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PEARLS OF LABORATORY MEDICINE

Pharmacokinetics

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CCTC Clinical Chemistry Trainee Council

Learning objectives

- Describe the differences between pharmacodynamics and pharmacokinetics
- Define parameters:
  - volume of distribution (V_d)
  - half-life ($t_{1/2}$)
  - clearance (CL)
  - area under the curve (AUC)
- Contrast kinetic models for drug elimination

Applications of Pharmacokinetics

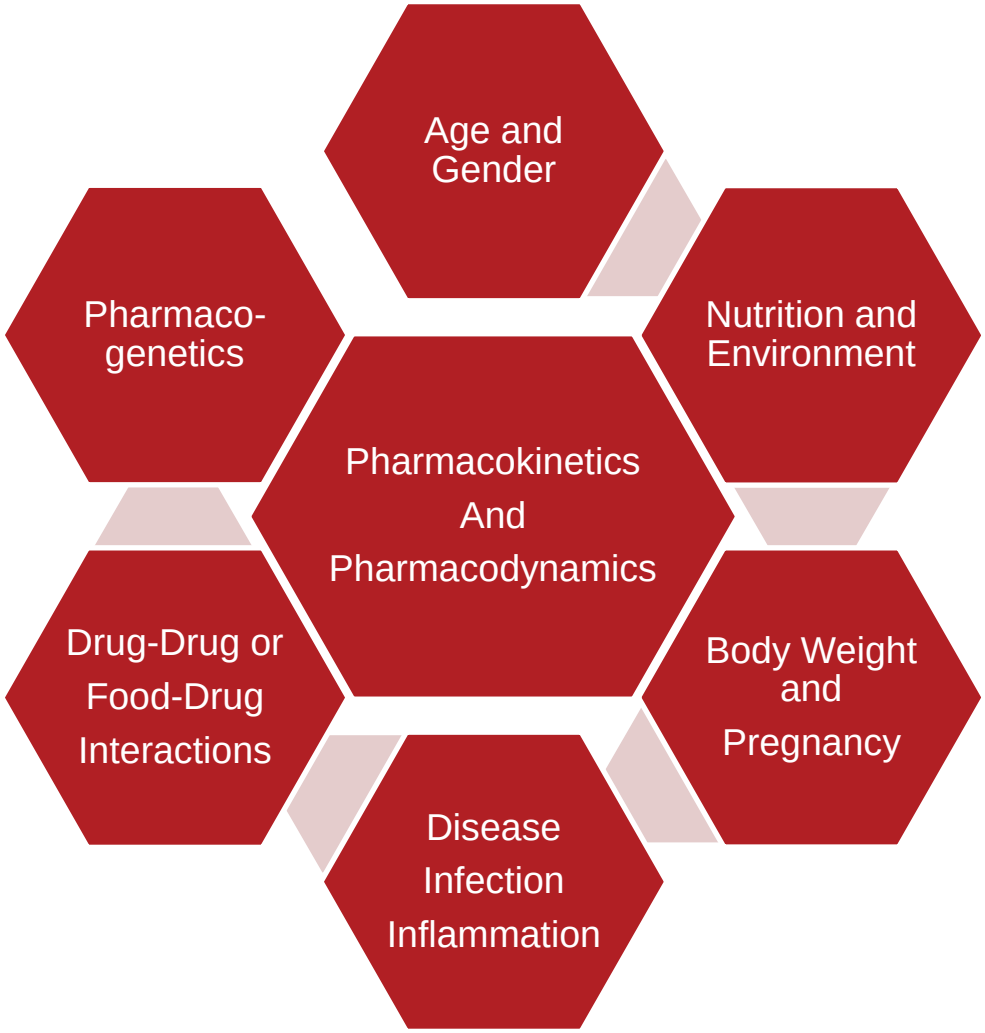
Therapeutic Drug Monitoring (TDM)

- Guide/optimize dosing
- Identify drug-drug interactions

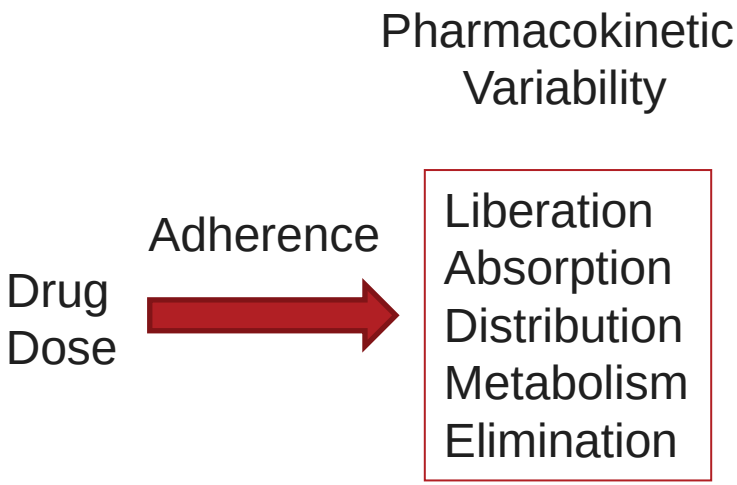
Toxicology

- Improve patient care through directed decontamination efforts of compounds involved in adverse drug reactions

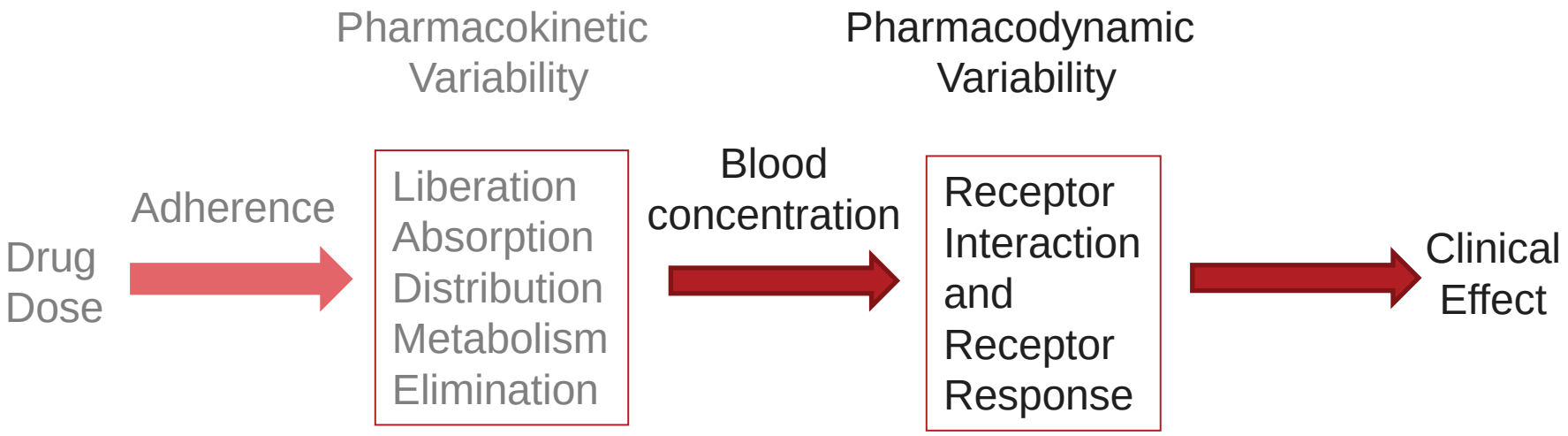
Factors that Affect Drug Therapy



Drug Therapy is impacted by Pharmacokinetics and Pharmacodynamics



Drug Therapy is impacted by Pharmacokinetics and Pharmacodynamics



Liberation – *related to 'solubility' of the drug*

- Formulation (solid, enteric-coated, liquid)
- Dose and dosing interval (λ)
- Chemistry of drug – pKa, water soluble, lipid soluble
- Stability – acidic pH, breakdown from digestive enzymes
- Route of administration based on surface area and permeability – (intravenous, oral, intramuscular, subcutaneous, sublingual, transdermal, inhalation, topical, etc.)

Factors that affect Absorption

- Drug characteristics: polarity, pKa, formulation
  - Ionization
  - Protein binding
  - Passive and active drug transport

Only free, unionized drugs can cross membranes.

- Gastrointestinal motility influences the rate of drug absorption

- Pathology of patient - Inflammation (IBD) or other diseases can affect absorption

Volume of Distribution

- Theoretical volume in the body to contain the total amount of drug administered
  - Distributed at the same concentration found in serum or plasma
- Polar drugs are soluble in water - distribute to blood circulation and are primarily eliminated by the kidneys
- Nonpolar drugs are lipid soluble - typically distribute to the central nervous system, tissue and fat – eliminated in feces and bile

Bioavailability (F)

- The amount of drug that reaches systemic circulation
- Oral drugs – undergo first-pass metabolism → decrease in bioavailability
- Drugs administered IV – bypass first-pass metabolism → 100% bioavailability
- Drug bioavailability from intermuscular injection is influenced by blood perfusion in the muscle

Protein Binding

- The binding of drugs to protein carriers also affect its distribution into tissues.
  - Acidic drugs bind to albumin
  - Basic drugs bind to α1-acid glycoprotein and lipoproteins

- Plasma protein binding – affected by disease states or acute phase reactant response

- Pharmacological activity of a drug is proportional to the free (unbound) concentration in blood.

Drug Metabolism

- Purpose – convert drugs into more hydrophilic metabolites to enhance elimination from the body
- Effects
  - Terminates pharmacological activity of drug
  - Activate pharmacological activity of a drug (codeine → morphine)
  - Decreases bioavailability (first pass metabolism)

Drug Metabolism

Phase I reactions (oxidation, reduction, hydrolysis)

- Cytochrome P450 enzymes
  - CYP3A4/5, 2D6, 1A2, 2A6,2B6
  - CYP2C8, 2C9, 2C19, 2D6, 2E1)

- Monoamine oxidase (MAO)
- Esterase
- Alcohol dehydrogenase (ADH)
- Aldehyde dehydrogenase (ALDH)
- Epoxide hydrolase
- Flavin-containing monooxygenase (FMO)

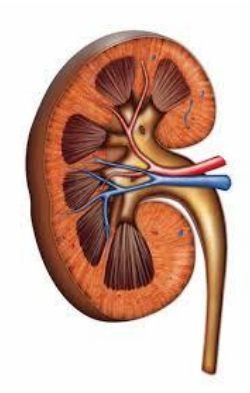
Drug Metabolism

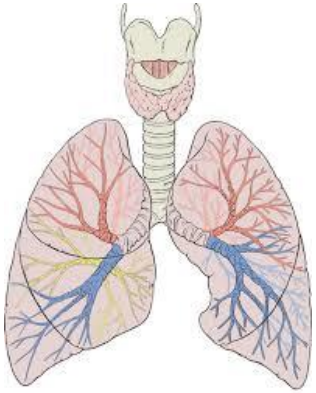
Phase II reactions –

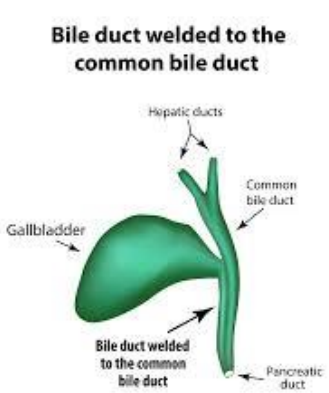
- conjugation reactions with glutathione, glucuronide, sulfate, methyl group, acetyl group
    - Glutathione S-transferases (GST)
    - UDP-glucuronosyltransferases (UGT)
    - Sulfotransferases (SULT)
    - Methyltransferases (MT)
    - N-acetyltransferases (NAT)

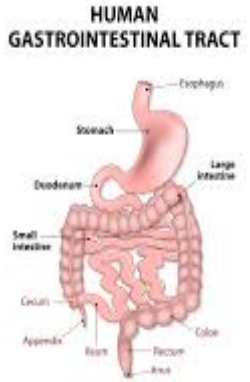
Drug Excretion/Elimination

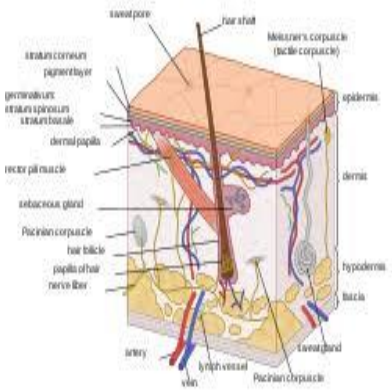
- Organs involved in drug excretion:
  - Kidneys, lung, bile ducts, GI tract, skin





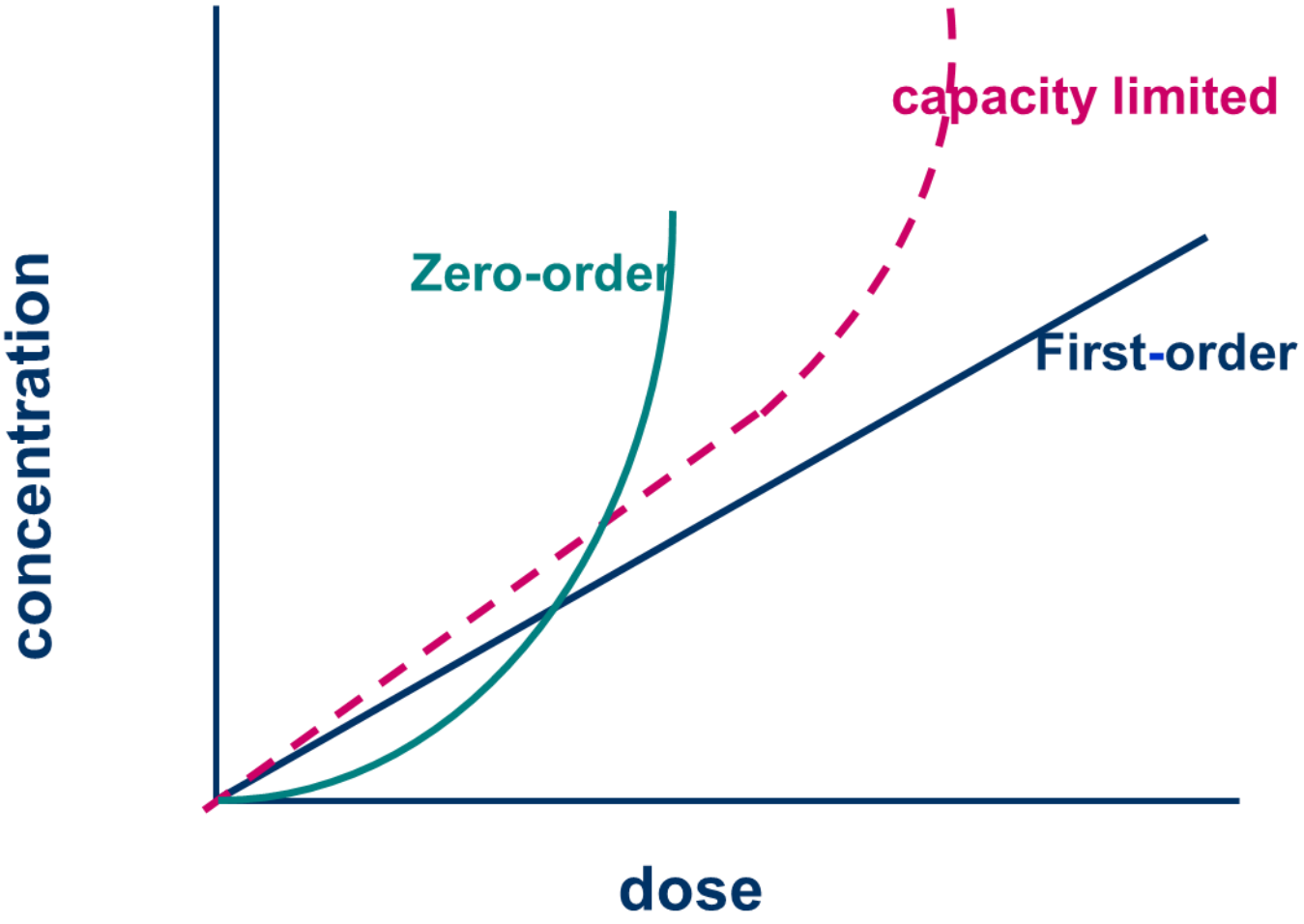






- Changes in renal function affects the clearance and half-life of the drug

Kinetic models

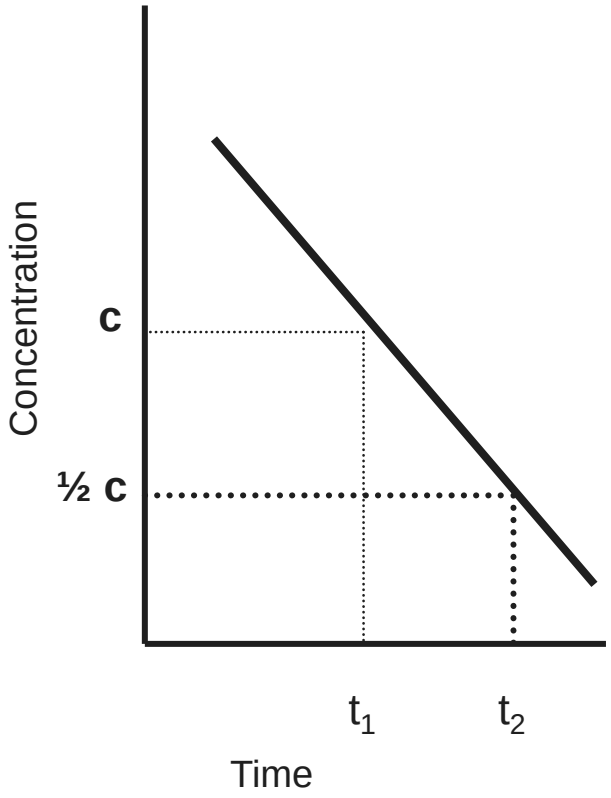


Clearance (CL) and Elimination half-life ($t_{1/2}$)

- Clearance describes the elimination of a drug from blood and the body
- Elimination half-life - the time it takes for plasma drug concentration (C) in the body to be reduced by 50%
- Important formulas

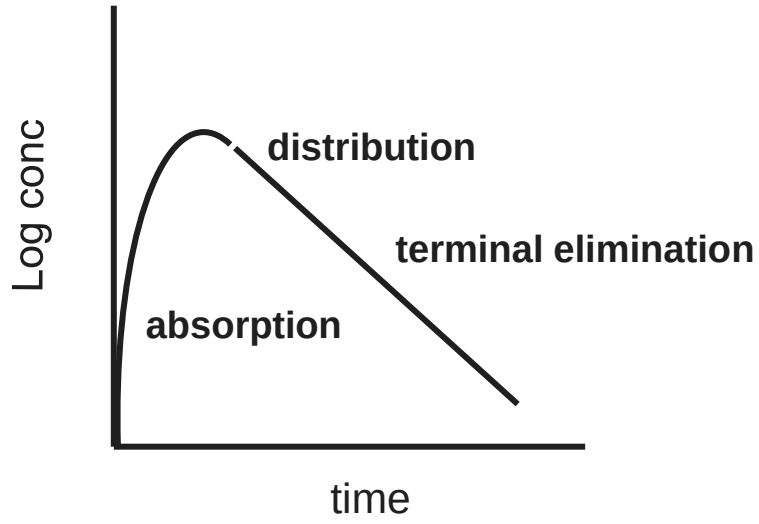
  Ke = elimination rate constant

  - $Ke = CL/V_d$
  - $t_{1/2} = \ln 2/Ke$



Pharmacokinetic modeling: one-compartment model

Orally administered drug



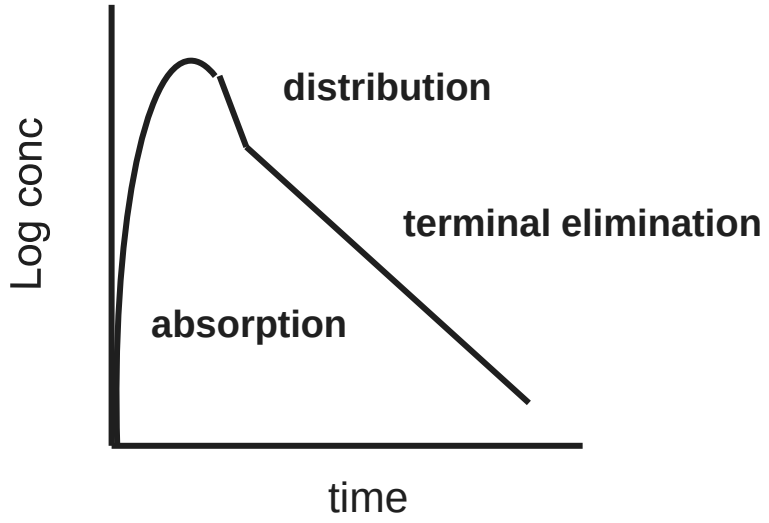
One-compartment

- Drug rapidly distributes to tissue compartment

Pharmacokinetic modeling: two-compartment model

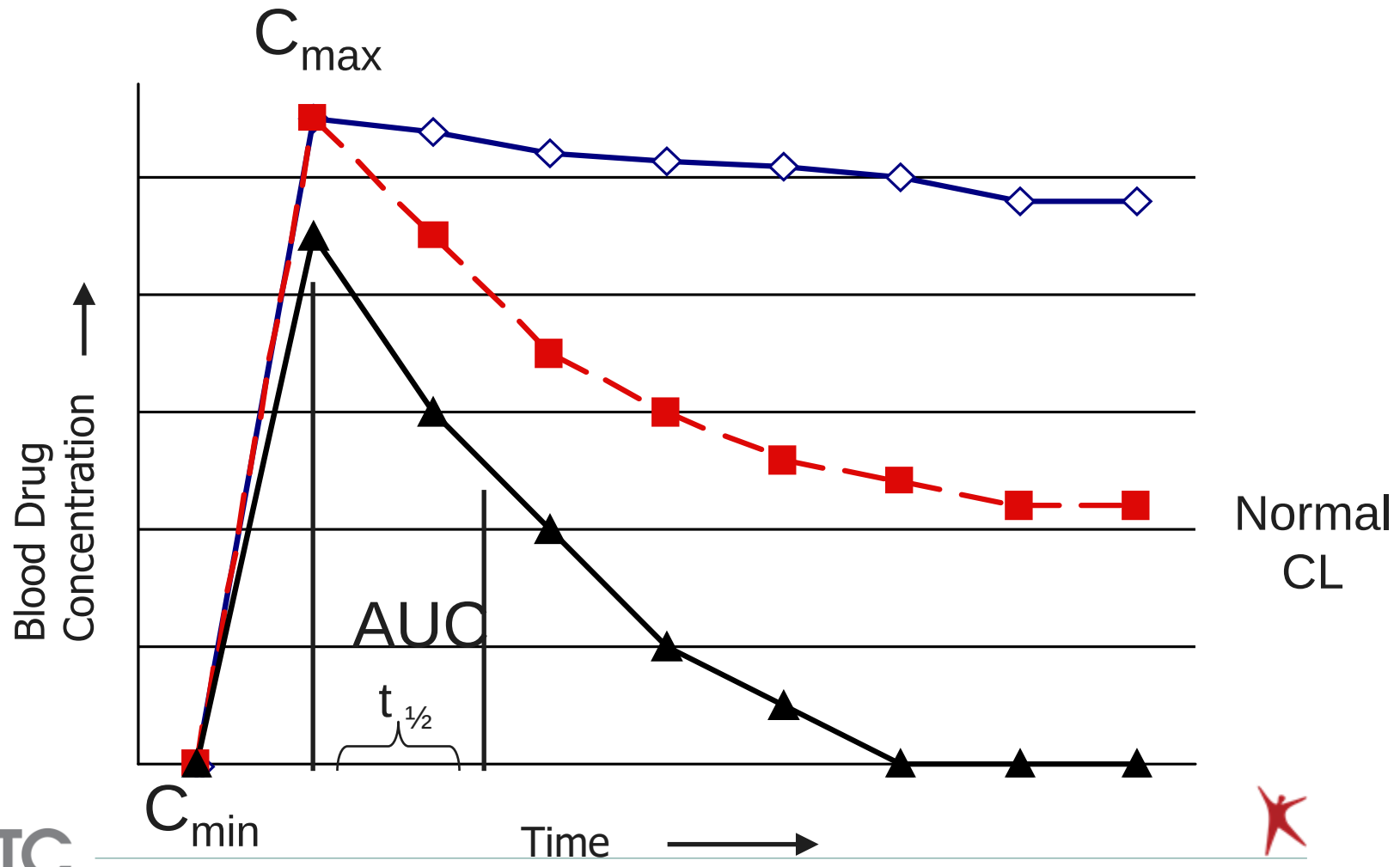
Orally administered drug

- Drug equilibrates slowly with peripheral tissues



Two-compartment

Area Under the Concentration Curve (AUC)



Summary

Pharmacokinetics is useful to:

- Optimize drug dose and dosing intervals
- Identify of drug-drug interactions
- Minimize the risk of drug toxicity

References:

- Tietz textbook of Clinical Chemistry and Molecular Diagnostics, Sixth edition, Nader Rifai, Andrea R. Horvath, Carl T. Wittwer
  - Chapter 40 Therapeutic Drugs and their Management
  - Chapter 44 Chapter 54 Pharmacogenetics

- Contemporary Practice in Clinical chemistry, Third edition, edited by William Clarke
  - Chapter 44, Pharmacokinetics for the Practicing Clinical Chemist
  - Chapter 45 Therapeutic Drug Monitoring

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
- **Consultant or Advisory Role:** No disclosures
- **Stock Ownership:** No disclosures
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- **Research Funding:** No disclosures
- **Expert Testimony:** No disclosures
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