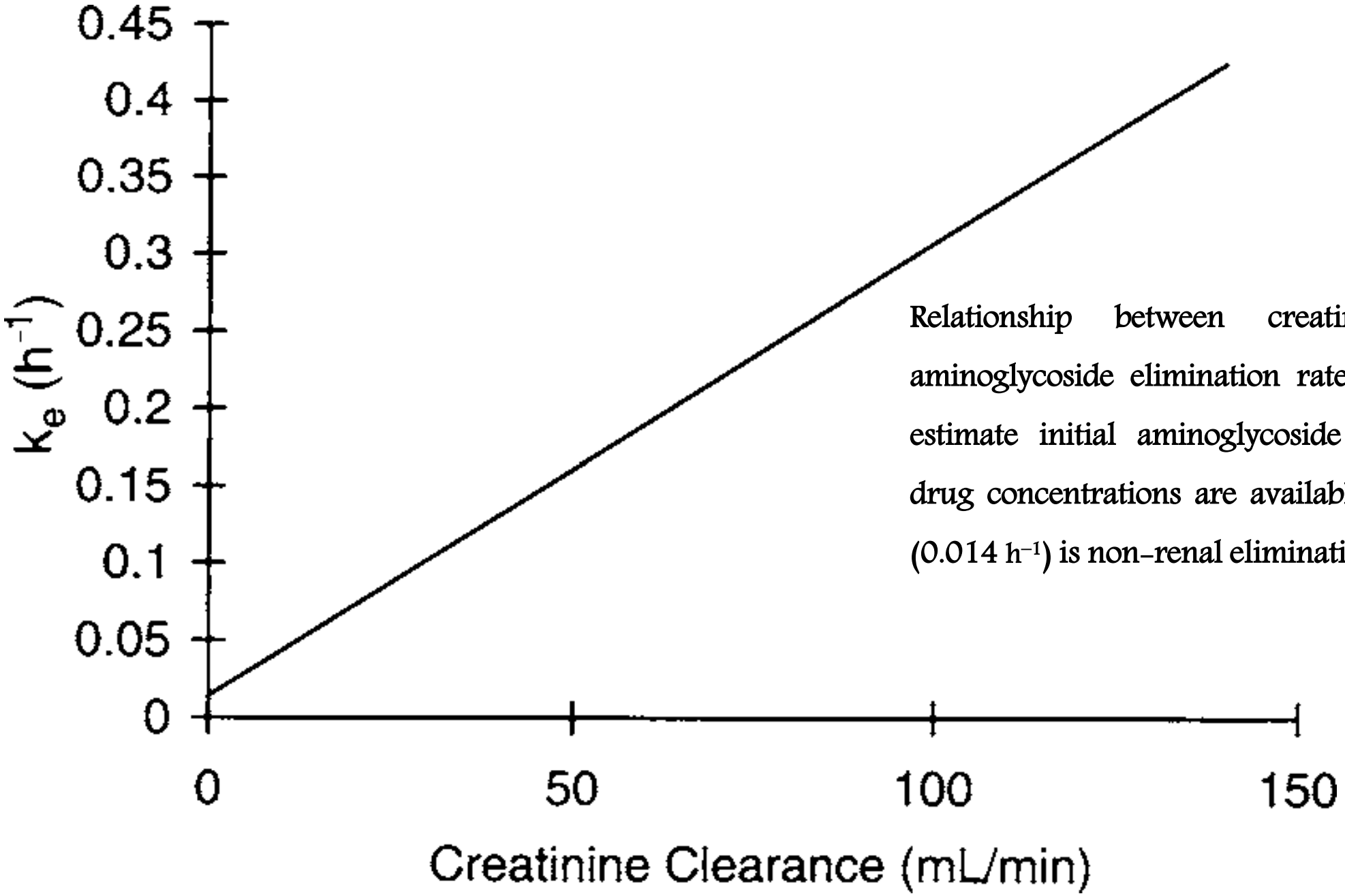
Relationship between creatinine clearance and digoxin clearance used to estimate initial digoxin clearance when no drug concentrations are available. The y-axis intercept (40 mL/min) is non-renal clearance for digoxin in patients with no or mild heart failure. If the patient has moderate to severe heart failure, non-renal clearance is set to a value of 20 mL/min.

Elimination rate constant (k_e)

- It is a dependent pharmacokinetic parameter whose result is reliant on the relative values of clearance and volume of distribution

$(ke = Cl/V)$

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



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 non-renal elimination for aminoglycosides

Volume of distribution

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

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

- where CrCl is in mL/min.

✓ OBESITY

- Excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution

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

OBESITY

- Lipophilic drugs 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 diazepam, carbamazepine.
- Hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution is not different in obese and normal weight patients. Examples digoxin, cimetidine, and ranitidine.

Obesity may affect:

- Extracellular fluid & V ---- (↑Aminoglycoside, ↔ Digoxin and vancomycin)
- GFR & Cl ---- (↑Aminoglycoside, vancomycin, cimetidine)
- Hepatic Cl ----- (↑diazepam,↓methylprednisolone, ↔carbamazepine and cyclosporine)

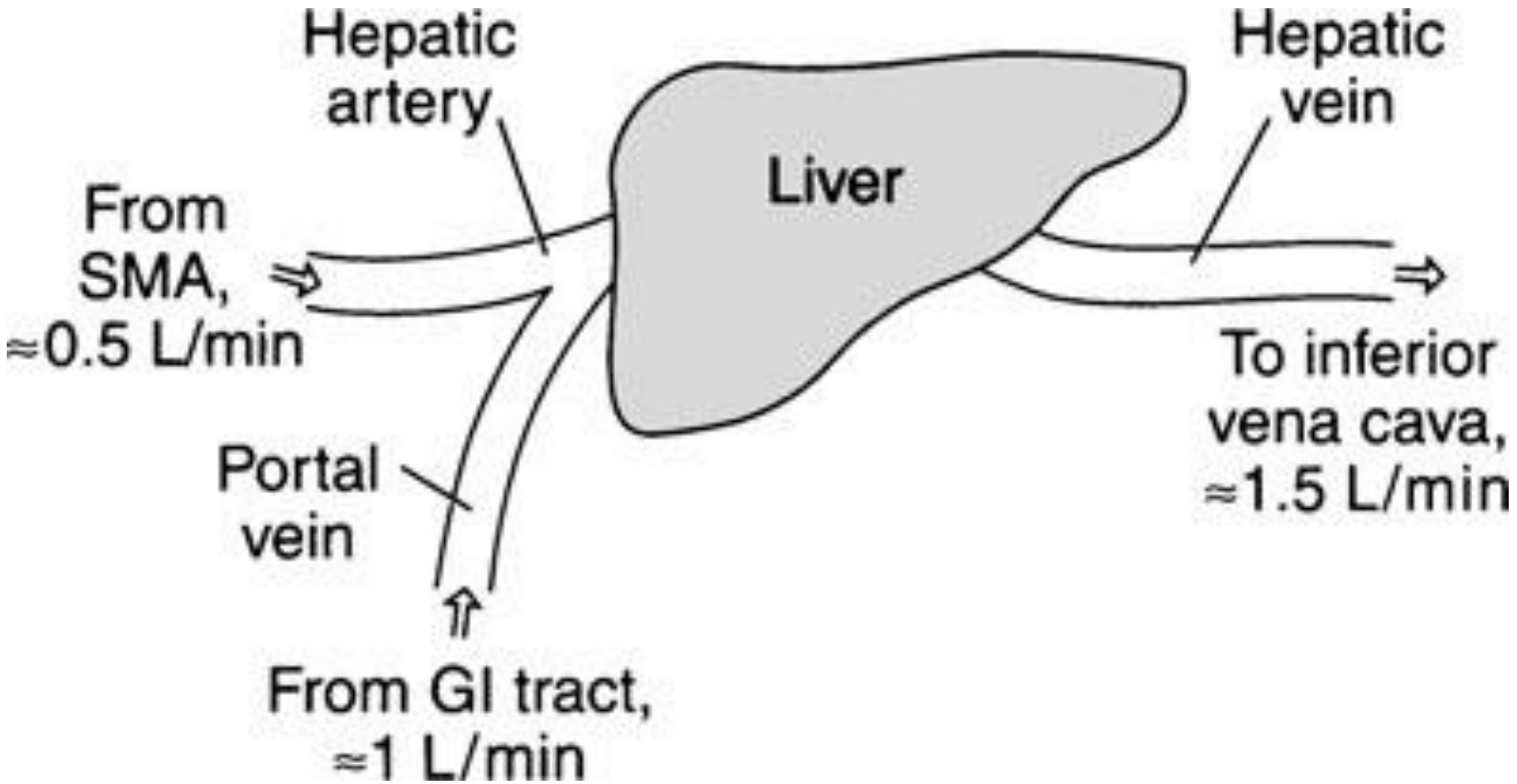
Obesity ⟶ t1/2

➢ $t_{1/2} = (0.693 \cdot V) / Cl$

✓ HEART FAILURE

- Decrease in CO
- Decrease in RBF & HBF
- Decrease blood to GIT ..... decrease absorption
- Decrease Vd .....
- Half-life affected

✓ HEPATIC DISEASE



Orally administered medications must pass through the liver before entering the systemic circulation

- The equation that describes hepatic drug metabolism is:

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

- LBF is liver blood flow,
- fB is the fraction of unbound drug in the blood,
- Cl′int is intrinsic clearance

Cases affect hepatic drug metabolism

- Neonate
- Elderly
- Hepatitis and cirrhosis

Determination of Child-Pugh Scores

Consists of five laboratory tests or clinical symptoms:

- Serum albumin,
- Total bilirubin,
- Prothrombin time,
- Ascites,
- Hepatic encephalopathy.

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

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

- The score for a patient with **normal liver function** is **5**
- 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 score = 8–9 is grounds for a moderate decrease (~25%) in initial daily drug dose for agents that are primarily (≥60%) hepatically metabolized,
- 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.

In order to modify doses for patients with hepatic impairment:

- Decrease the drug dose and retain the usual dosage interval,
- Retain the usual dose and increase the dosage interval, or
- Decrease the dosage and prolong the dosage interval.

➢ Depends on the route of administration, the dosage forms available, and the pharmacodynamic response to the drug.

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

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

- Drugs with a low hepatic extraction ratio (≤30%)
- Drugs with a high hepatic extraction ratio (≥70%)
- Drugs with intermediate hepatic extraction ratios

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 >>fB· Cl'int), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [LBF ≈ LBF + (fB · Cl'int)].
- 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%)

- The numeric value of liver blood flow is much less than the product of unbound fraction of drug in the blood and the intrinsic clearance of the agent (LBF << fB · 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 [fB · Cl'int ≈ LBF + (fB · Cl'int)].
- 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.

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

✓ Drug interactions

1- The hepatic clearance → $(Cl_H = f_B.Cl')$ $(Cl_H = LBF)$

2- Volume of distribution → $(V = V_B + [f_B/f_T]V_T)$

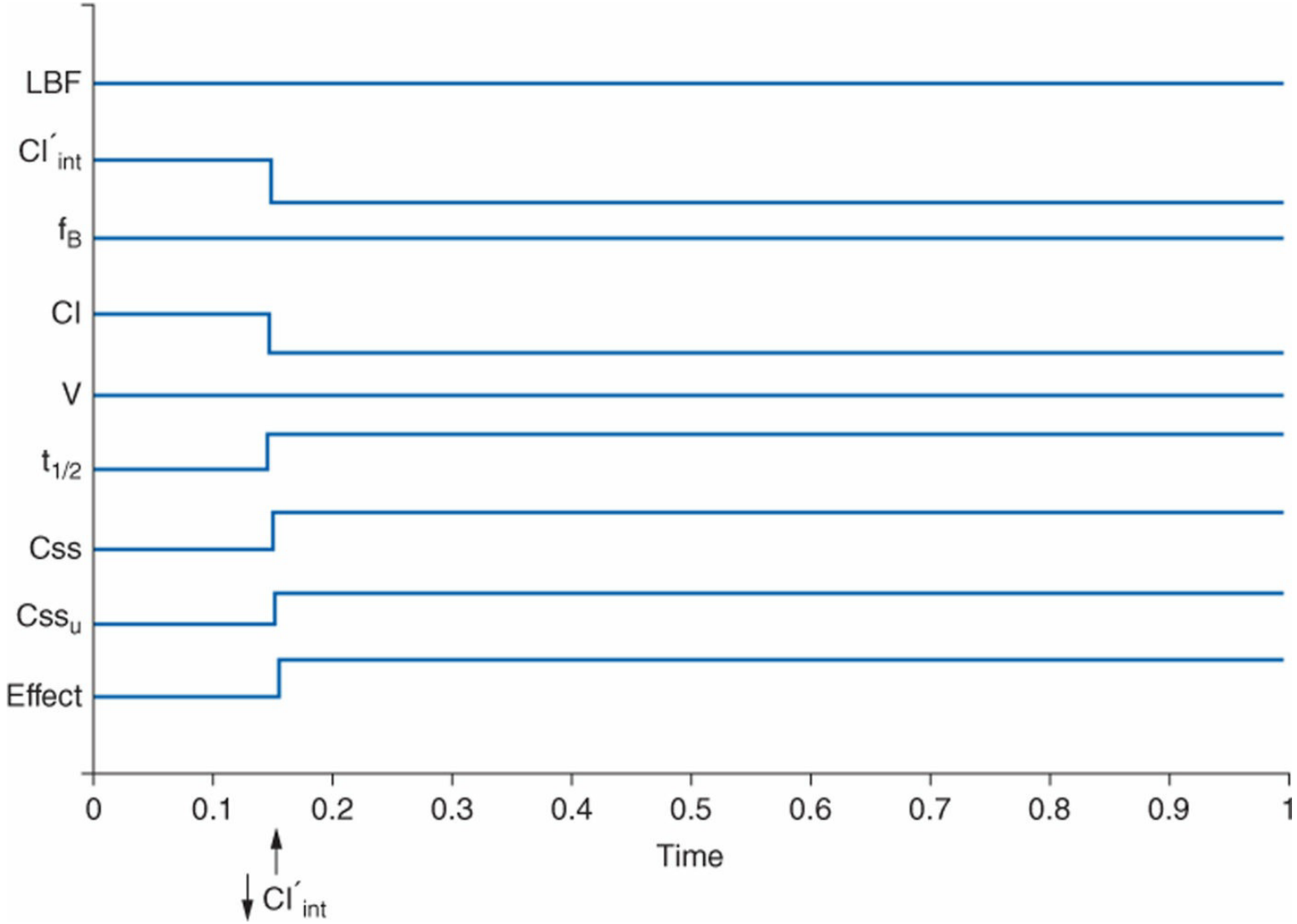
3- Half-life → $(t_{1/2} = [0.693 \cdot V]/Cl)$

4- Steady-state concentration → $Css = [F(D/\tau)]/Cl$

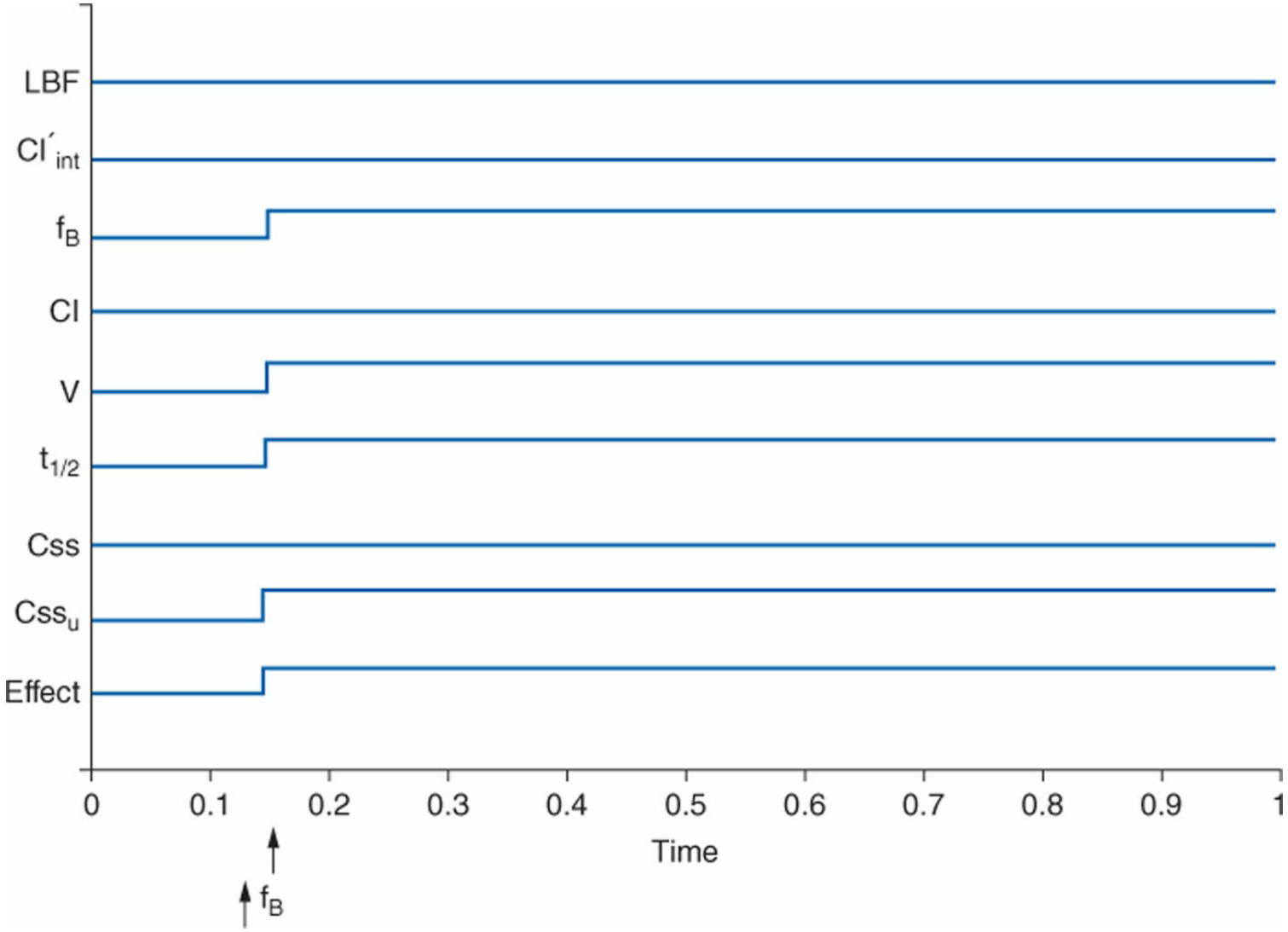
5-The unbound steady-state concentration → $Css_u = f_B Css$

6-The effect of the drug → f_B α effect

Ex: Drug with Low ER



Ex: Drug with High ER+ Protein binding displacement



Ex: Drug with High ER+ Enzyme inhibitor

- See examples and questions in the book

Thank u....