Introduction to Pharmacokinetics

What is pharmacokinetics?

- Pharmacokinetics is the study of kinetics of absorption, distribution, metabolism and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic responses in man and animals''

Review of ADME processes

- ADME is an acronym representing the pharmacokinetic processes of:

A ➔ Absorption

D ➔ Distribution

M ➔ Metabolism

E ➔ Excretion

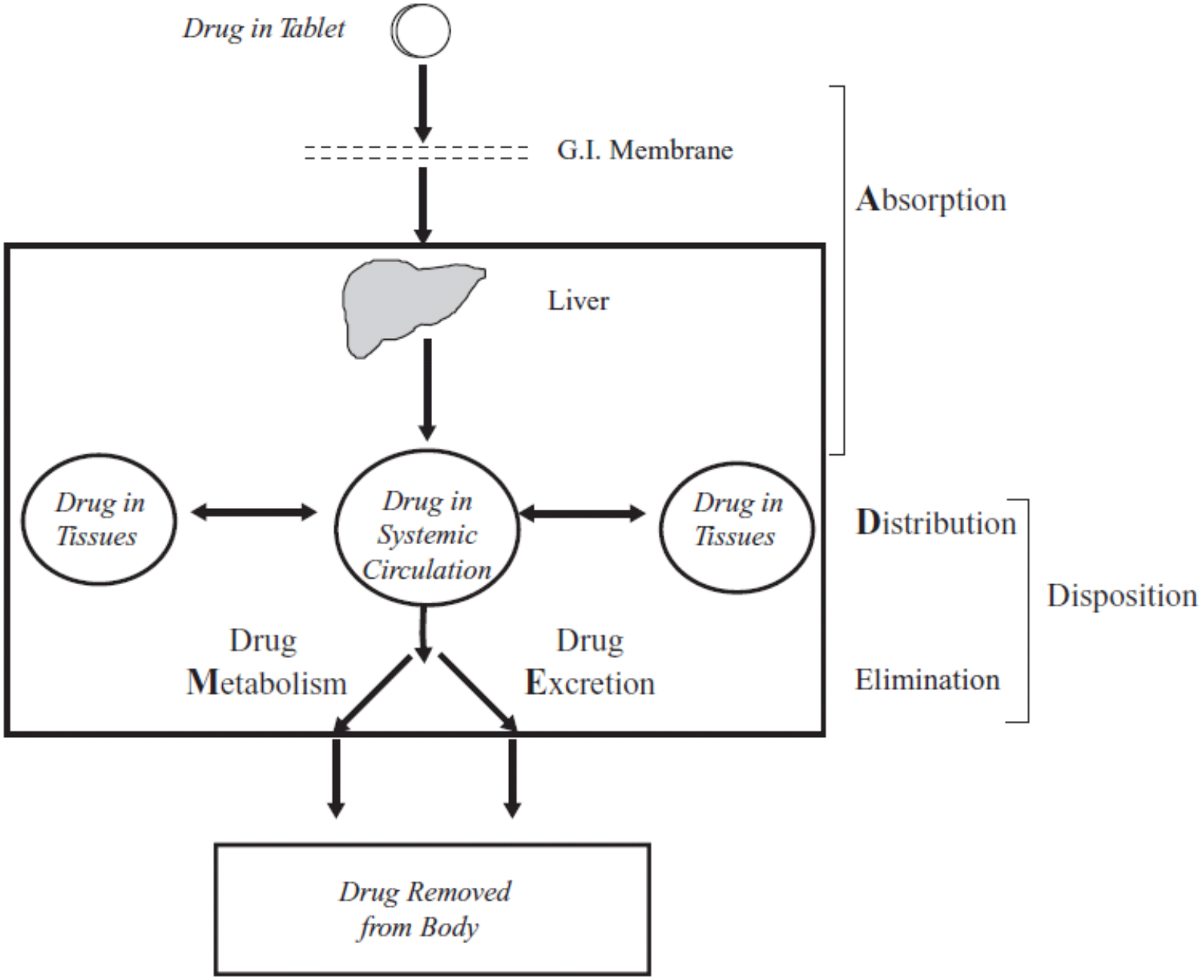
Review of ADME processes

- Absorption is defined as the process by which a drug proceeds from the site of administration to the site of measurement (usually blood, plasma or serum)

- Distribution is the process of reversible transfer of drug to and from the site of measurement (usually blood or plasma)

Review of ADME processes

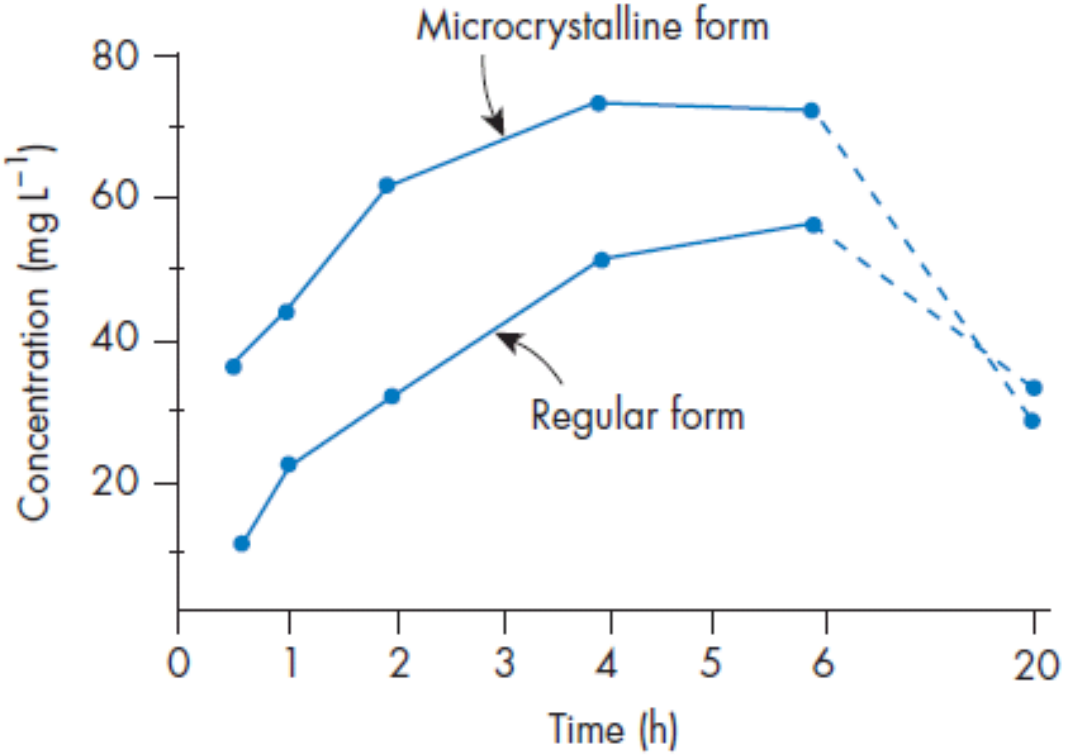
- Metabolism is the process of a conversion of one chemical species to another chemical species
- Excretion is the irreversible loss of a drug in a chemically unchanged or unaltered form
- Metabolism and excretion processes represent the **elimination process**


Drug in Tablet
G.I. Membrane
Absorption
Liver
Drug in Tissues
Drug in Systemic Circulation
Drug in Tissues
Distribution
Disposition
Drug Metabolism
Drug Excretion
Elimination
Drug Removed from Body

Applications of pharmacokinetics

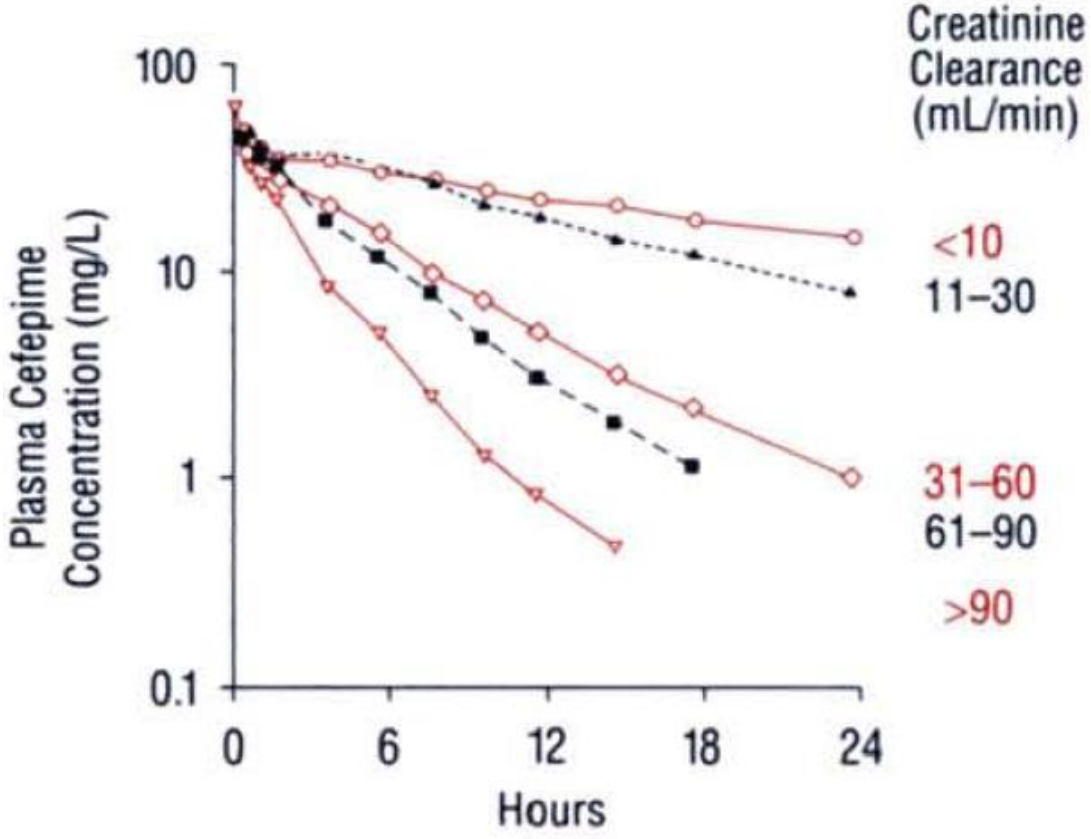
- bioavailability measurements
- effects of physiological and pathological conditions on drug disposition and absorption
- dosage adjustment of drugs in disease states, if and when necessary
- correlation of pharmacological responses with administered doses
- evaluation of drug interactions
- clinical prediction: using pharmacokinetic parameters to design a dosing regimen and thus provide the most effective drug therapy

Applications of pharmacokinetics



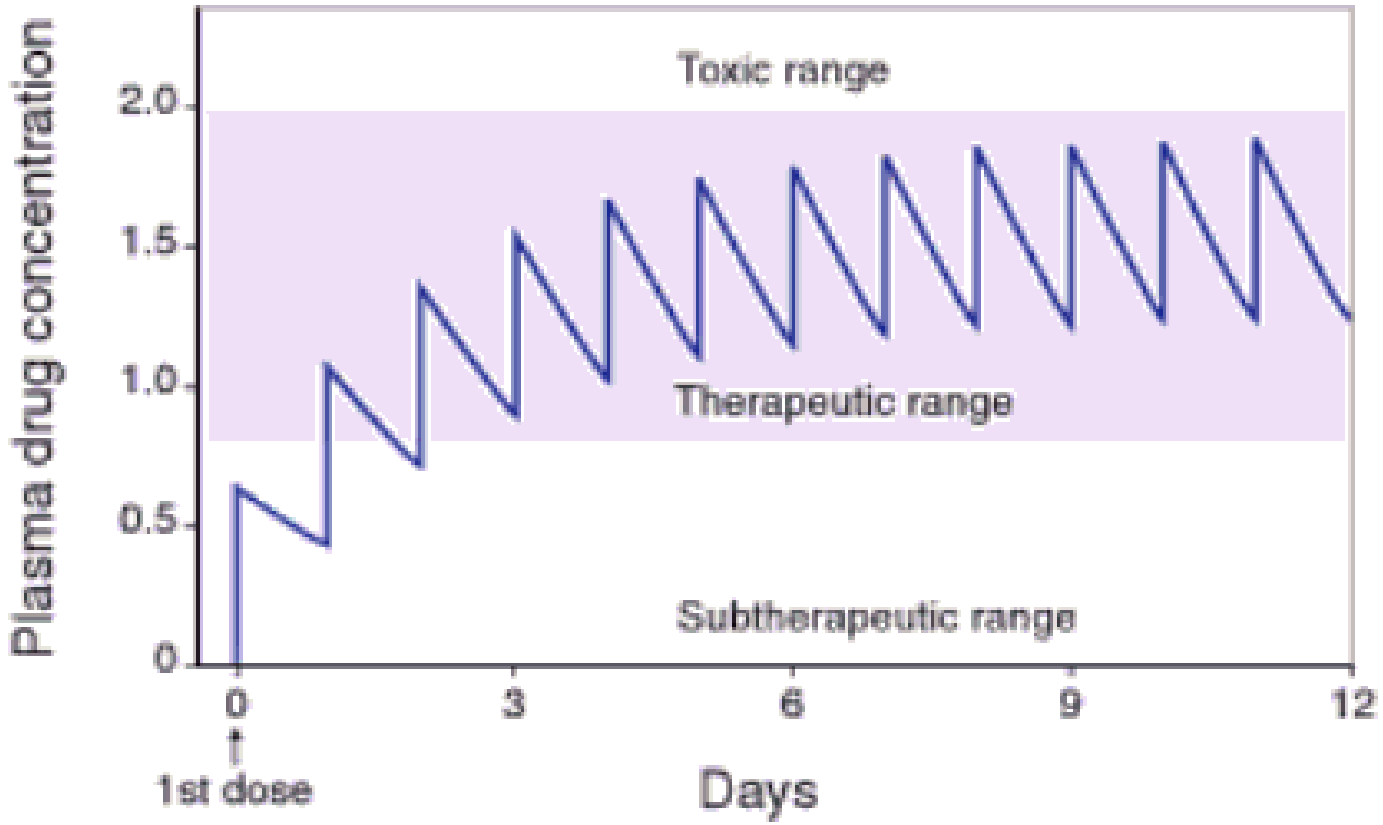
Bioavailability measurements: Blood sulfadiazine concentration in human following the administration of a 3 g dose. A comparison of the behavior of microcrystalline sulfadiazine with that of regular sulfadiazine in human

Applications of pharmacokinetics

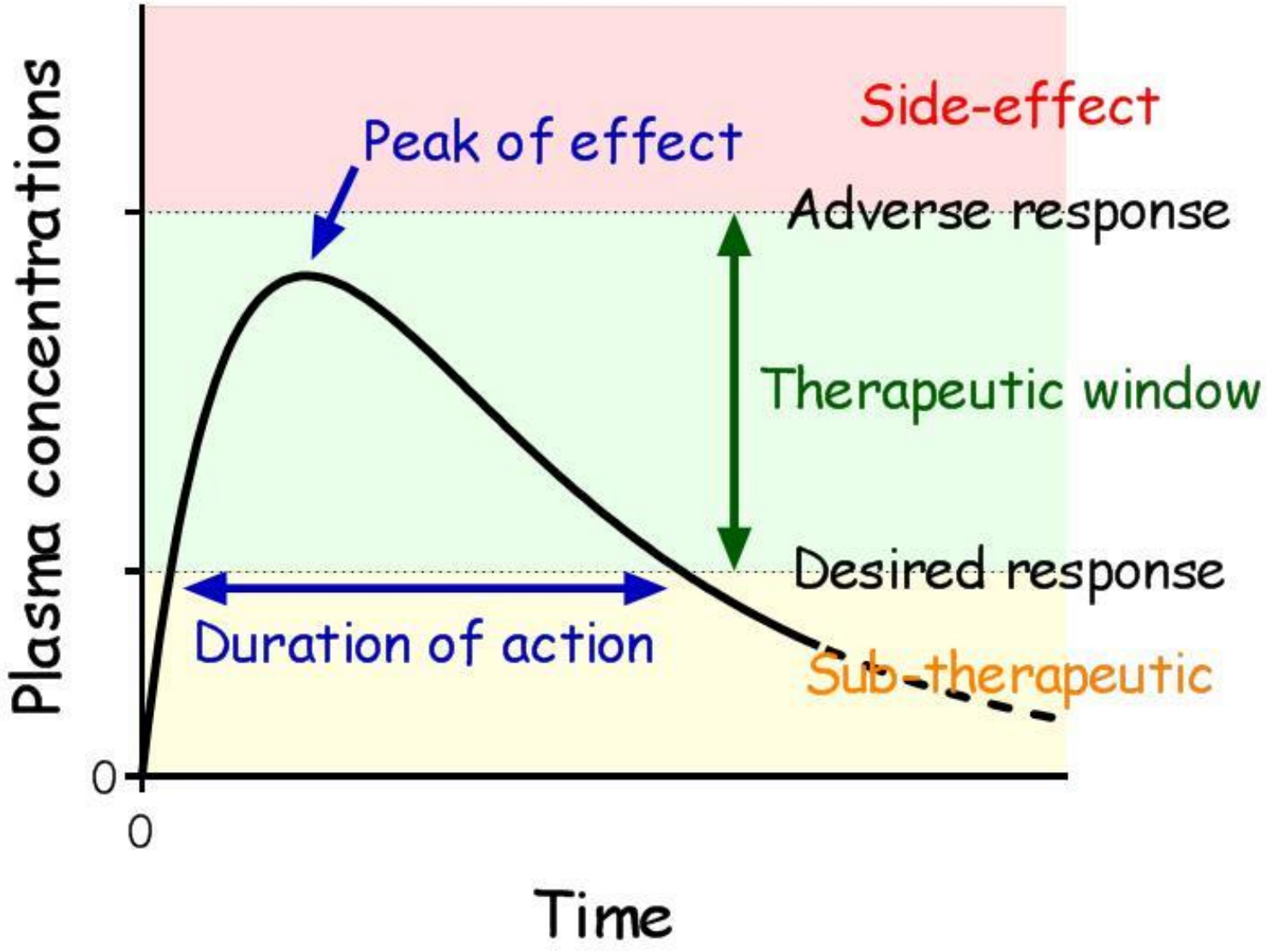


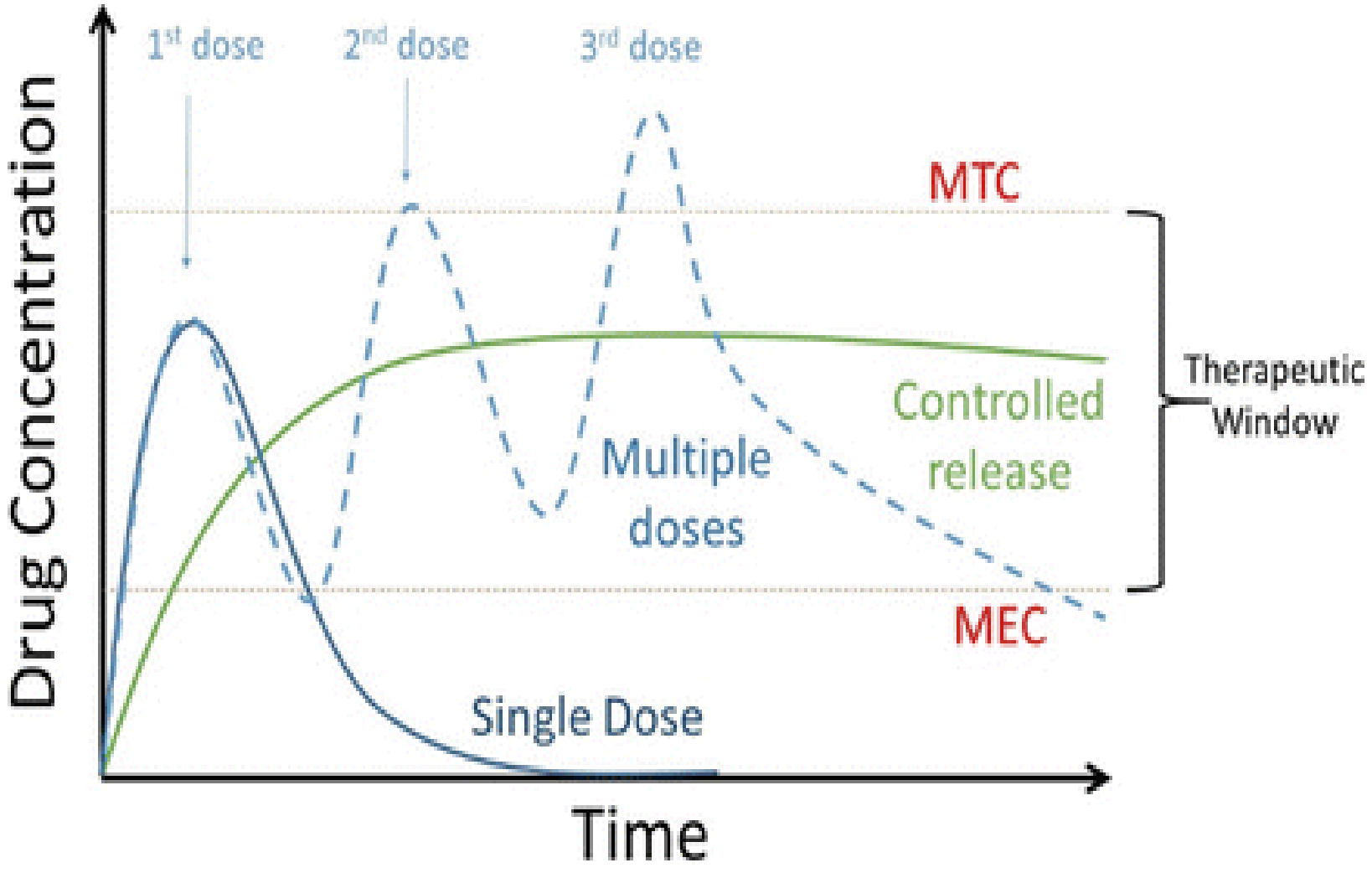
Effects of physiological and pathological conditions on drug disposition and absorption: plasma conc-time profile of cefepime after a 1000 mg IV infusion dose

Applications of pharmacokinetics



Using pharmacokinetic parameters to design a dosing regimen and thus provide the most effective drug therapy


Plasma concentrations
Side-effect
Peak of effect
Adverse response
Therapeutic window
Desired response
Duration of action
Sub-therapeutic
0
0
Time


1st dose
2nd dose
3rd dose
MTC
Therapeutic Window
Controlled release
Multiple doses
MEC
Single Dose
Drug Concentration
Time

Zero-Order Reactions

- Consider the rate of elimination of drug A from the body. If the amount of the drug, A, is decreasing at a constant rate, then the rate of elimination of A can be described as:

  where k* is the zero-order rate constant.

$$\frac{dA}{dt} = -k^*$$

- The reaction proceeds at a constant rate and is independent of the concentration of A present in the body. An example is the elimination of alcohol

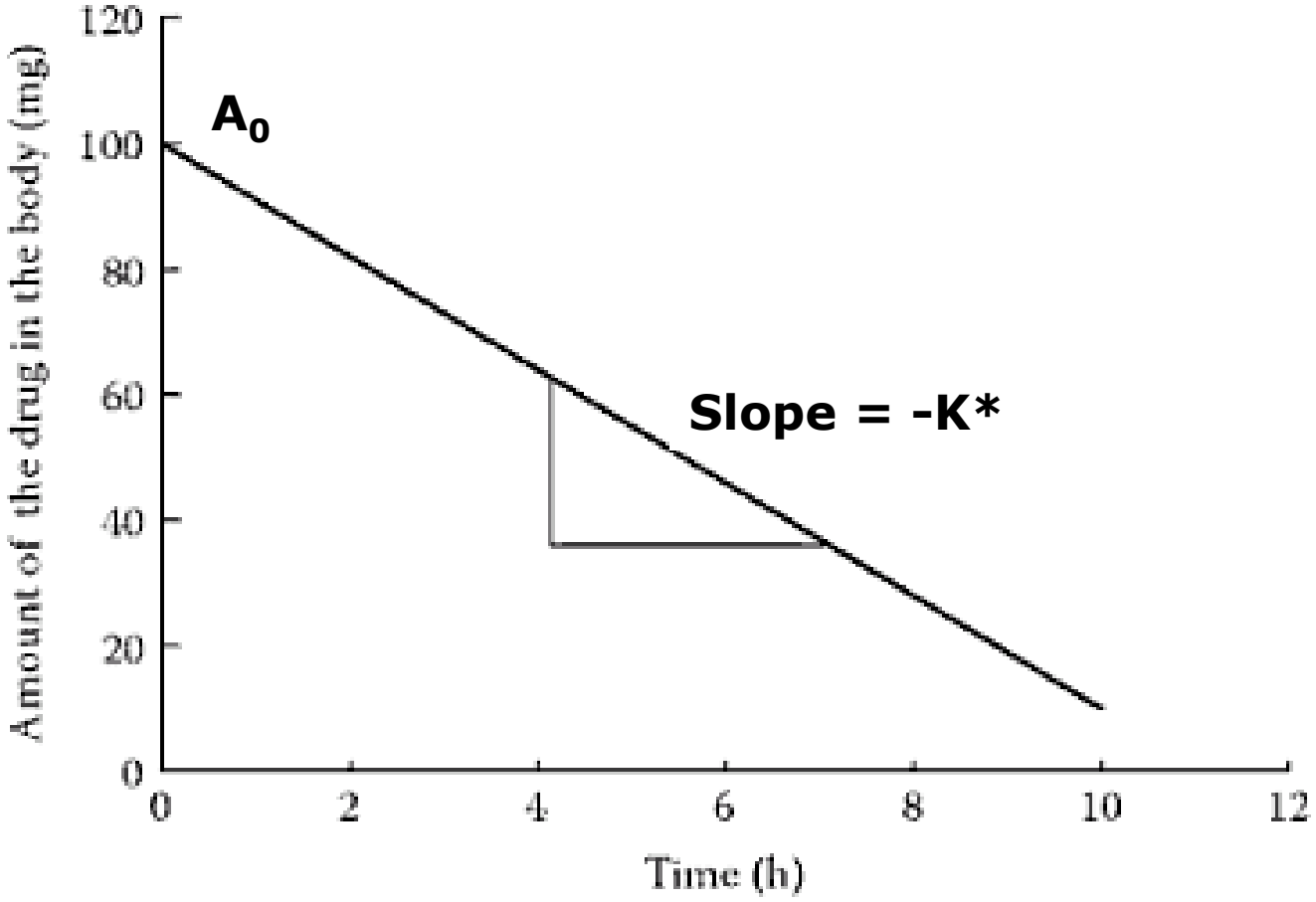
Zero-Order Reactions

- The amount of a drug with zero order elimination is described according to the following equation:

$$A = A_0 - k^* \cdot t$$

where A is the amount of drug in the body, A_0 is the amount of the drug at time zero (equal to the dose in the case of IV bolus)

Drug with zero order PK



First-order Reactions

- If the amount of drug A is decreasing at a rate that is proportional to A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

  where k is the first-order rate constant

$$\frac{dA}{dt} = -K \cdot A$$

- The reaction proceeds at a rate that is dependent on the concentration of A present in the body
- It is assumed that the processes of ADME follow first-order reactions and most drugs are eliminated in this manner

First-Order Reactions

- The amount of a drug with first order elimination is described according to the following equation:

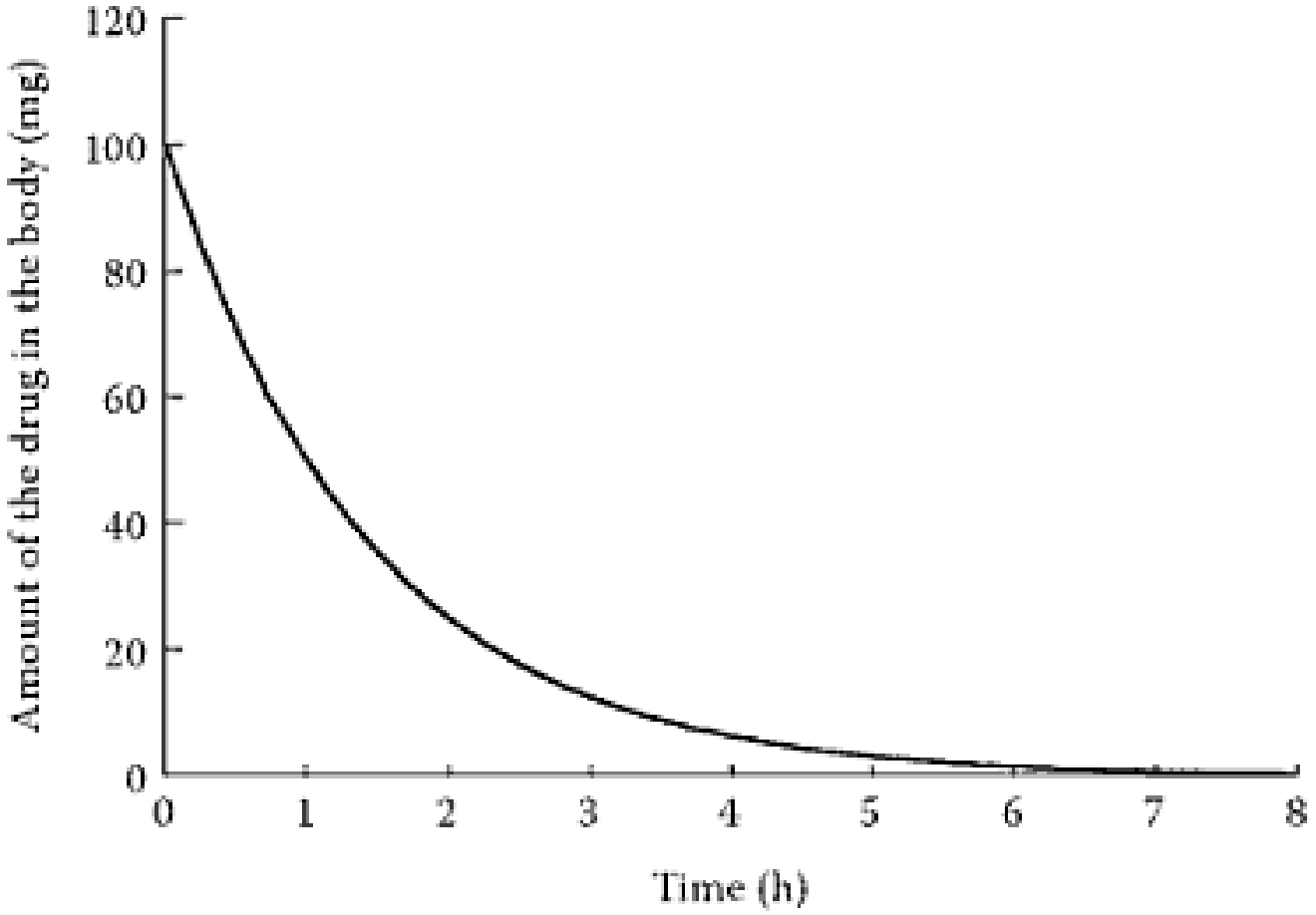
$$A = A_0 e^{-k^* \cdot t}$$

where A is the amount of drug in the body, A_0 is the amount of the drug at time zero (equal to the dose in the case of IV bolus)

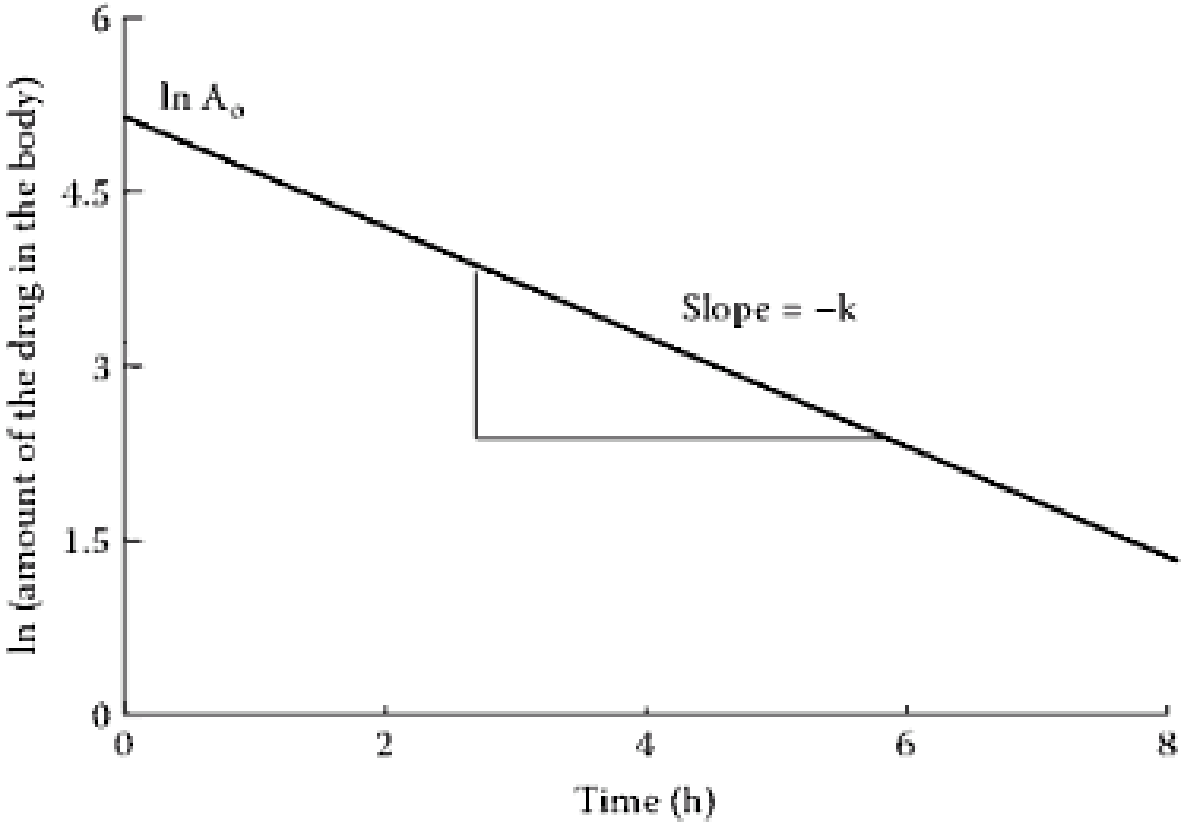
- This equation is equivalent to:

$$\ln(A) = \ln(A_0) - k^* \cdot t$$

D


Amount of the drug in the body (mg)
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
Time (h)

Drug with first order PK: log transformation



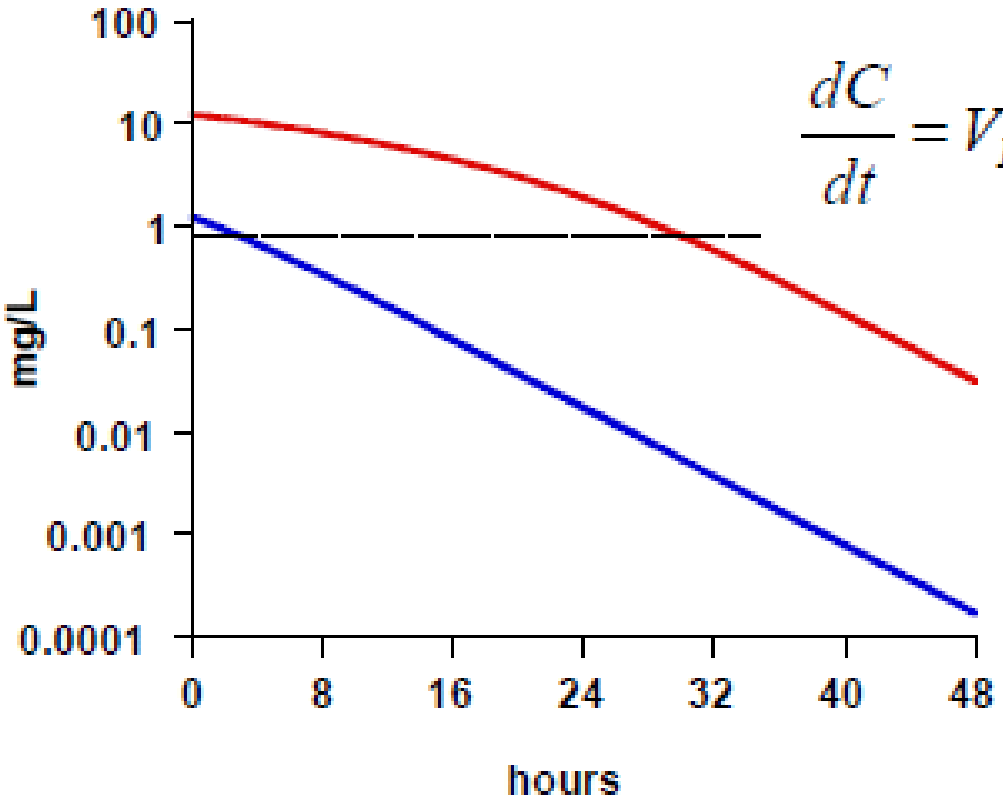
Nonlinear kinetics

- Nonlinear pharmacokinetics is also known as dose-dependent and concentration dependent pharmacokinetics because the pharmacokinetic parameters are dependent on the drug concentration or the drug amount in the body
- At least one of the absorption, distribution, and elimination processes, which affect the blood drug concentration—time profile, is saturable and does not follow first-order kinetics
- The change in drug dose results in disproportional change in the blood drug concentration— time profile after single- and multiple-dose administrations

Nonlinear kinetics

Michaelis-Menton kinetics

$$\frac{dC}{dt} = V_{MAX}\left(\frac{C}{C + K_m}\right)$$



Nonlinear kinetics:

Linear kinetics:

Linear PK	Nonlinear PK
1-Known as dose-independent or concentration-independent PK.	1-Known as dose-dependent or concentration-dependent PK.
2-The absorption, distribution and elimination of the drug follow first-order kinetics	2-At least one of the PK processes (absorption, distribution or elimination) is saturable.
3-The pharmacokinetic parameters such as the half-life, total body clearance and volume of distribution are constant and do not depend on the drug conc	3-The pharmacokinetic parameters such as the half-life, total body clearance and volume of distribution are conc-dependent
4-The change in drug dose results in proportional change in the drug concentration.	4-The change in drug dose results in more than proportional or less than proportional change in the drug conc.

Important drugs with saturable metabolism

Cause	Drug
Saturable metabolism	Phenytoin, salicyclic acid, theophylline, valproic acidb
Cofactor or enzyme limitation	Acetaminophen, alcohol
Enzyme induction	Carbamazepine
Altered hepatic blood flow	Propranolol, verapamil