كلية الطب البيطري – جامعة تكريت

ماجستير أدوية

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((4))

Advanced Pharmacology

Pharmacokinetic Principles

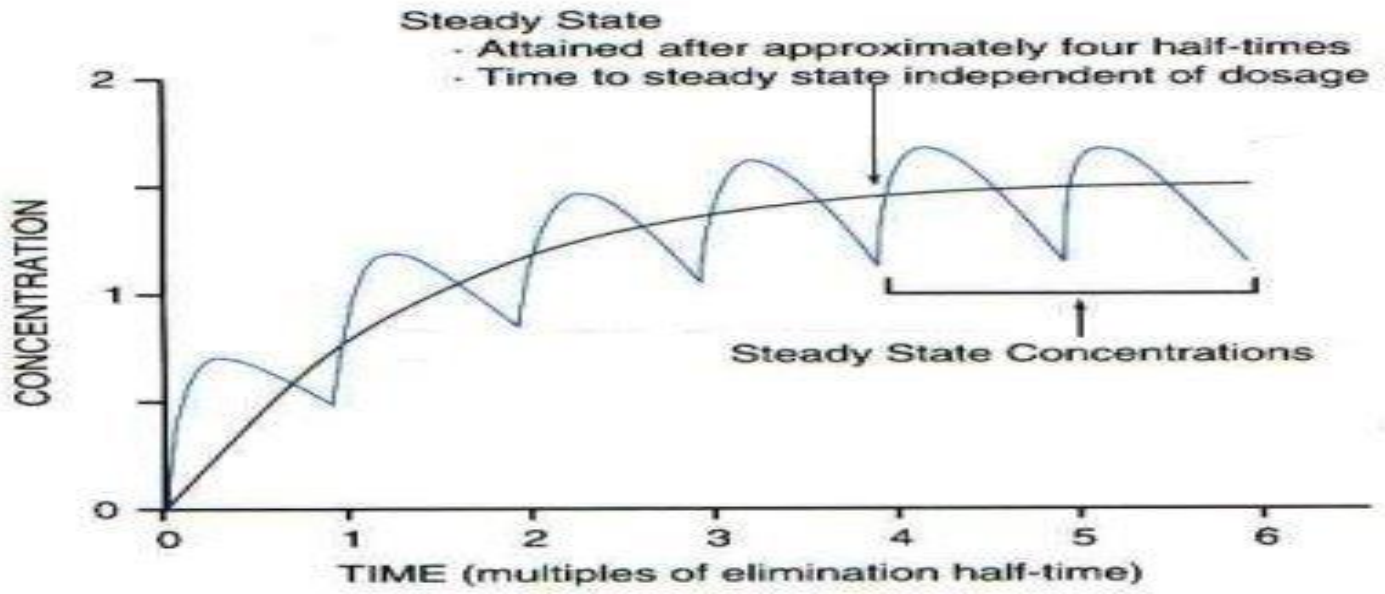
Pharmacokinetic Principles

Pharmacokinetic principles aid in the selection & adjustment of drug dosage schedules & facilitate interpretation of plasma drug concentration.

Half-life (t½):

Is the time required to decrease drug concentration in the body by 50%.

- It provides a good indication of the time required to reach steady state conc (4 X t½) & a means to estimate dosing interval in repeated doses. It is affected by any change in CL & Vd due to diseases, aging or protein binding.



- **Pharmacokinetics orders:**
- For a chemical reaction, the order of a reaction refers to the way in which the concentration of a drug or a reactant influences the rate of the reaction.

1. **First order kinetic**

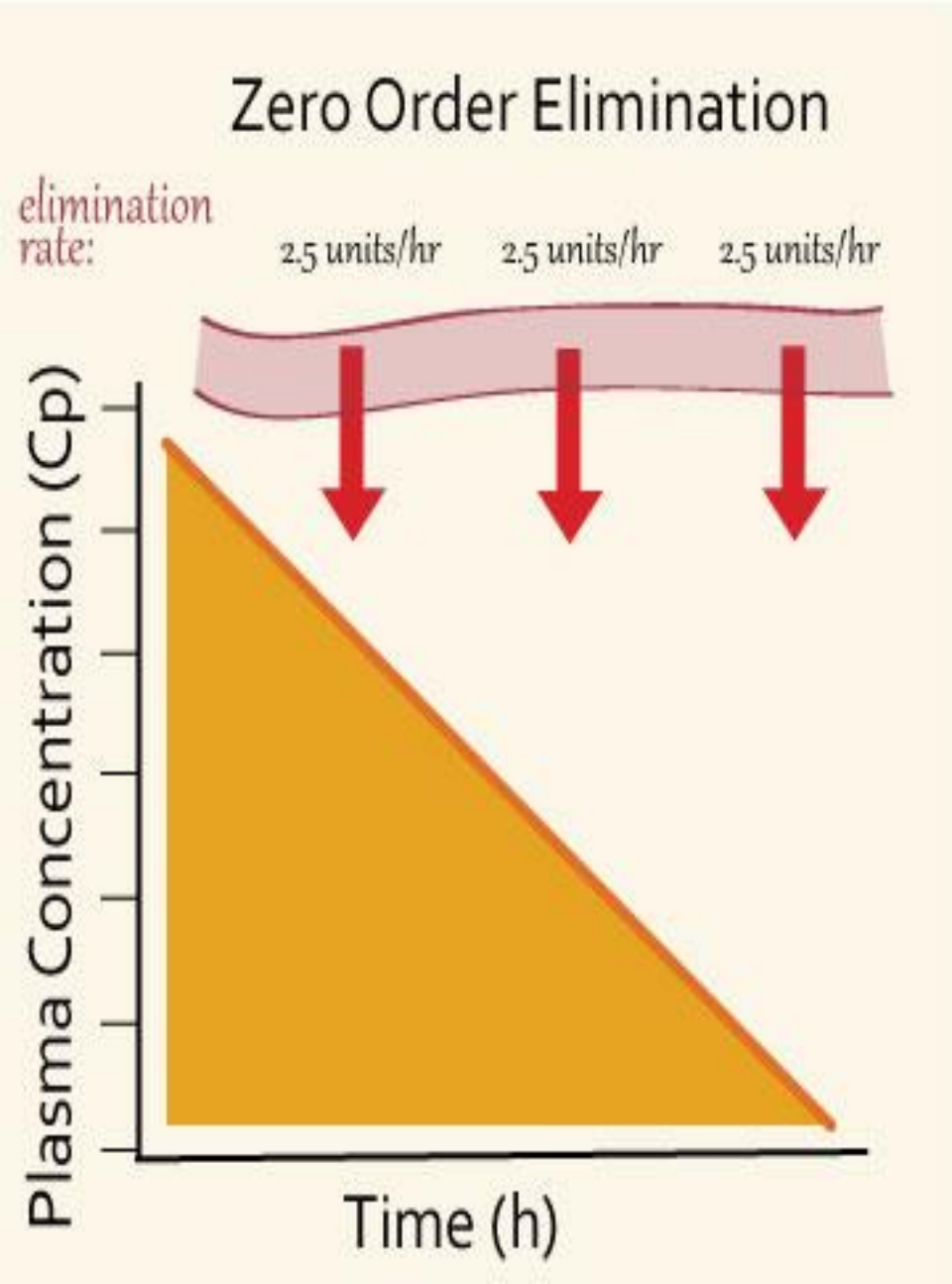
   The change in concentration with respect to time is directly proportional to the concentration of the reactants i.e the rate of the process (ADME) is directly proportional to the amount or concentration of the drug in the body.

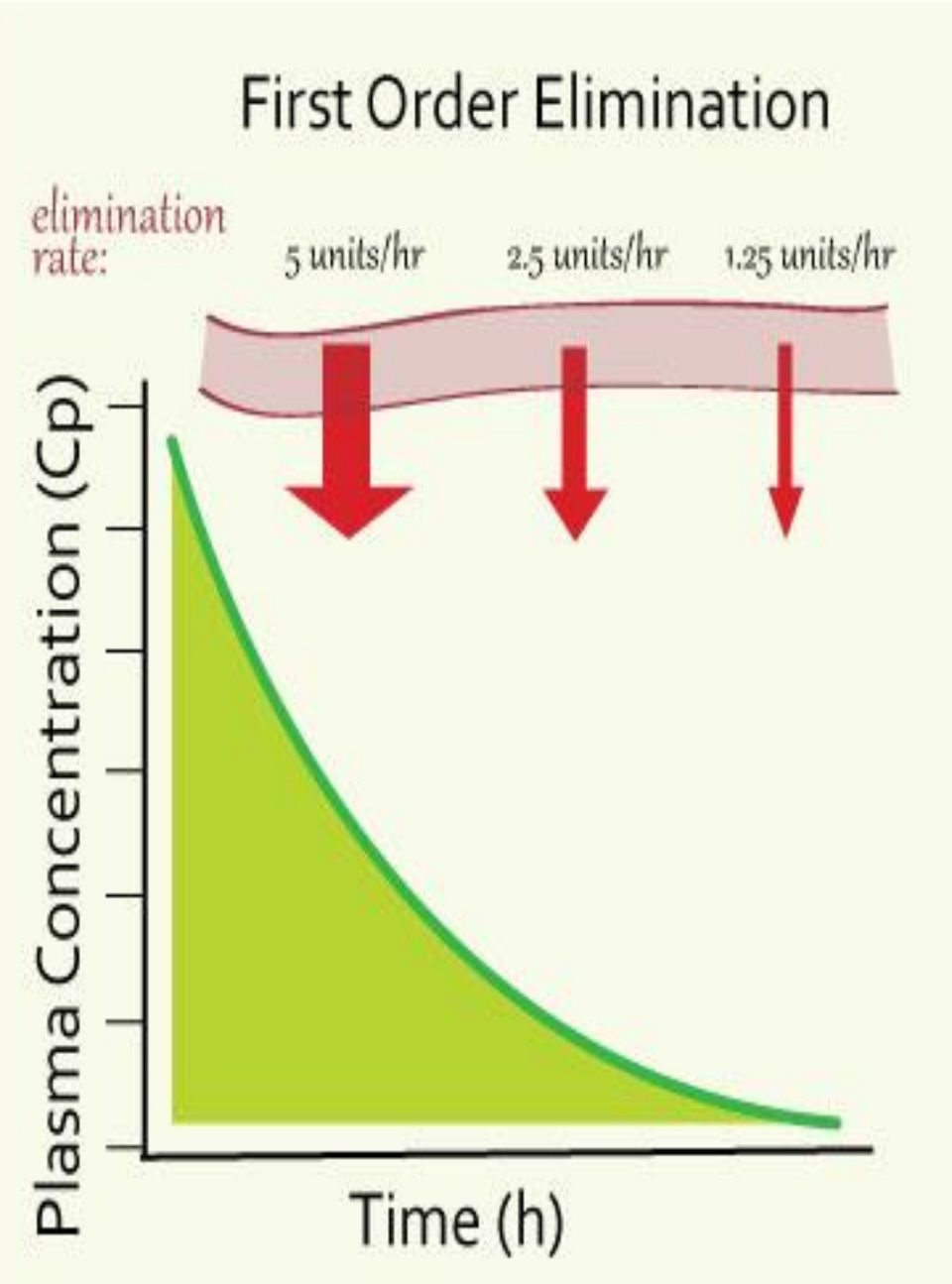
Zero order kinetic :saturation kinetic

The rate of the process is constant regardless of the concentration.

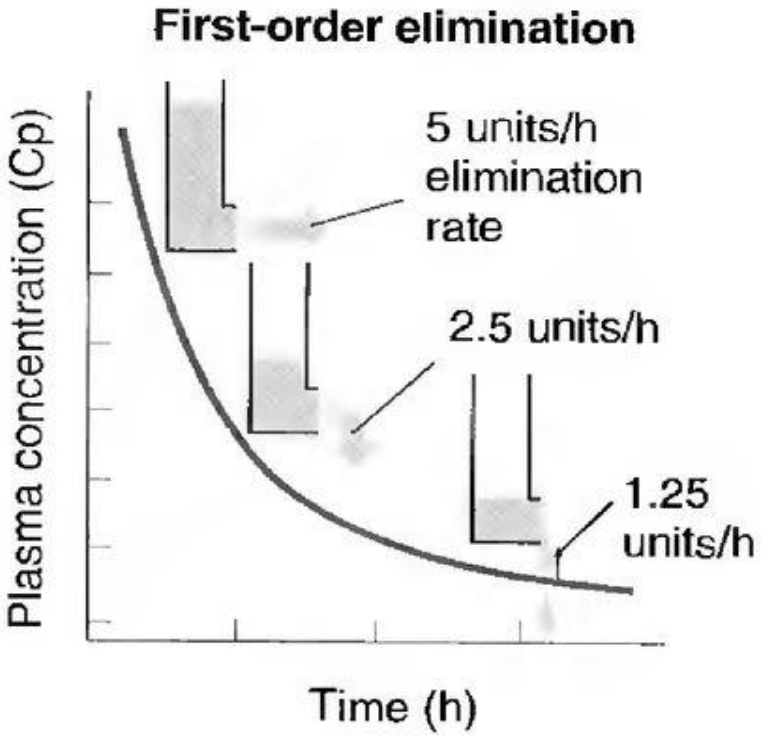
Zero-order process occurs when an enzyme or carrier system is saturated, then the rate can not further increased by increasing the substrate conc. and consequently the rate remain constant i.e. It is a capacity-limited process e.g. ethanol, phenytoin, aspirin (↑dose), prednisolone elimination.

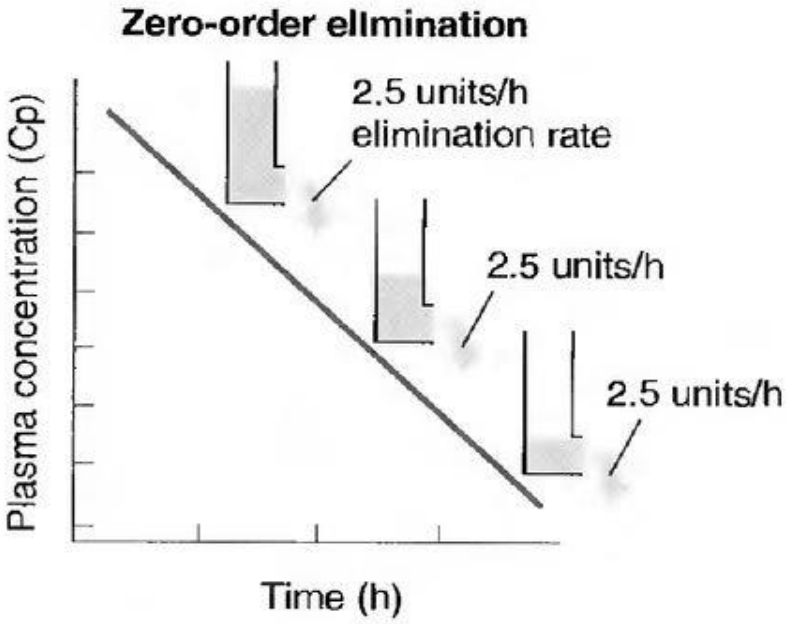
Drug Elimination





1st order elimination vs. zero order elimination





Drug half-life is often used as a measurement of drug CL, as , **V_d is a constant** for many drugs.

Most drug absorption or elimination follow first-order kinetics except when the process is saturated.

- Paracetamol (acetaminophen) is safe at therapeutic dose. [glucuronide and sulfate conjugation (95%). CYP450-dependent GSH conjugation. (5%)].
- Paracetamol overdose leads to saturation of glucuronidation and sulfation pathways and the CYP450-dependent pathway dominates, leading to accumulation of reactive intermediate (N-acetyl-p-benzoquinone imine).
- Little or no toxicity occurs as long as glutathione is available but when it is depleted, the accumulated reactive metabolites can produce hepatotoxicity.
- Cysteamine and N-acetylcysteine are used as antidote.

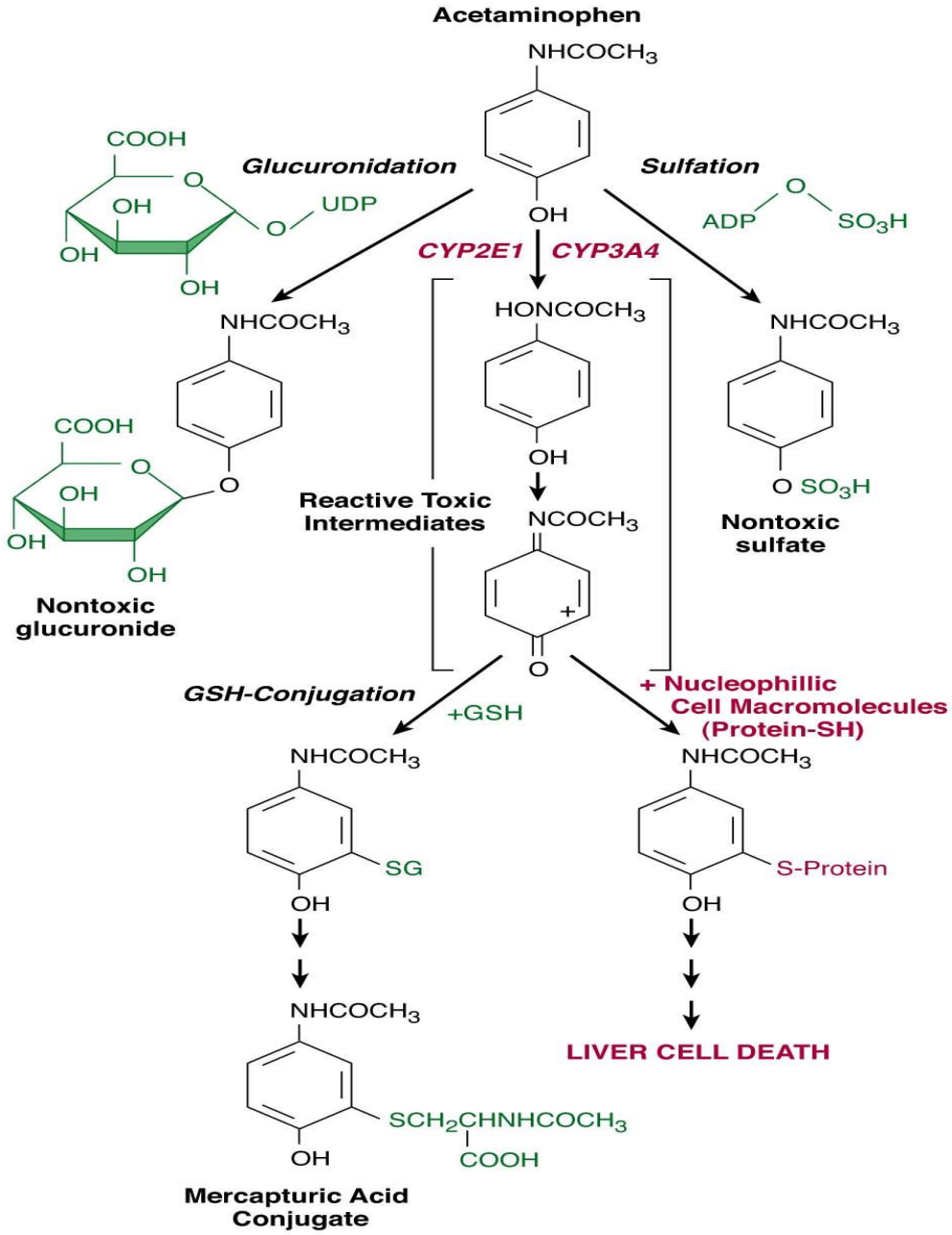
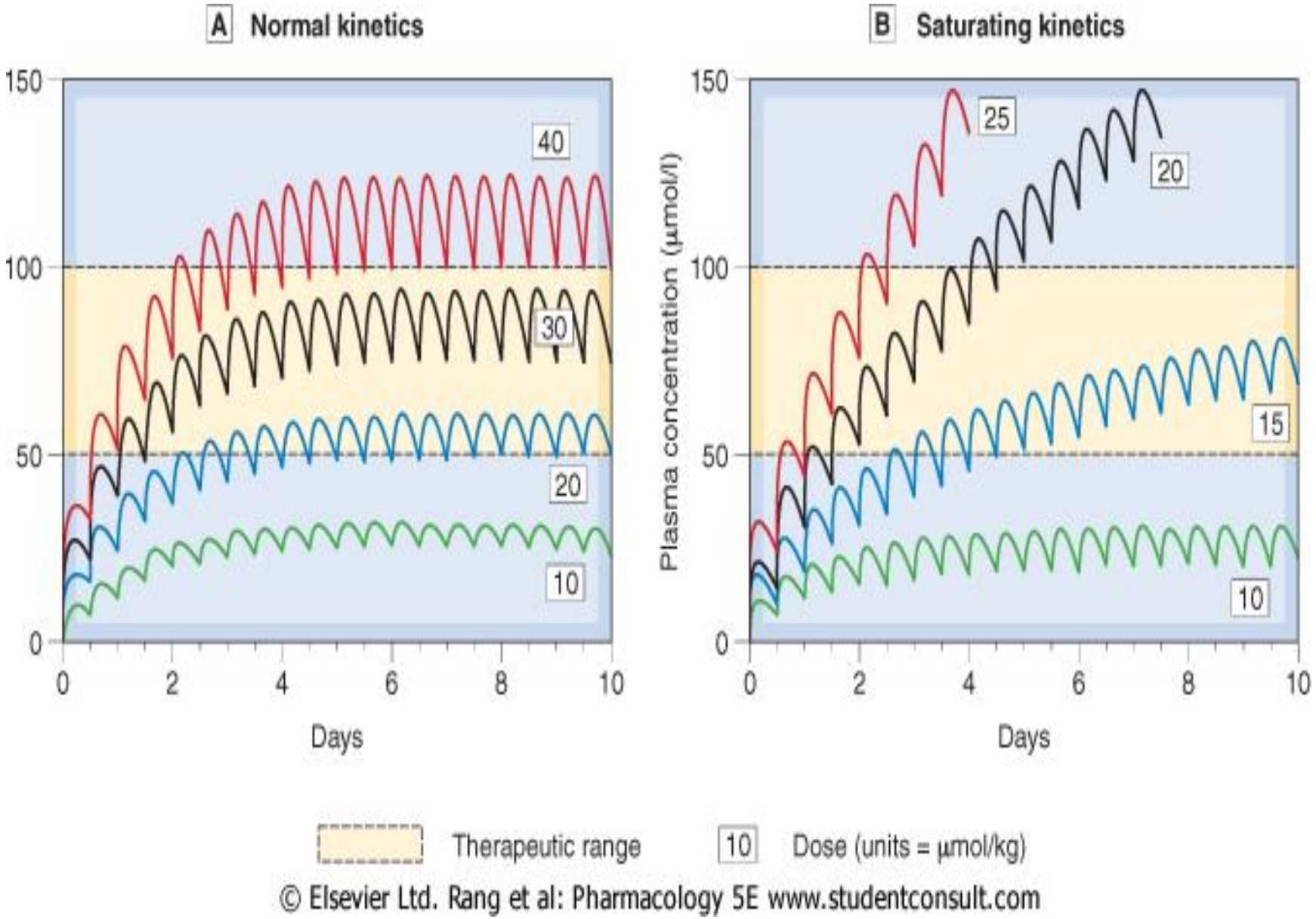


FIGURE 4–5 Metabolism of acetaminophen (top center) to hepatotoxic metabolites. GSH, glutathione; SG, glutathione moiety.



Clearance:

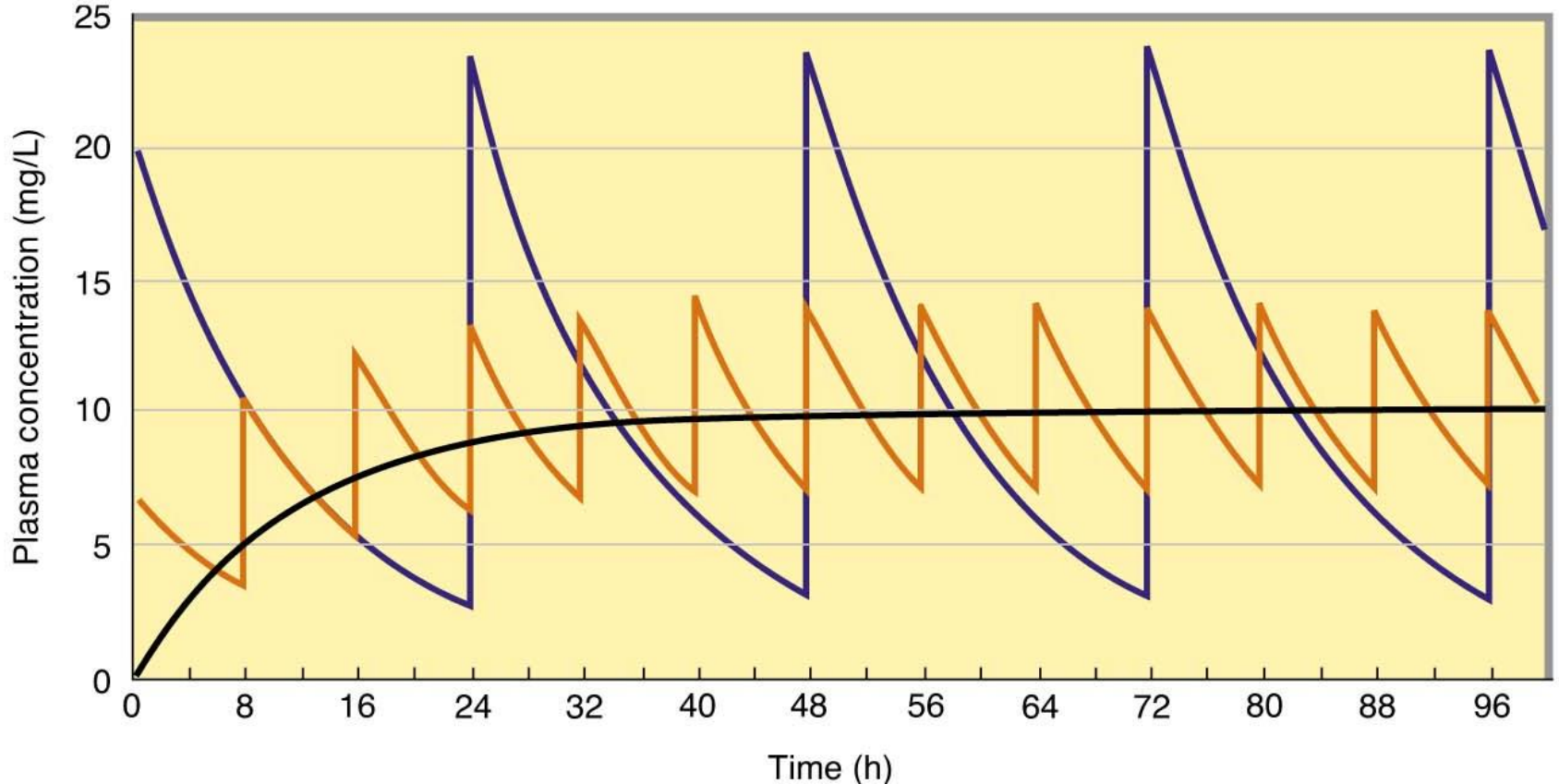
It is the volume of plasma completely cleared of the drug / unit time (ml / min).

- CL can be determined by :
- measuring plasma concentration of the drug at steady in an individual during a constant-rate i.v. infusion.
- At steady state: input (infusion rate) = output (elimination rate)

- **Renal clearance :**
- Is the volume of plasma that is cleared of the drug by the kidney in unit time.
- $CL_R = UER / C_p$
- UER : urinary excretion rate
- **Creatinine clearance (CL_{cr}):** It is the rate of elimination of creatinine in urine relative to its serum or plasma conc.

- **Hepatic clearance (CL_H):**
- Following absorption, drug can be metabolized in the gut wall, in the portal circulation, but most commonly in the liver before reaching the systemic circulation (first pass metabolism).
- The effect of first pass metabolism on the drug's bioavailability is expressed as hepatic extraction ratio (HER).
- **CL_H** = hepatic blood flow x HER
- Drugs with high (HER) have reduced bioavailability.
- e.g. organic nitrates, propranolol, lidocaine and morphine.

- At steady state , plasma drug concentration fluctuate between maximum (C^{ss}_{max}) and minimum (C^{ss}_{min}) plasma concentrations.
- The steady state conc. should be within the therapeutic window.



EFFECT OF DISEASES ON PHARMACOKINETICS

- **Renal disease:**

a. **↓ Elimination of drugs** (↓ GFR) → toxicity

- Creatinine clearance is usually the most practical index of GFR and it is widely used to determine the degree of renal impairment

- **Distribution:** ↓ protein binding of acidic or neutral but not basic drugs due to hypoalbuminemia → ↑ free drug conc.

- **Hepatic disease:**

a. Portal hypertension ↓hepatic blood flow → delayed oral absorption.

b. **↓metabolism**(↓ metabolizing enzyme activity)
↓1st pass effect → ↑drug bioavailability & t½ → toxicity.

c. **↓protein binding of the drug** (due to hypoproteinemia) → ↑Vd → toxicity (if it is accompanied by ↓ hepatic clearance) e.g toxicity of diazepam & theophylline.

- **Congestive heart failure:**

a. **↓GIT absorption of drugs due to**

- ↓C.O.P→ ↓GIT blood supply.
- Causes mucosal edema → ↓GIT absorption

b. **↓Vd** due to ↓ tissue blood supply → ↑plasma drug conc. → toxicity (highly perfused organs receive ↑ amount of the drug e.g lignocaine & procainamide toxicity.

c. ↓**metabolism of drugs** due to ↓hepatic blood flow & ↓metabolizing enzyme activity → ↑plasma drug conc. → toxicity

d. ↓GFR

- **Respiratory disease (COPD):**

  ↓**metabolism of drugs** (hypoxia → ↓ metabolizing enzyme activity) → ↑t½ of theophylline or tolbutamide

- **GIT disease:**
- **Achlorohydria:** ↑aspirin absorption(↑ gastric pH → ↑aspirin dissolution)
- **Gastrectomy:** ↓levodopa & quinidine absorption
- **Peptic ulcer:** ↓G.E.R & ↓ absorptive surface area→ ↓drug absorption.
- **Diarrhea:** ↑intestinal motility→ ↓drug absorption.
- **Crohn's disease** ↓drug absorption
- **Pancreatic disease:** Decreases absorption of lipophilic drugs such as Vit A,D,K