Pharmacokinetics

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Lecture objectives

1. Define Pharmacokinetics
2. Describe and discuss different routes of drug administration
3. Discuss drug disposition processes: Absorption, distribution, plasma protein binding, metabolism, and excretion.
4. Discuss drug absorption process; mechanism of drug permeation, drug bioavailability, factors affecting bioavailability, bioequivalence.
5. Discuss first-pass metabolism and its clinical relevance.
6. Discuss drug distribution and redistribution; rate of protein binding, apparent volume of distribution (Vd), factors affecting protein binding and Vd.
7. Discuss drug metabolism; hepatic drug metabolism (phase I and II reactions), role of cytochrome in drug metabolism, factors affecting drug metabolism.
8. Discuss drug excretion process; renal excretion, enterohepatic circulation.

Lecture objectives

9. Describe and discuss the main pharmacokinetic parameters; bioavailability, volume of distribution (Vd), clearance (Cl), plasma half-life (t1/2).
10. Describe plasma concentration-time curve after single and repeated oral and IV dose and factors affecting plasma concentration-time curve: rate of absorption, extent of absorption, route of administration, dose and formulation.
11. Discuss the concept of steady state, correlation between t1/2 and time to reach steady state.
12. Discuss first and zero order kinetics.
13. Describe the concept of loading and maintenance dose (DL and DM) and methods to calculate DL, DM and other pharmacokinetic parameters.

Pharmacokinetics

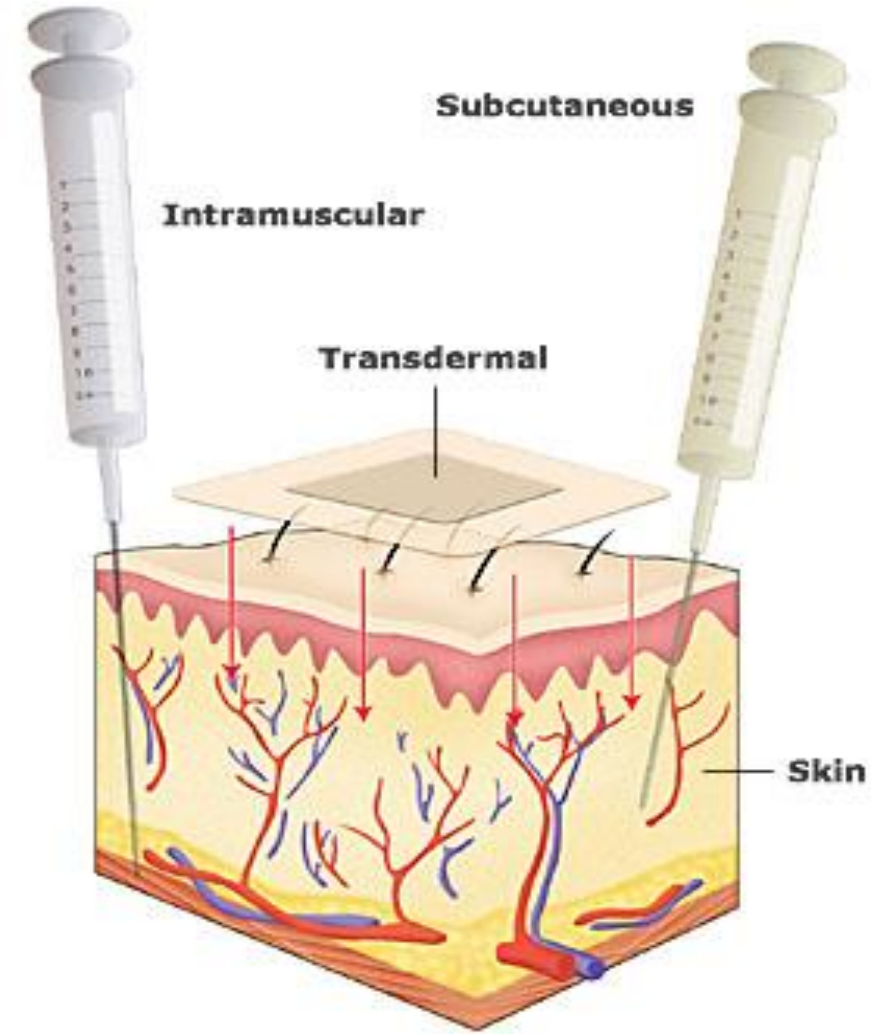
- Pharmacokinetics studies processes that a drug undergoes after administration.

What the body does to the drug?

Routes of drug administration

Enteral

- oral
- sublingual
- rectal



Parenteral

- intravenous
- intra-arterial
- intramuscular
- subcutaneous
- transdermal
- intranasal
- inhalation
- intrapleural

Oral Route of Administration

Benefits

- Easy and convenient for most of the patients
- Painless
- Most economical
- Safe

Drawbacks

- Less bioavailability
- Slow-down effect
- Requires patient compliance
- Not suitable / convenient for some categories of the patients

IV Route of Administration: Bolus&Infusion

Benefits

- Bioavailability is 100%
- Potentially fast onset
- Permits maintain plasma concentration at the same level particular for short-actin drugs (IV infusion)
- Permits titration of dosage (IV infusion)
- Suitable for large volumes (IV infusion)

Drawbacks

- Not suitable for poorly soluble substances
- Painful
- Increased risk of toxic reactions and ADRs
- High risk of infections
- Have to be provided in special conditions
- Have to be provided by specially trained staff
- More costly

Drug disposition processes

- Absorption
- Distribution
- Metabolism
- Excretion
  - renal
  - bile

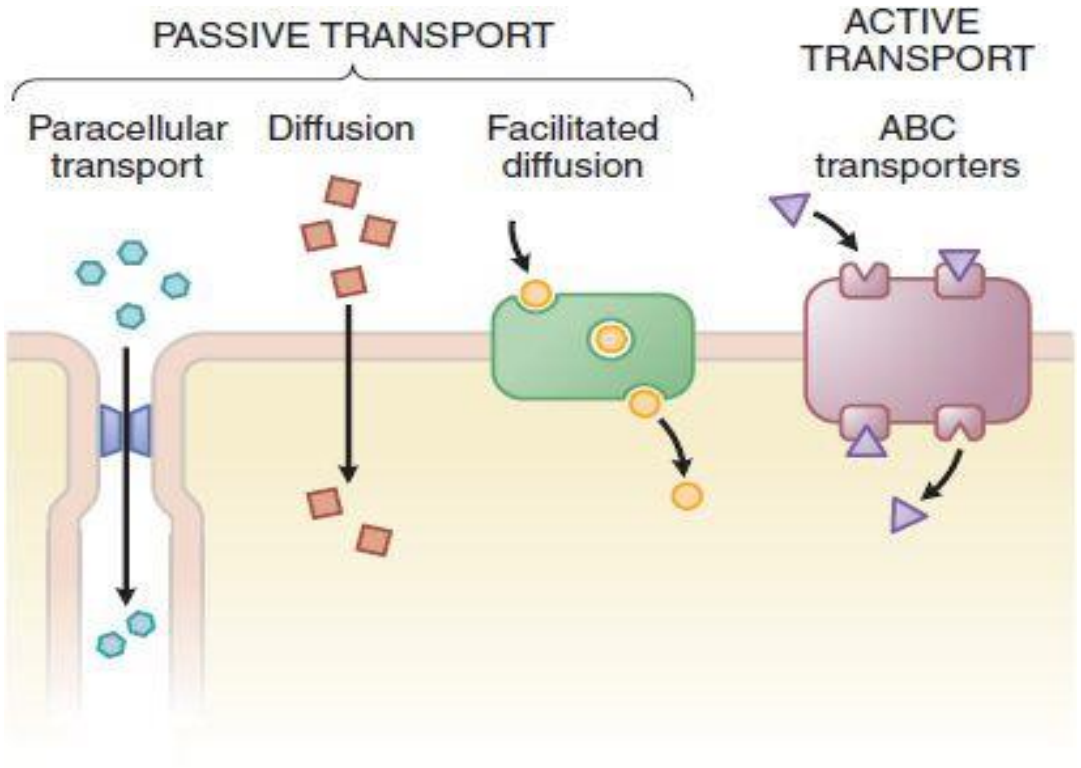
Elimination

Absorption

- Absorption is the process by which drug pass from the site of administration to the blood stream.
- Factors that affect absorption:
  - The particle size – smaller is better
  - Concentration gradient
  - Surface area and vascularity of that area
  - Lipid solubility / Water solubility
  - Nature of the drug… acidic or basic
  - Ionized or non ionized
  - The pH levels on either side of cell membrane
- Absorption is characterized by Bioavailability (F)

Drug Transport Across Membrane

- Passive Transport: Without energy and mostly along a concentration gradient
  - Paracellular transport
  - Diffusion
  - Facilitated diffusion (co-transporters)
- Active transport: Energy depended, against concentration gradient)
  - ATP-depended transporters
- Pinocytosis



Concept of ionization

Most of the drugs are either **weak acid** or a **weak base.**

Drug dissolved in body fluids presents in the state of **ionized/unionized**

Role of pH on ionization a

Weak Acids

- Aspirin
- As pH increases, a weak acid will become more and more ionized , lipid insoluble and will not be absorbed. Also becomes more water soluble and better excreted .
- As pH decreases, a weak acid will become more and more unionized , lipid soluble and better absorbed .

Weak Base

- Lidocaine
- As pH increases, a weak base will become more and more unionized, lipid soluble and better absorbed
- As pH decreases, a weak base will become more and more ionized, lipid insoluble, and will not be absorbed. Also becomes more water soluble and better excreted.

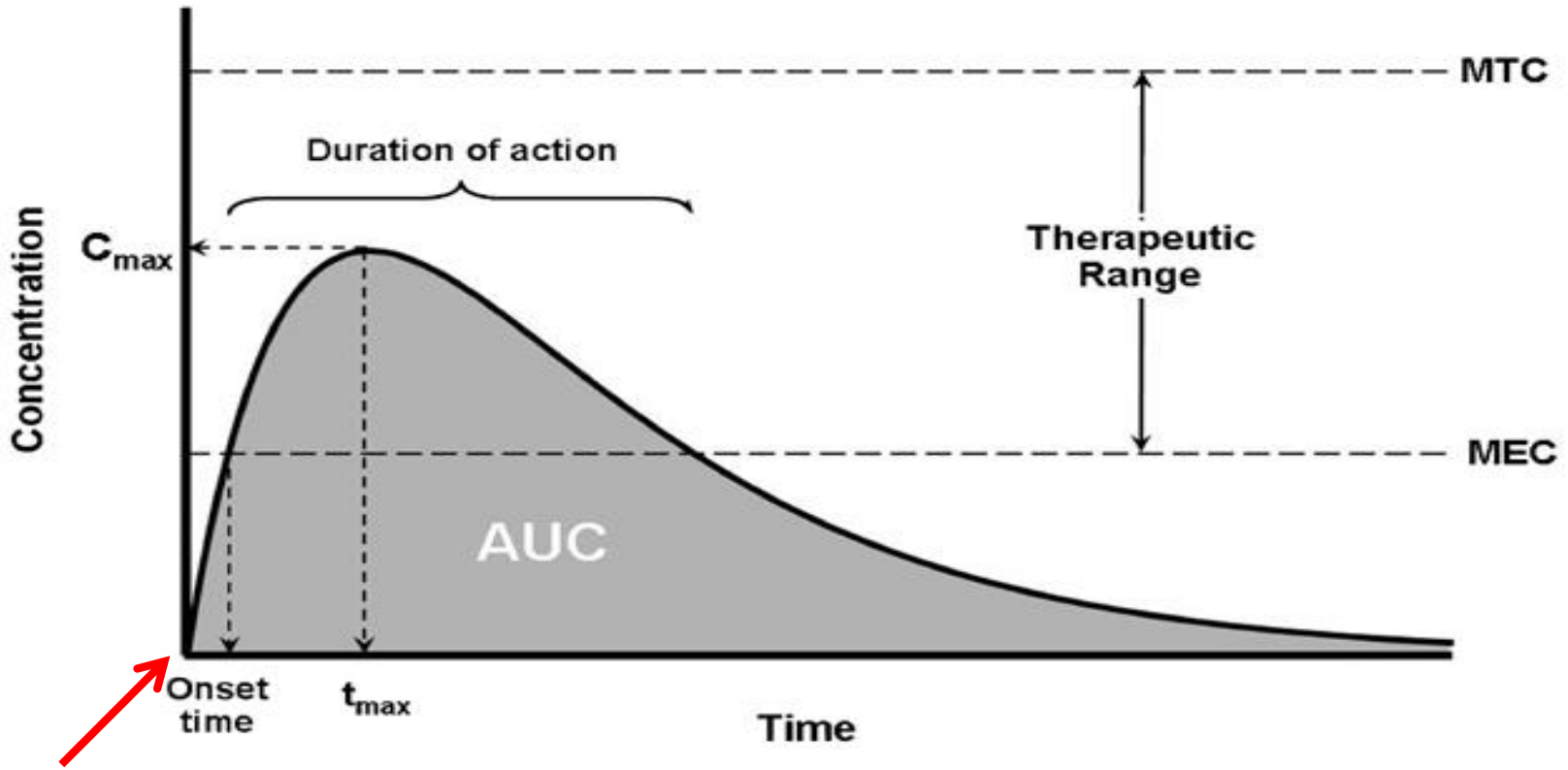
Acidic drugs are Absorbed best in Acidic environments

Basic drugs are Best absorbed in Basic environments

Bioavailability

- *Bioavailability:* The amount of the drug reaches systemic circulation unchanged from its site of administration
- Factors affecting bioavailability
  - Rout of administration:
    - IV rout – 100% bioavailability
    - Any other rout of administration <100% bioavailability (due to incomplete absorption and/or first-pass metabolism)
  - Properties of the drug:
    - Molecular weight, formulation, lipid solubility etc.
  - Patient:
    - Gastric emptying time; food; intestinal motility (in oral route of administration)

Bioavailability



Drug administered

AUC = bioavailability

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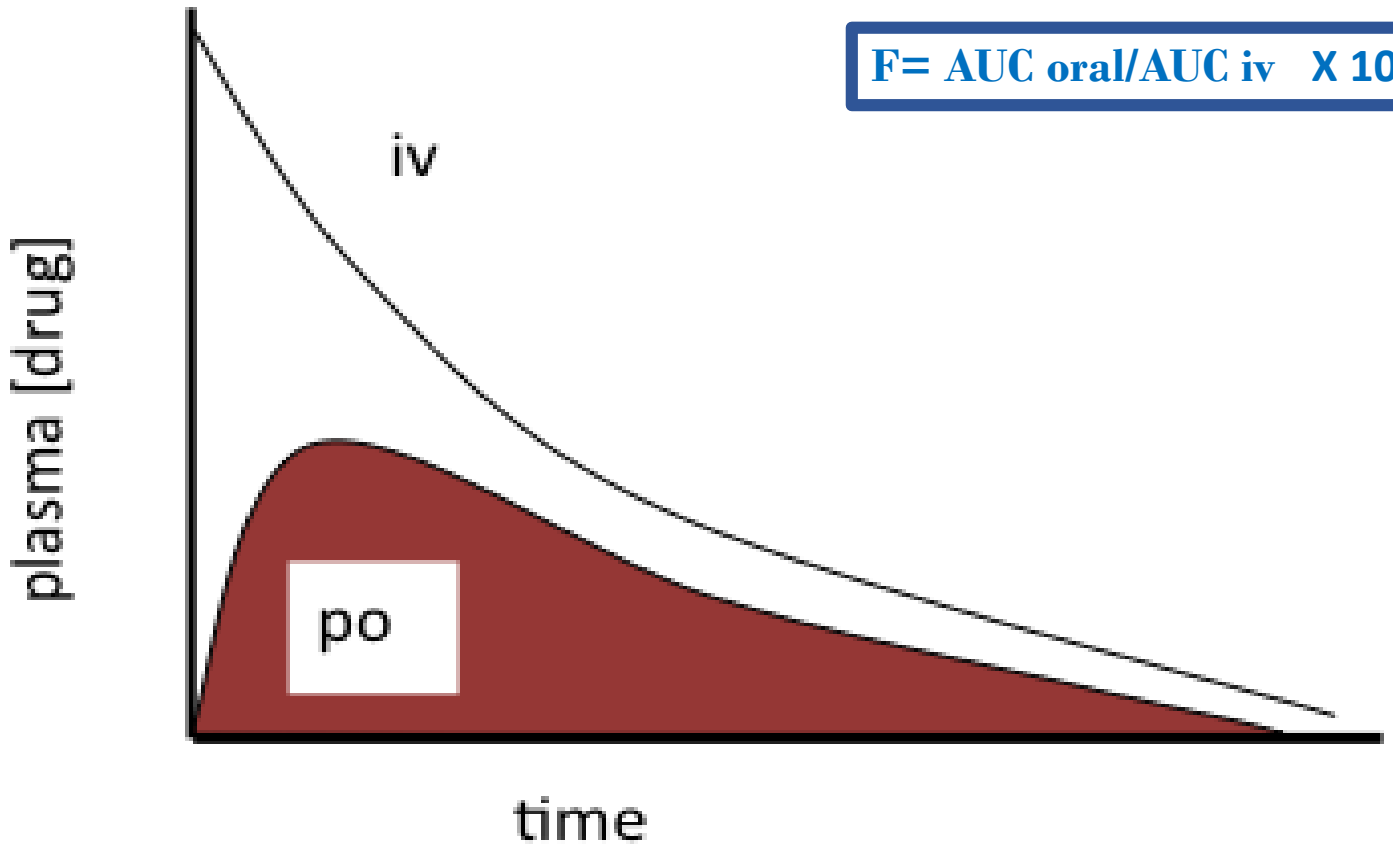
Bioavailability: Oral vs IV



F= AUC oral/AUC iv X 100

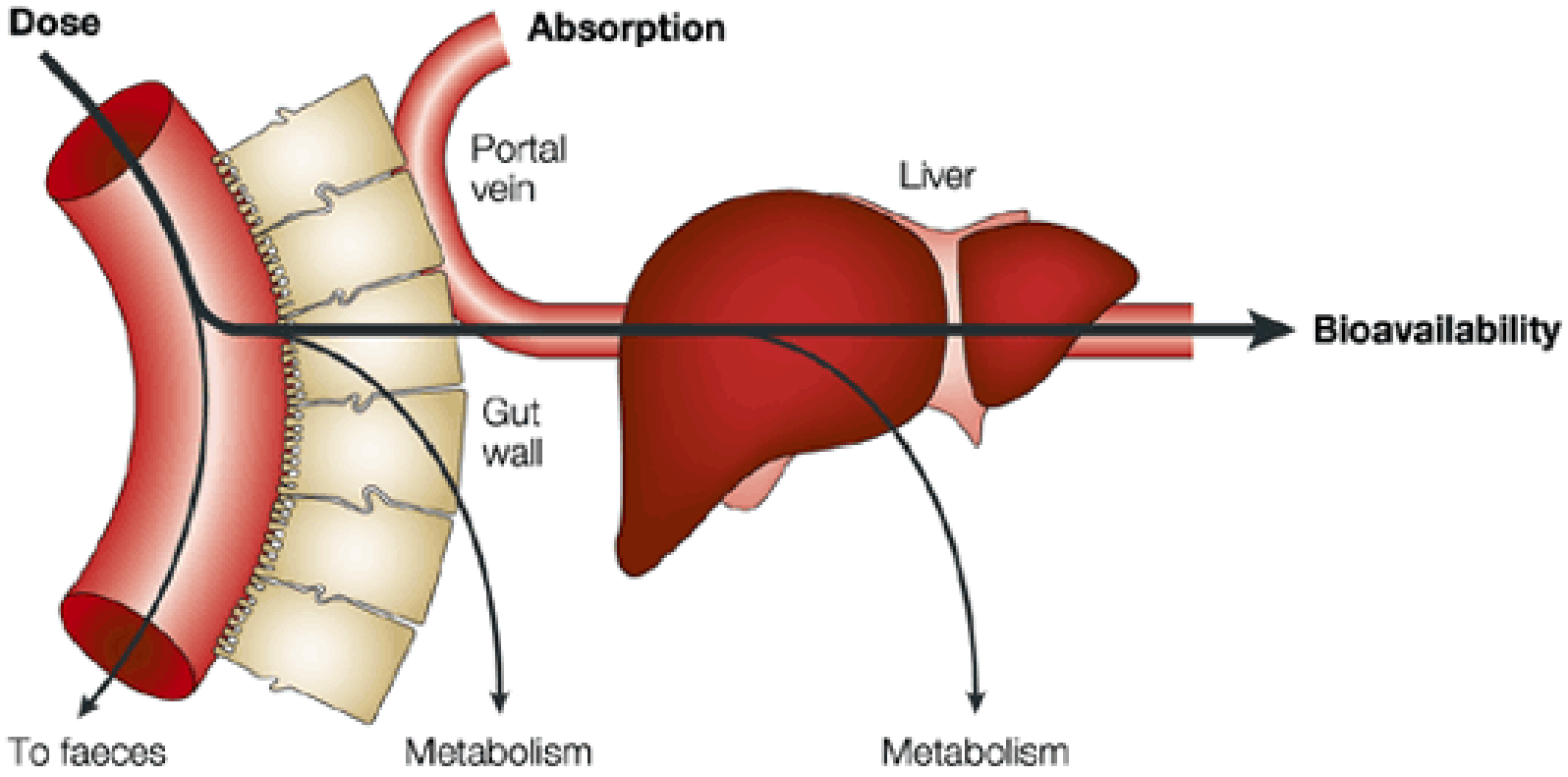
Bioavailability is determined by comparing plasma levels of drug after administration (via any route other than IV) compared to IV route (~100% bioavailability).

tmedweb.tulane.edu/pharmwiki/doku.php/bioavai

Bioequivalence

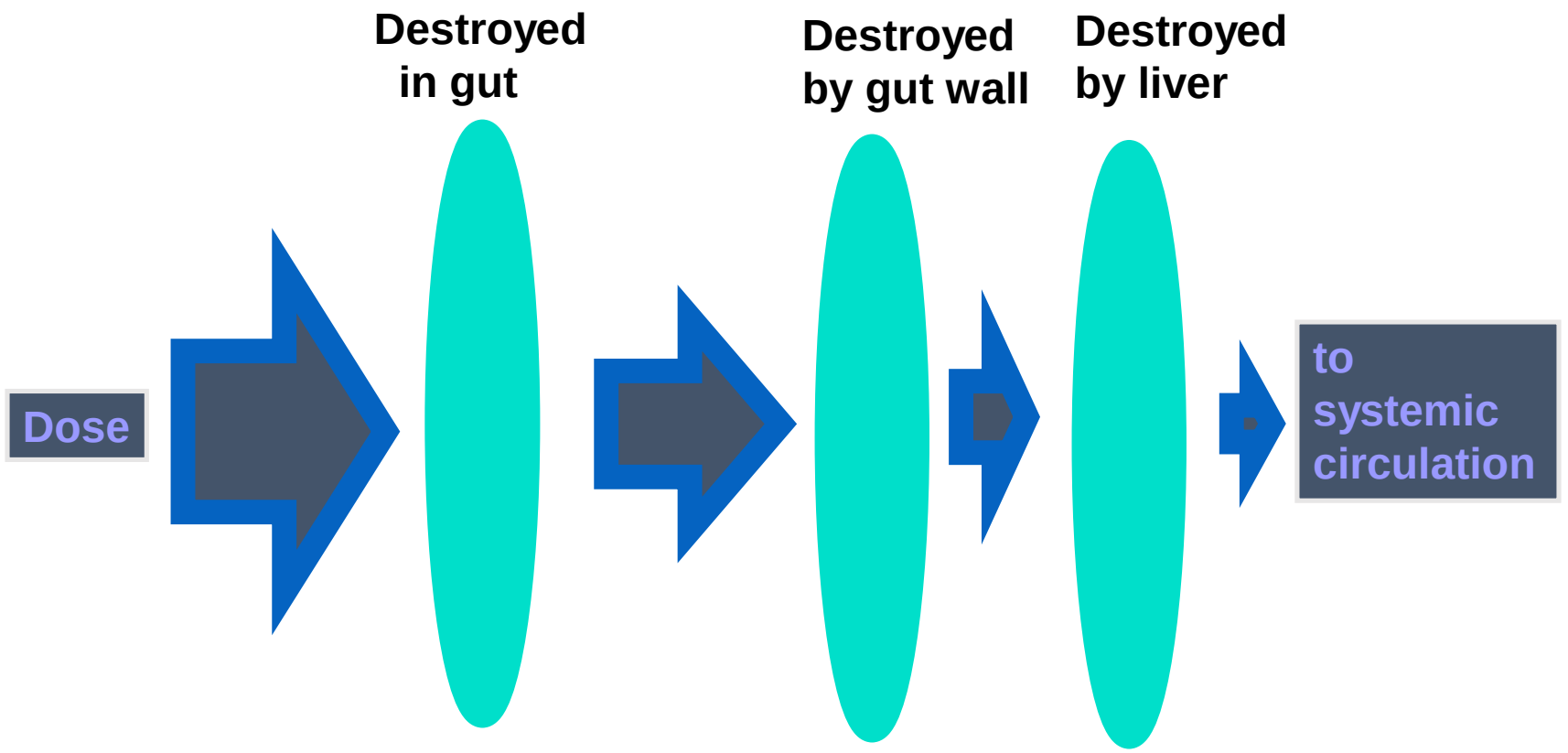
- Bioequivalence is *in vivo* biological equivalence of two proprietary preparations (generic drug).
- Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent (same active substance at the same formulation) and their bioavailabilities (rate and extent of availability) after administration in the same molar dose and using the same rout of administration are the same. (Birkett, 2003)
- Pharmacokinetic parameters that have to be comparable:
  - area under the curve (AUC),
  - peak concentration (Cmax),
  - time to reach peak concentration (Tmax),
  - absorption lag time (tlag).

First-pass metabolism



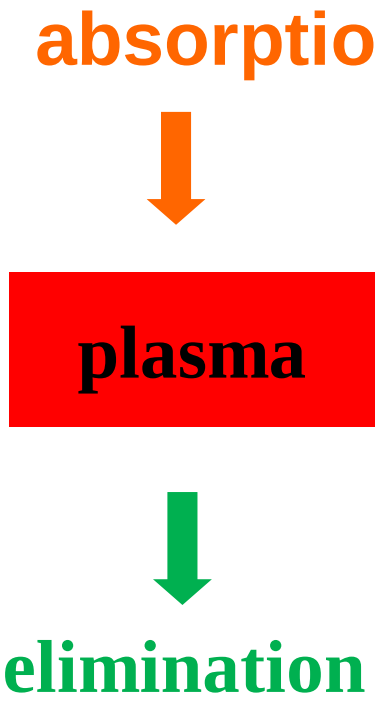
Pre-systemic metabolism (first-pass) is the drug metabolism occurs before the drug achieves the systemic circulation

First-pass metabolism

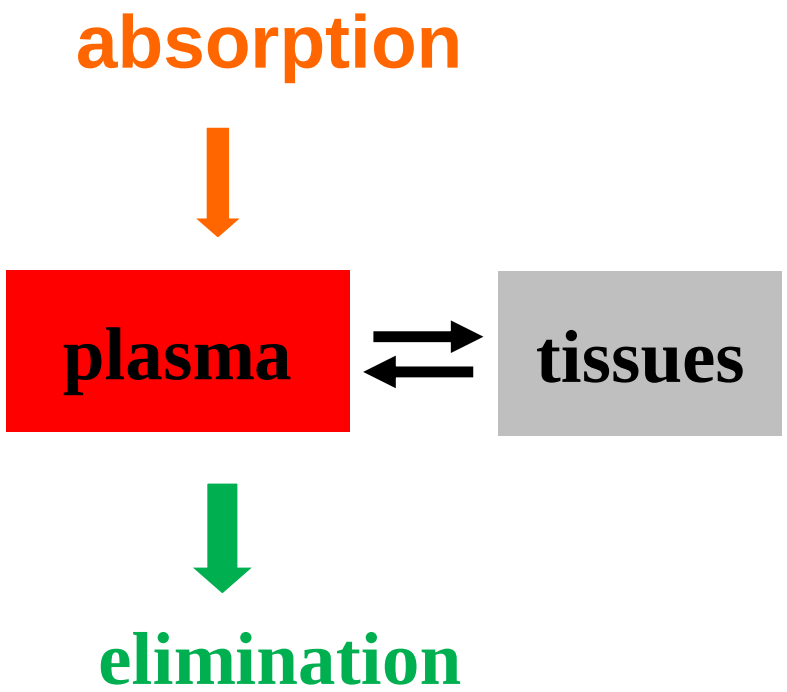


Drug distribution

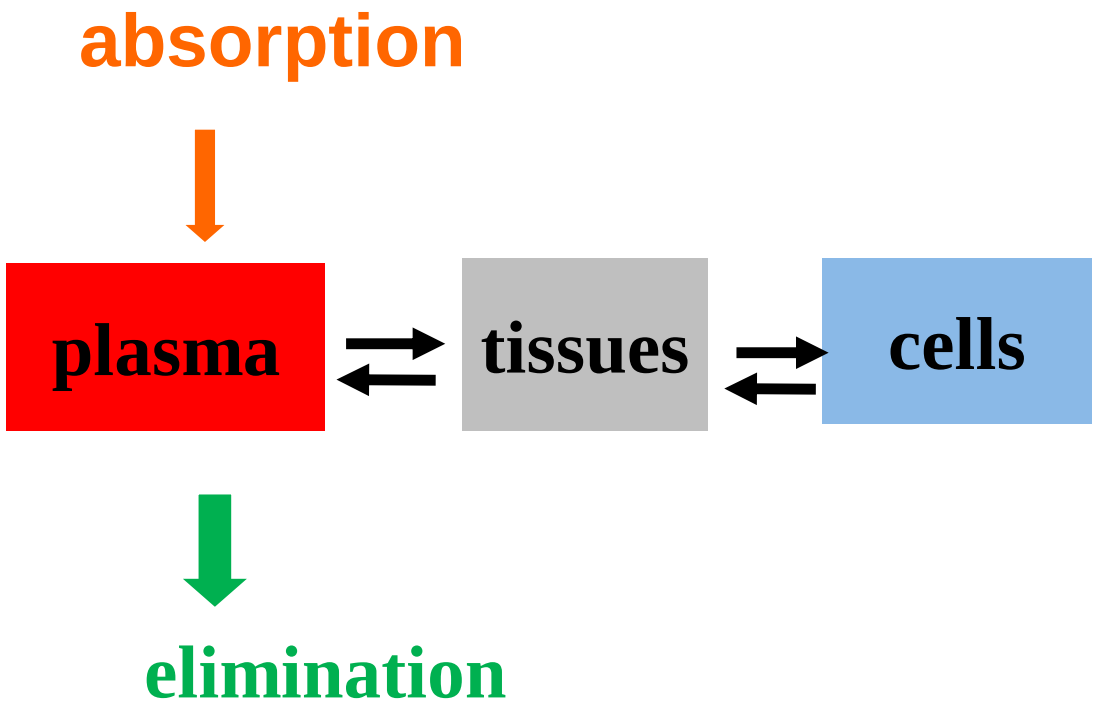
One compartment model



Two compartment model

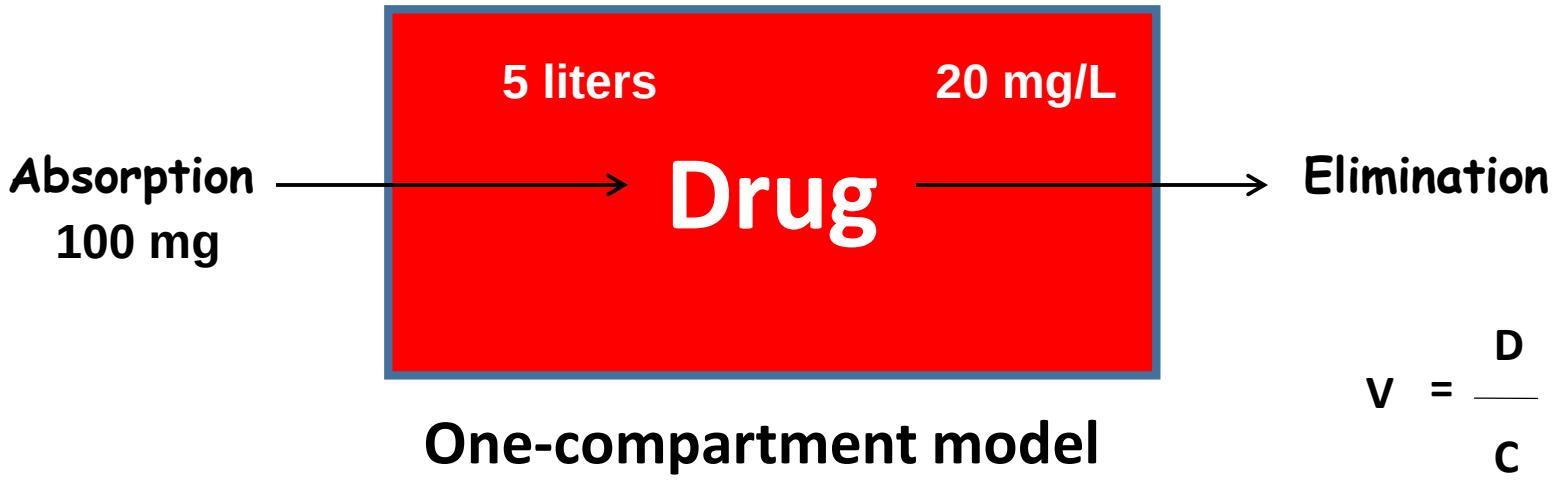


Three compartment model



Drug distribution (One Compartment Model)

In the simplest form the body can be considered as one compartment into which the drug is absorbed, the volume of this one compartment will be the volume of drug distribution.

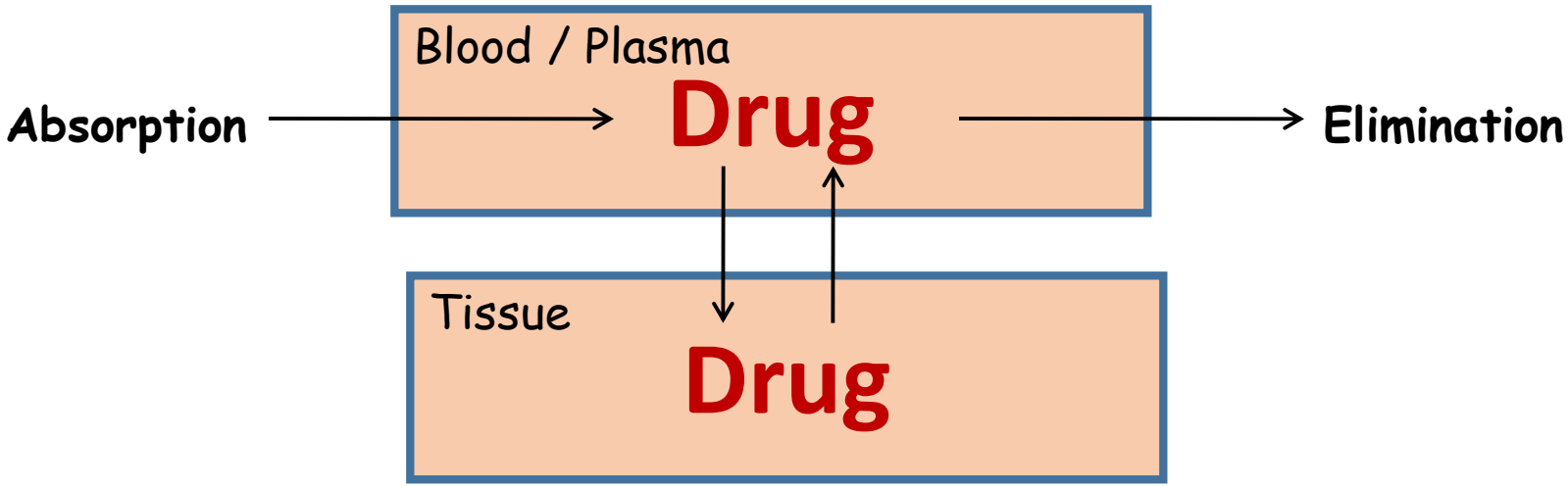


One-compartment model

Volume of distribution is equal to the volume of intravascular compartment

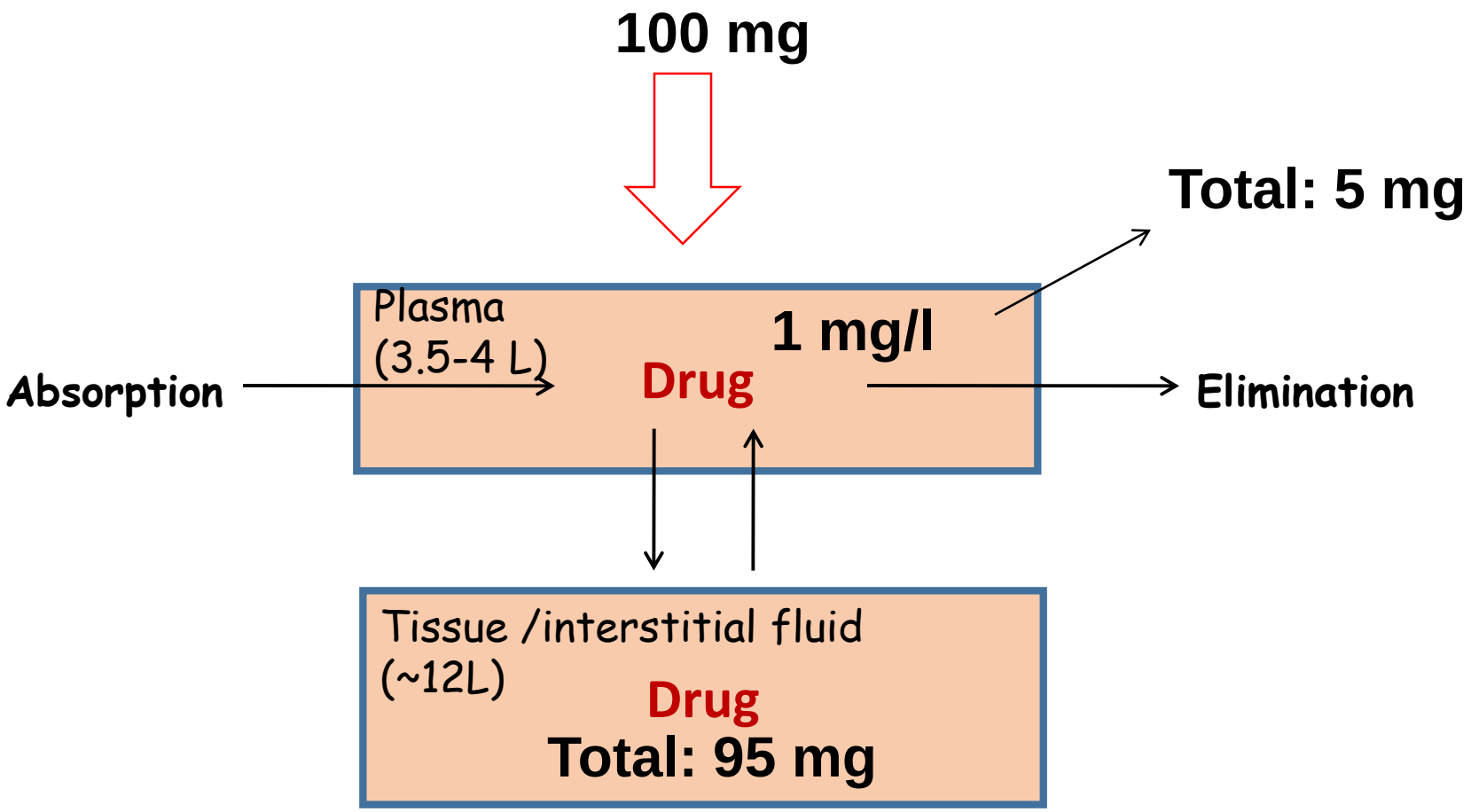
Drug distribution (Two Compartment Model)

- Human body is not a single compartment.
- Drug is distributing in and out of many tissue compartments while it is simultaneously being eliminated.



Two-compartment model

Volume of distribution (Two Compartment Model)



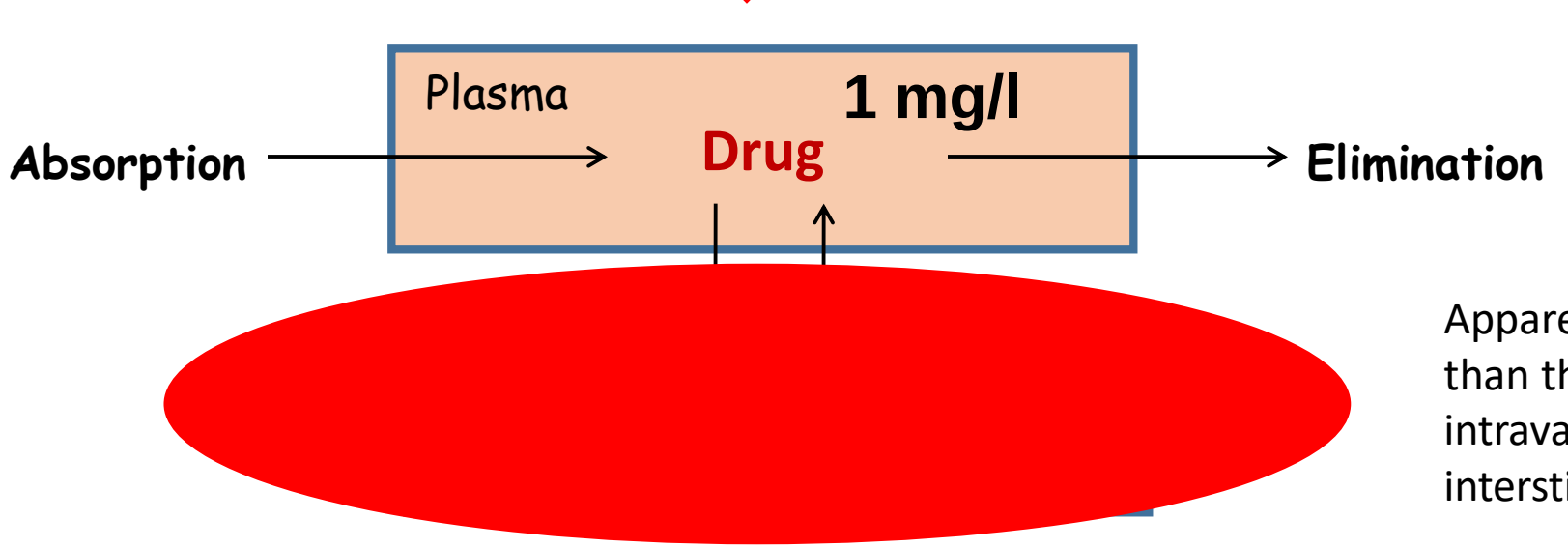
Apparent volume of distribution (Vd or VD)

The volume of fluid into which a drug appears to be distributed or diluted at the same as plasma concentration is called the **apparent volume of distribution**.

Vd = amount of drug in the body / C

100 mg

100/1 = 100 L



Apparent Vd is more than the volume of intravascular as well as interstitial volumes

Apparent Vd : 100 L

Many drugs exhibit volumes of distribution far in excess of total body volume.

Factors that affect distribution

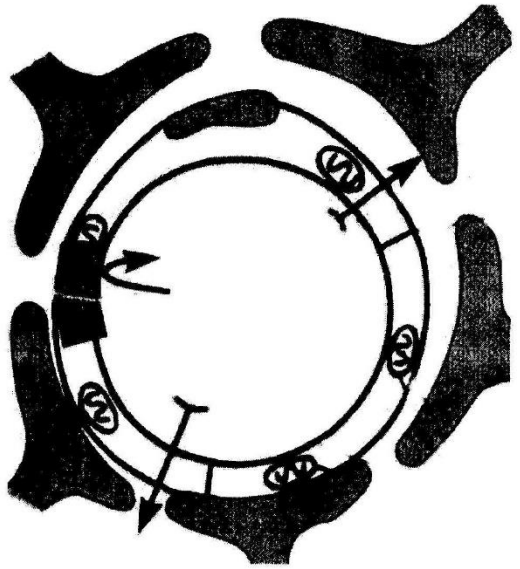
- **Physical and chemical characteristics of the drug (the main factor)**
- Lipid content of the tissue
- Cardiac output and blood circulation
- Capillary permeability in various tissues, anatomic barriers

Volume of distribution (Vd)

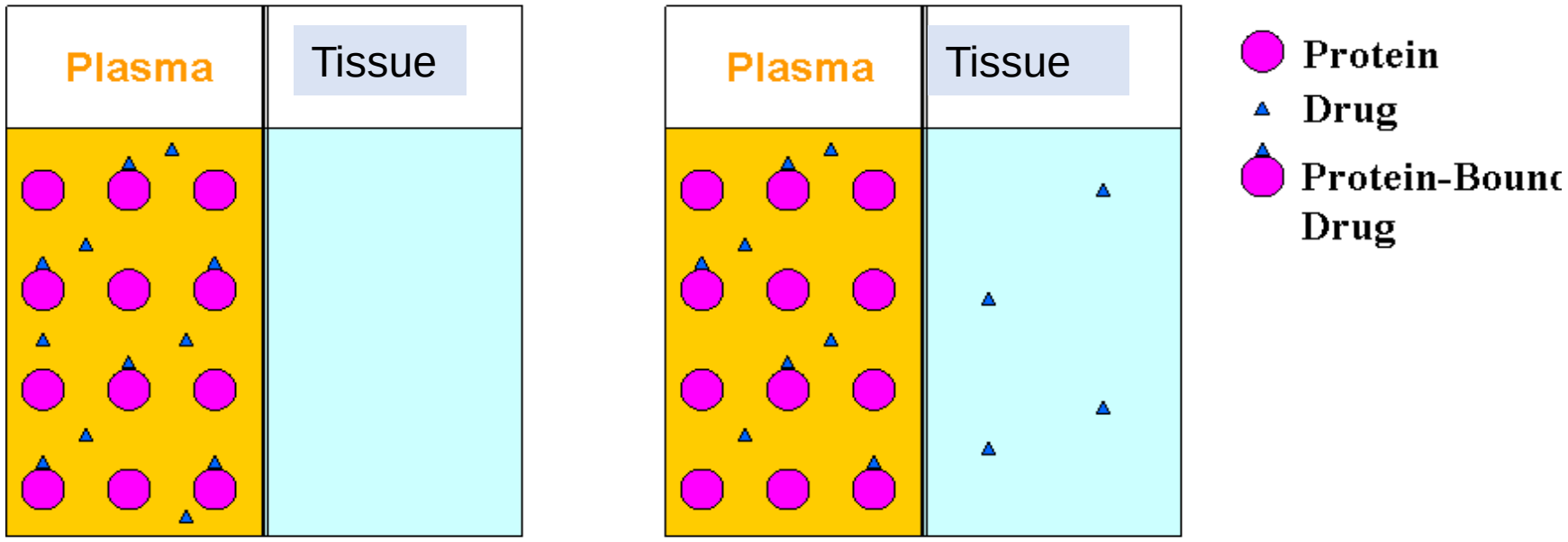
< 12 L **(< 0.17 L/kg)**	**12 – 40 L** **(0.17 - 0.57 L/kg)**	**40 – 100 L** **(0.57 - 1.43 L/kg)**	**100 – 200 L** **(1.43 - 2.86 L/kg)**	**> 200 L** **(> 2.86 L/kg)**
Diclofenac	Alcohol	Aciclovir	Atropine	Amiodarone
Furosemide	Aminoglycosides	Allopurinol	Bromocriptine	Amiloride
Ibuprofen	Aspirin	Caffeine	Ciprofloxacin	Azithromycin
Heparin	Atenolol	Captoprile	Clonidine Enalaprile	Amlodipine
Warfarine	Insulin	Isoniazid	Diazepam	Clonazepam
	Losartan	Lidocaine	Metoclopramide	Chloroquine
	Penicillin	Metronidazole	Propranolol	Diltiazem
	Prednisolone	Nifedipine		Digoxin
	Phenobarbital	Paracetamol		Haloperidol
	Theophylline Quinidine	Ranitidine		Tricyclic antidepressants

Anatomic barriers

- Types of anatomical barriers:
  - **Blood-brain barrier**
  - Blood-ocular barrier
  - Blood-placenta barrier
- Blood-brain barrier consists of a continuous layer of endothelial cells joined by tight junctions.
- The brain is inaccessible to hydrophilic drugs.
- Inflammation (meningitis) can disrupt the integrity of the blood-brain barrier, allowing normally impermeable substances to enter the brain.



Plasma protein binding



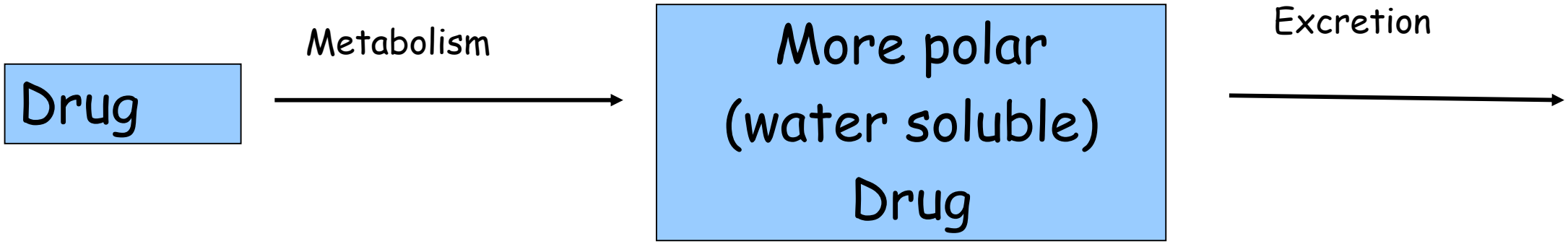
Unbound form is free to move into the tissue and is the active form

Bound form acts as reservoir

Plasma protein binding is affected only in sever hypoalbuminemia or due to drug-drug interactions

Drug metabolism

The chemical modification of drugs with the overall goal of getting the drug more soluble to be excreted



Drug metabolism outcomes:

Active drug → Inactive metabolites

Active drug → Active metabolites

Inactive prodrug → Active drug

Pro-drug	Active pharmacological compound
Enalapril	Enalaprilat
Perindopril	Perindoprilat
Lovastatin	Beta-hydroxy acid.
Valacyclovir	Acyclovir
Azathioprine	6-mercaptopurine (6-MP) and thioguanine (6-TGN)

Pro-drugs are the drugs without own pharmacological activity which is metabolized to the active compound

Sites of drug metabolism

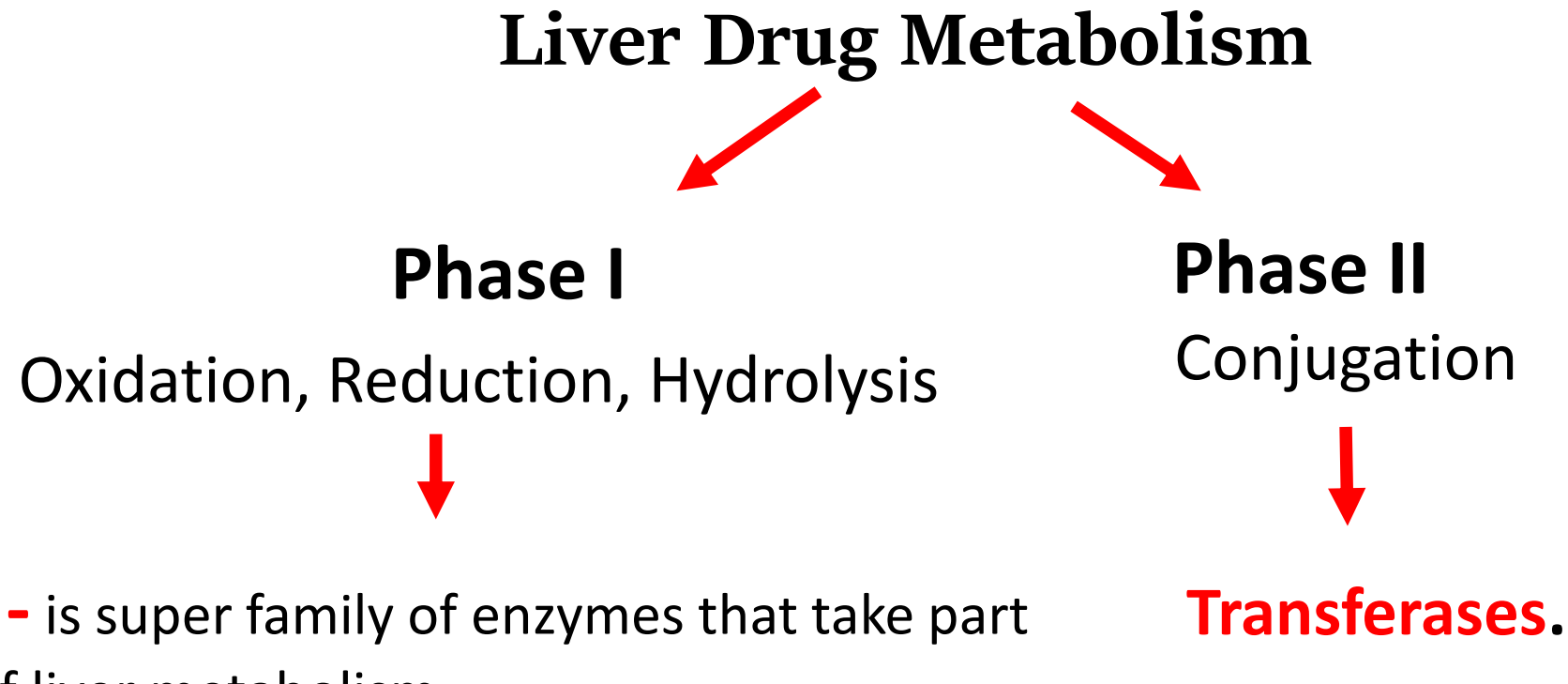
In the organs

- **Liver**
- Small intestine
- Kidney
- Skin
- Lungs
- Plasma
- All organs of the body

Intracellular

- Cytosol
- Smooth endoplasmic reticulum (microsomes)
- Mitochondria
- Lysosomes

Liver drug metabolism



CYP 450 - is super family of enzymes that take part in phase I of liver metabolism.

Transferases.

Drugs affecting CYP450

Inhibitors of CYP450

- Amiodarone
- Cimetidine
- Erythromycin
- Statins
- Valproate
- Omeprazole
- Isoniazid
- Itraconazole, Ketoconazole

Inducers of CYP450

- Rifampicin
- Phenobarbital
- Carbamazepine
- Alcohol
- Broccoli, cauliflower, cabbage

Drug excretion

- Excretion of the drugs and their metabolites may be via: Kidney, lung, bile, gut, skin, breast milk, tears etc.
- The kidney is the most important organ for excretion of drugs.
- Renal excretion includes:
  - Glomerular filtration
  - Tubular secretion
  - Tubular reabsorption

Pharmacokinetics parameters

Absorption

Distribution

Metabolism

Excretion

Bioavailability (F)

Volume of distribution (Vd)

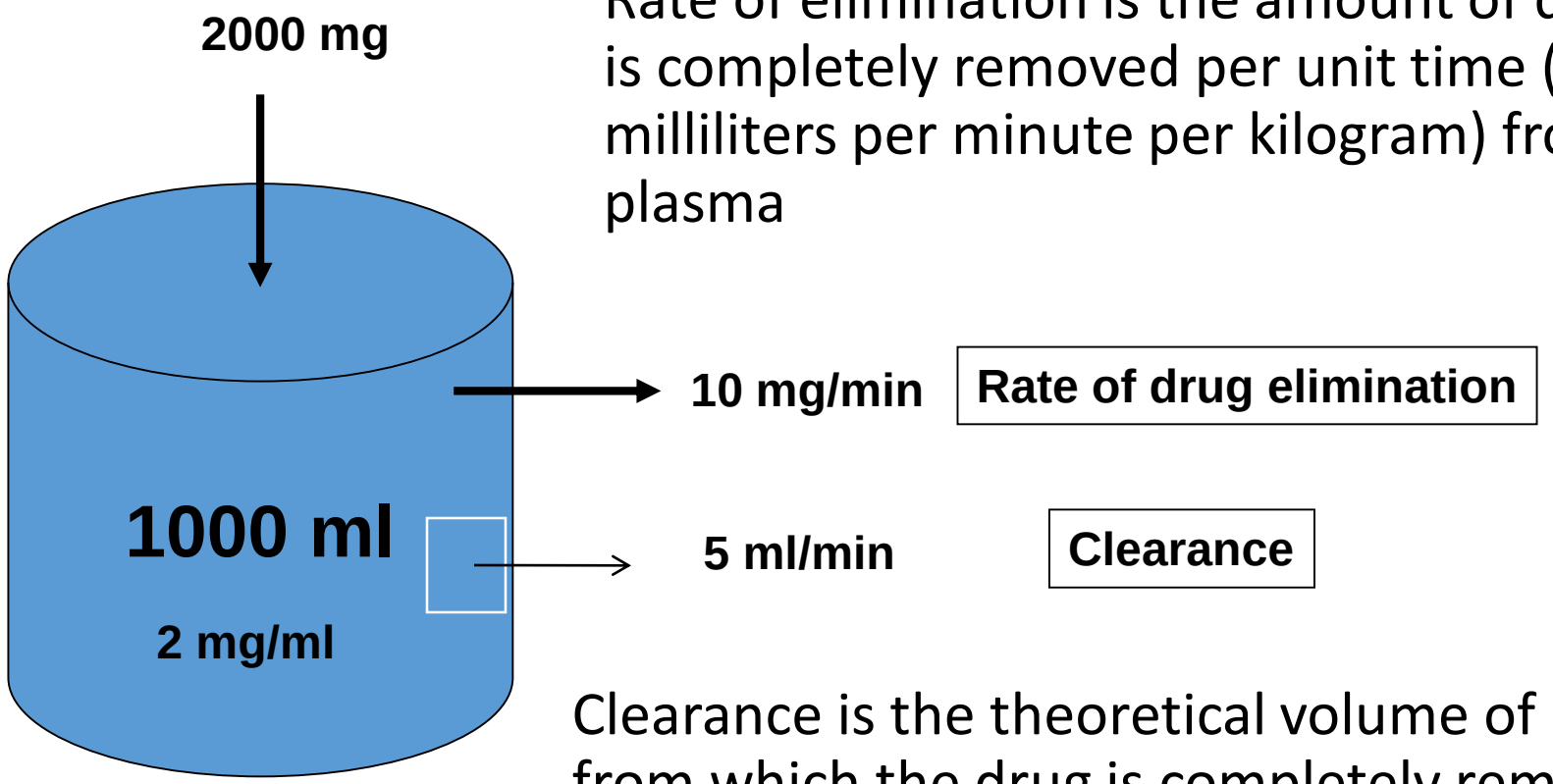
Elimination

Clearance (Cl)

Plasma half-life ($t_{1/2}$)

Steady-state concentration (Css)

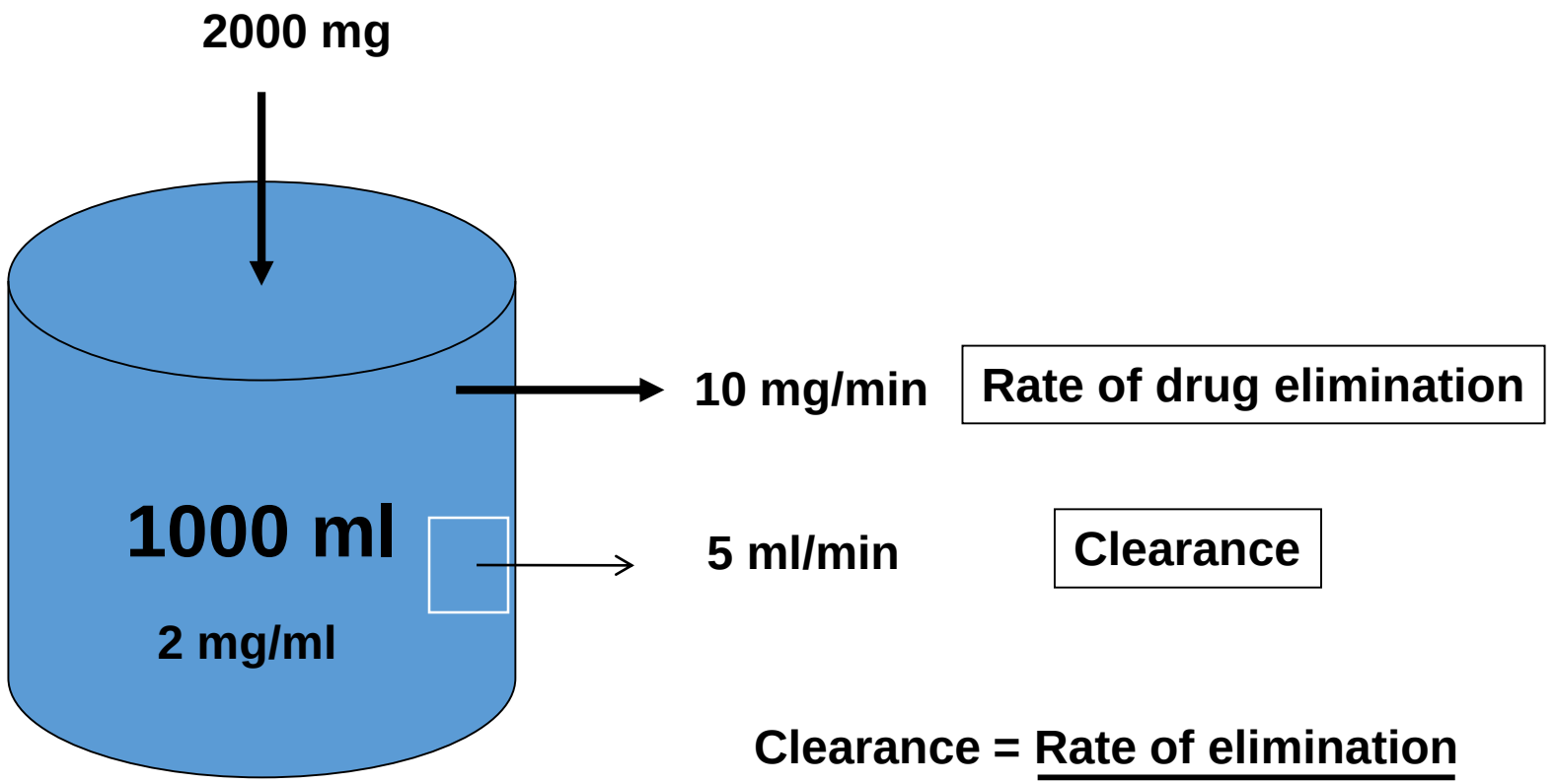
Pharmacokinetic parameters



Rate of elimination is the amount of drug that is completely removed per unit time (*e.g.,* milliliters per minute per kilogram) from the plasma

Clearance is the theoretical volume of plasma from which the drug is completely removed per unit time (*e.g.,* milliliters per minute per kilogram).

Pharmacokinetic parameters



$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Concentration}}$$

Clearance is the measure of the ability of the body to eliminate the drug.

Maintenance dose

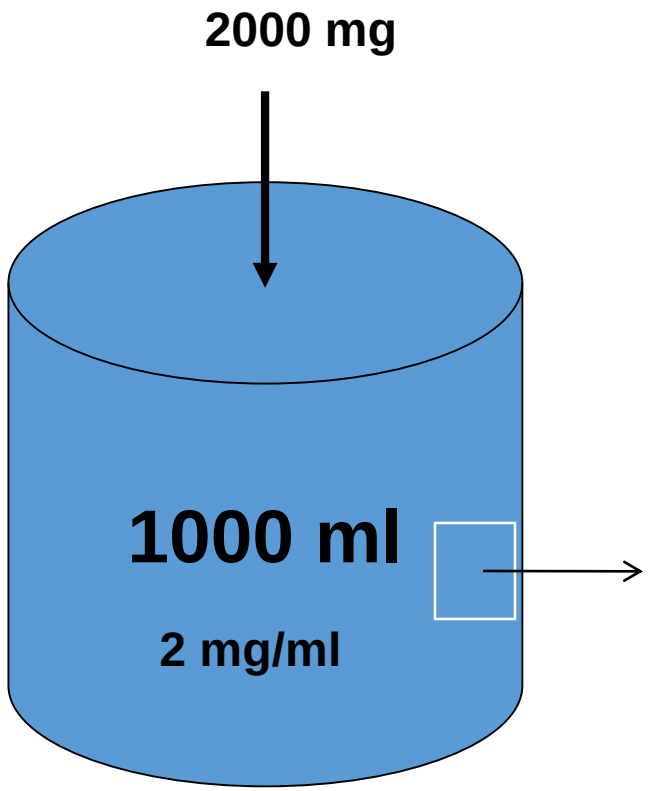
- Is defined as the theoretical volume of plasma from which the drug is completely removed per unit time (*e.g.,* milliliters per minute per kilogram).

What is the clinical significance of Cl??
Calculation of **MAINTENANCE DOSE**

Is used to maintain a steady-state concentration of drug within the therapeutic window.

Maintenance dose (Md) = Css(targeted) x Cl

Maintenance dose



5 ml/min (CLEARANCE)
=10 mg/min

MD = Clearance X target concentration

Elimination half-life

- Half-life ($t_{1/2}$) is the time required to reduce the amount of drug in the body by one-half.

- It is expressed as:

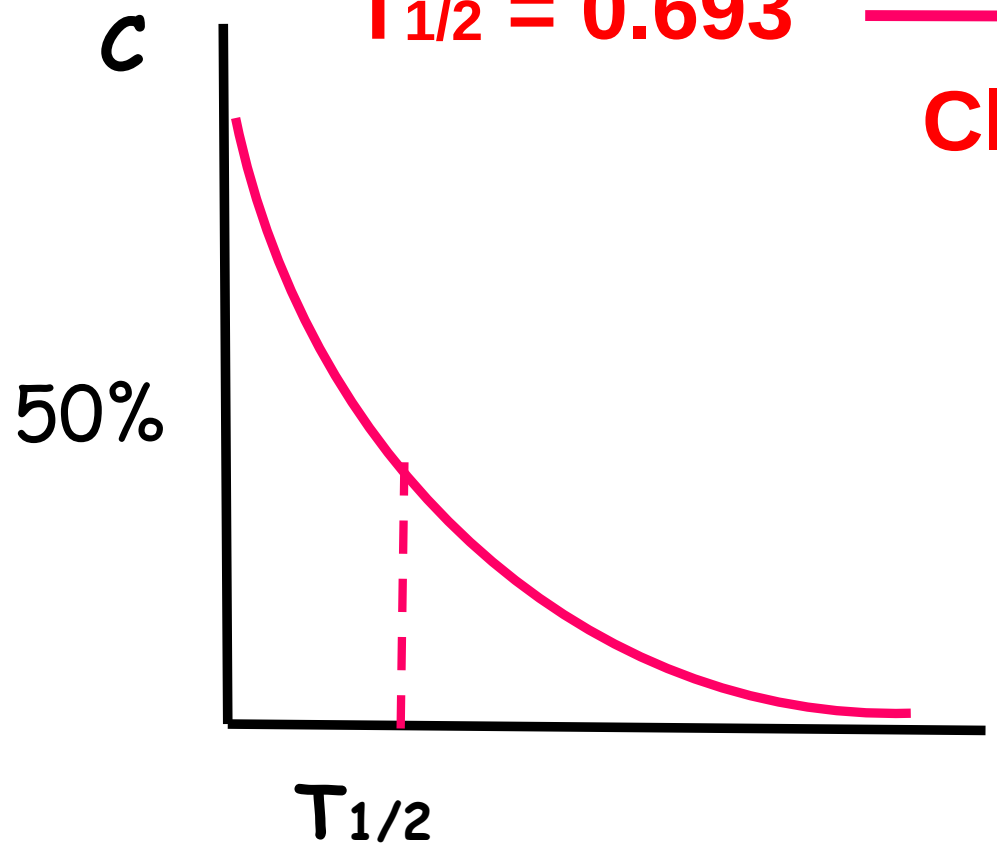
$$\textbf{Plasma half life } (t_{1/2}) = \frac{0.693}{k} \qquad \textbf{Plasma half life } (t_{1/2}) = \frac{0.693Vd}{Cl}$$

The constant 0.693 = log of 2. k=elimination rate constant

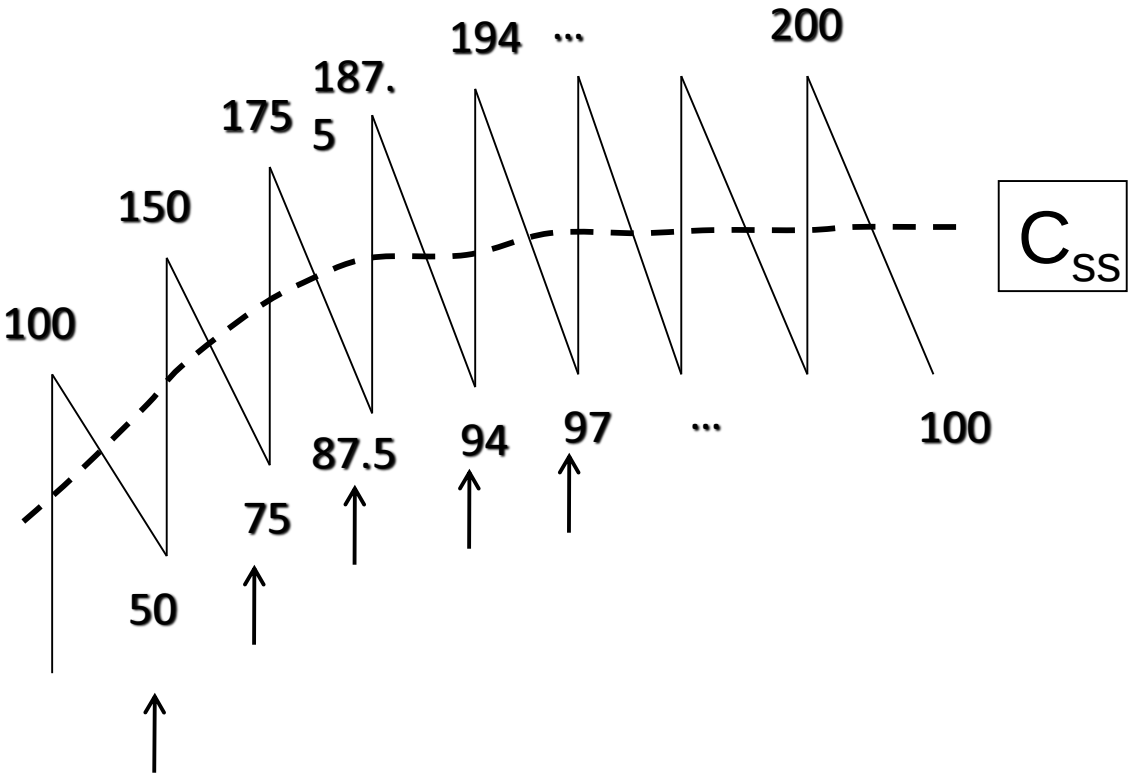
Half-life and Time to Reach Steady-state

- Half-life (t1/2) is the time required to change the amount of drug in the body by one-half.
- t1/2 does not change with increase in dose with first order kinetics but increases with zero order kinetics.
- t1/2 helps to calculate time required to reach steady state on repeated administration.

$$T_{1/2} = 0.693 \frac{Vd}{Cl}$$



Steady-state



- At steady-state is the rate of drug administration equals the rate of elimination:

  Rate in = Rate Out

Time required to reach the steady-state remains constant, non-dose related (1st order kinetics) and it takes from 4 to 5 T1/2

Time to reach Css/Steady-state

Drugs	Half life (hrs)	Time to reach Steady-state
Lidocaine	2	8 - 10 hrs
Valproate	6	24 - 30 hrs
Digoxin	32	6-7 days
Amiodarone	50 days	6-7 months

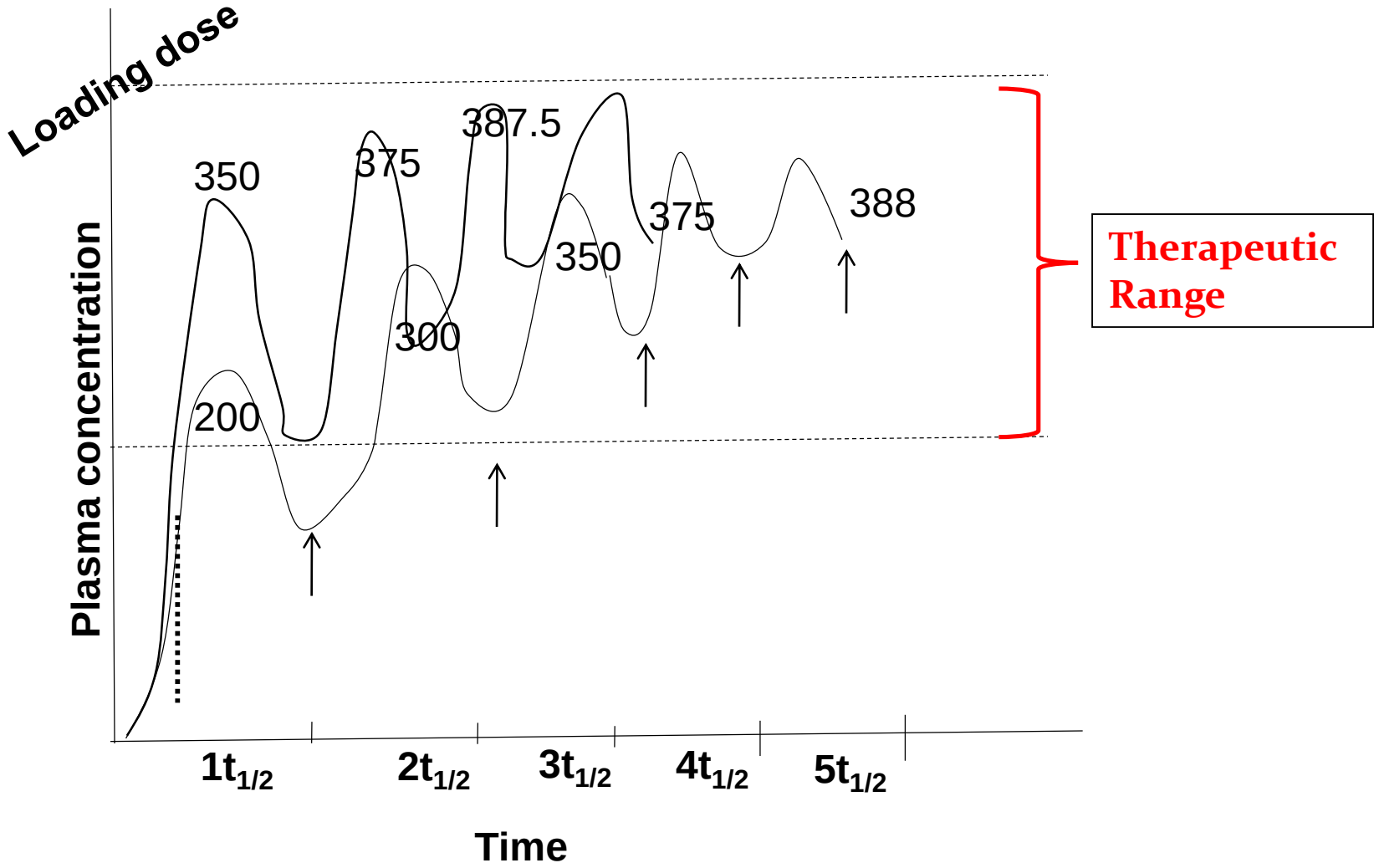
Loading dose

- The *loading dose* is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly but it does not reduce time to reach Css.
- Is required for the drugs with high Vd.
- Are often given parenterally and rapidly.

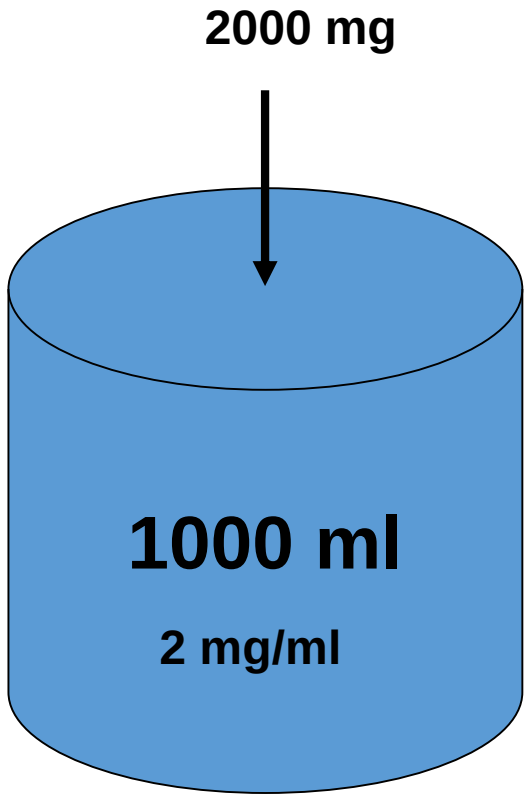
If we know the target concentration and volume of distribution, we can calculate the loading dose.

Loading dose (LD) = Cp(targeted) x Vd

Loading dose



Loading dose



Amount to be administered
=Volume X target concentration

1000 X 2 = 2000 mg

Loading dose =
Volume of distribution X target concentration

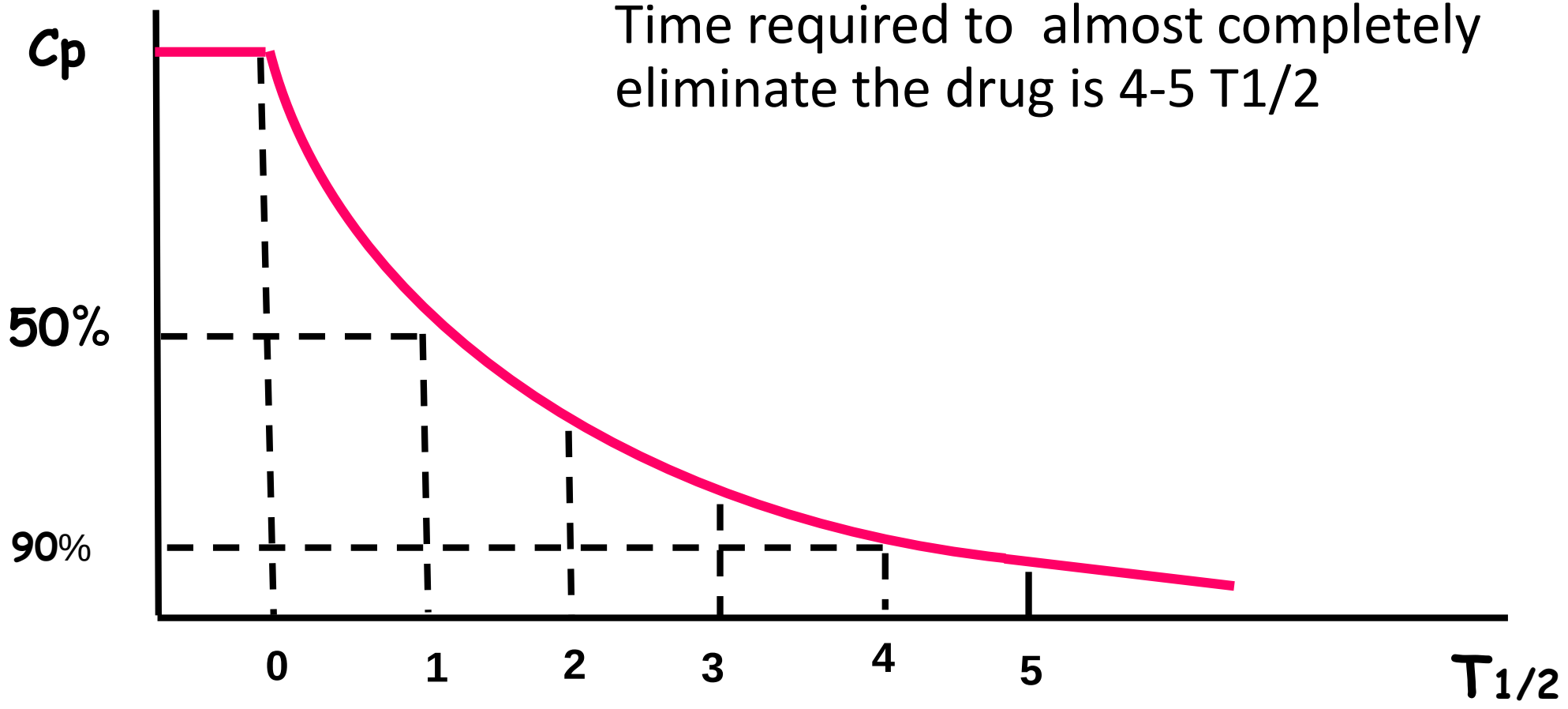
Loading dose

The high risk of toxic and adverse effects

Increases the risk of toxic effects as the plasma concentration may exceed maximum non-toxic level.

- To avoid the toxicity
  - loading dose can be given into a number of smaller fractional doses over a period of time.
  - Alternatively, the loading dose can be administered as a continuous intravenous infusion over a period of time.

Drug Elimination

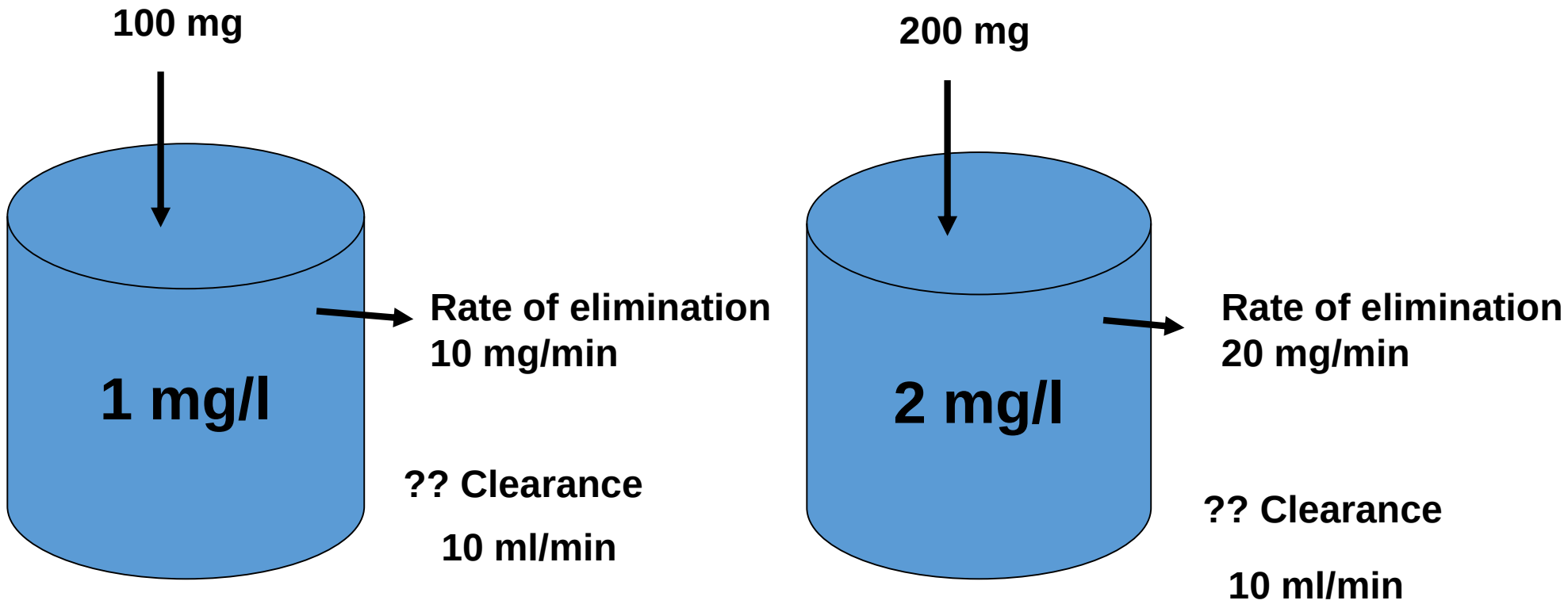


Time required to almost completely eliminate the drug is 4-5 T1/2

First order kinetics

Majority of drugs follow **first order kinetics.**

A **constant fraction** is excreted per unit time.

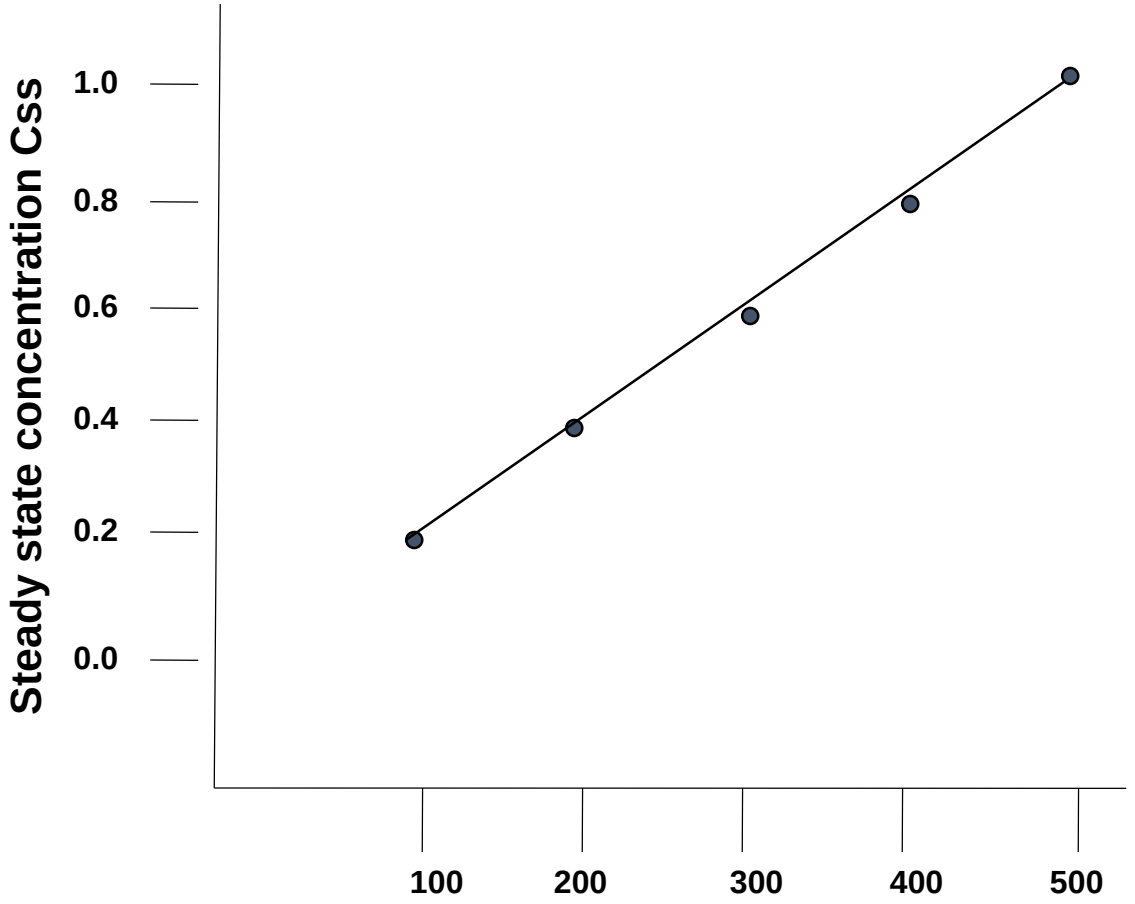


What about $t_{1/2}$???

First order kinetics

- A constant fraction is excreted per unit time.
- Amount excreted per unit time increases proportionately with increase in dose because Elimination processes are not saturated.
- Clearance remains constant with change in dose.
- t1/2 does not change with increase of does.

First order kinetics



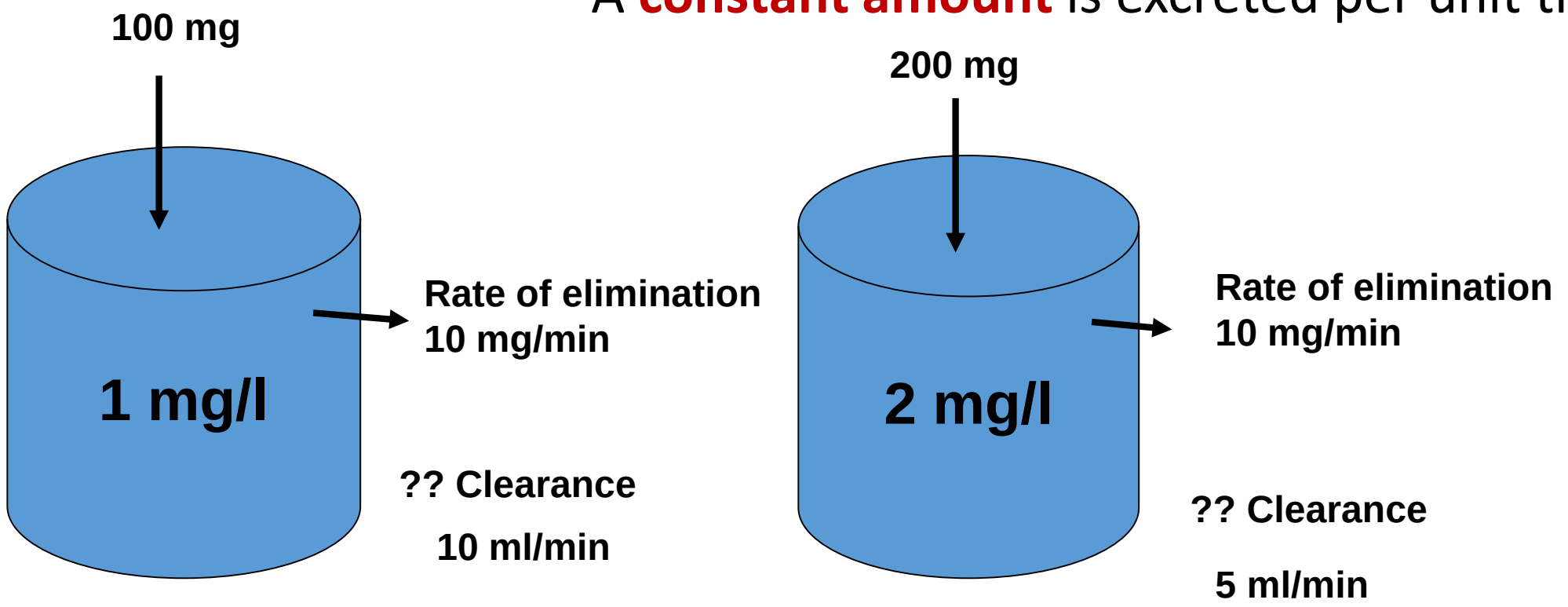
Steady state concentration increases proportionately with increase in dose

LINEAR KINETICS

Zero order kinetics

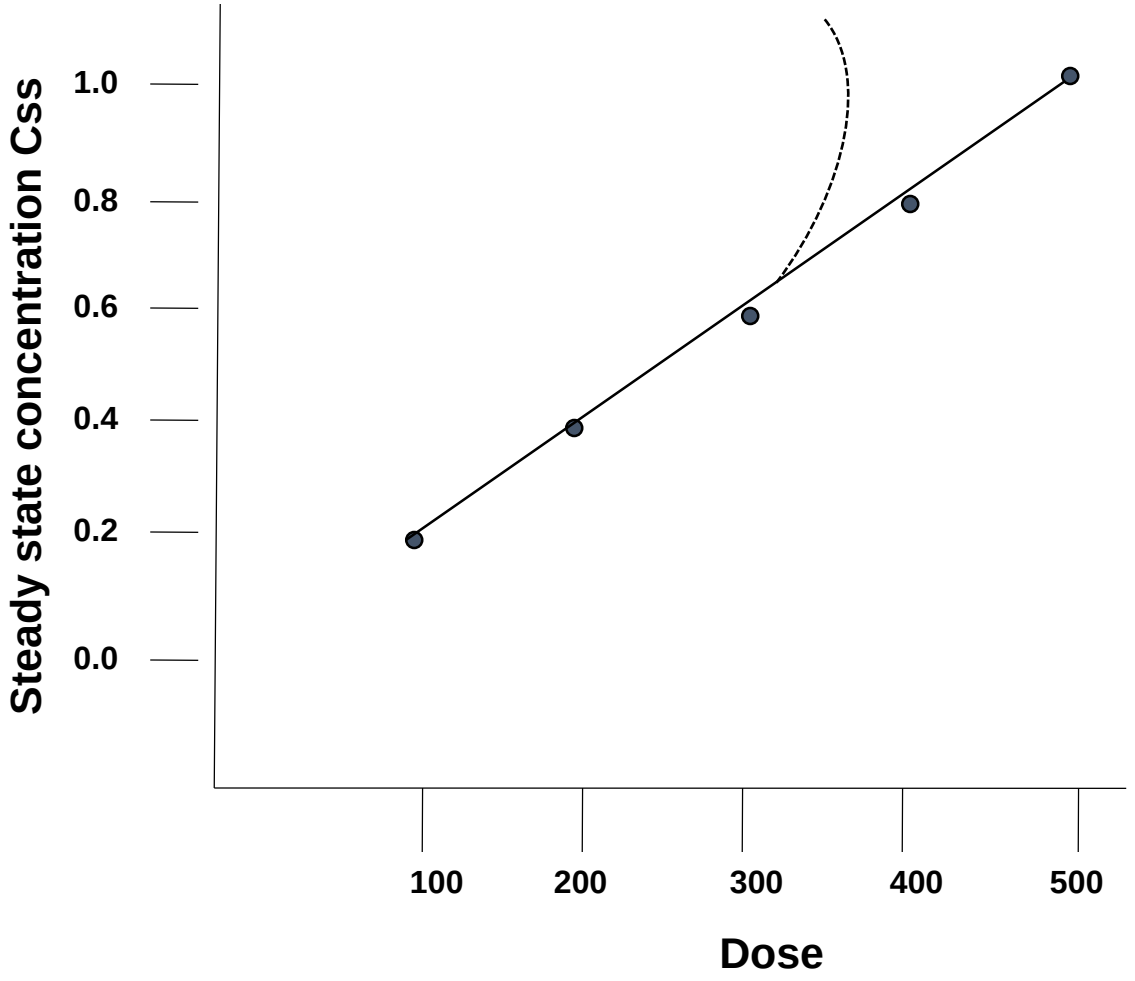
If the elimination processes become saturated elimination follows **zero order kinetics.**

A **constant amount** is excreted per unit time.



What about $t_{1/2}$???

Zero order kinetics



Steady state concentration increases disproportionately with incraese in dose

NONLINEAR KINETICS

Zero order kinetics

- A constant amount is excreted per unit time.
- Amount excreted per unit time does not increase proportionately with increase in dose because Elimination processes are saturated.
- Clearance decreases with increase in dose.
- $t_{1/2}$ increases with increase of dose.

Drug dosing calculations

Clinical problem № 1

The therapeutic concentration of theophylline is

Css = 15 mg/L

The apparent volume of distribution of theophylline is Vd = 0.5 L/kg.

The clearance of theophylline is

Cl = 0.04 L/h · kg.

Define the loading (Ld) and maintenance (Md) daily doses of this drug for 50 kg patient.

Drug dosing calculation

Loading dose (Ld)= Cp x Vd,

$$Ld = 15\ mg/L \cdot 0.5\ L/kg \cdot 50\ kg = 375\ mg$$

Maintenance doses (Md) = Cp x Cl

$$Md = 15\ mg/L \cdot 0.04\ L/h \cdot kg \cdot 50\ kg \cdot 24\ h =$$

$$= 720\ mg/day$$

Drug dosing calculation

Clinical problem No. 2

The therapeutic concentration of amitriptyline is

Css = 0.15 mg/L

The apparent volume of distribution of amitriptyline is Vd = 15.5 L/kg.

The half-life of amitriptyline is

$T_{1/2}$ = 17 h.

Define the loading (Ld) and maintenance (Md) daily doses of this drug for 70 kg patient.

Drug dosing calculations

Loading dose (Ld)= Cp x Vd,

$$Ld = 0.15\ mg/L \cdot 15.5\ L/kg \cdot 70\ kg = 162.75\ mg$$

Half-life ($T_{1/2}$) = 0.693 · Vd / Cl, so Cl = 0.693 · Vd / $T_{1/2}$

$$Cl = 0.693 \cdot 15.5\ L/kg / 17\ h = 0.63\ L/h \cdot kg$$

Maintenance doses (Md) = Cp x Cl

$$Md = 0.15\ mg/L \cdot 0.63\ L/h \cdot kg \cdot 70\ kg \cdot 24\ h =$$

$$= 159.2\ mg/day$$

Drug dosing calculation

Clinical problem No. 3

The dose (Md) 500 mg/day of theophylline is prescribed to male patient. This dose allows to maintenance the therapeutic plasma concentration (Cp) of theophylline 10 mg/L. Th clearance (Cl) of theophylline in female patient decreases on 30%.

Define the dose of theophylline to reach 15 mg/L concentration for female patient.

Drug dosing calculation

Md = Cl x Cp so Cl/hr = Md / Cp / 24h

Cl_{male} = 500mg / 10mg/L / 24h = 2.1L/h

Cl_{female} = 30% from Cl_{male} = 0.7CL_{male}

Cl_{female} = 2.1L/h x 0.7 = 1.47L/h

Md_{female} = 15mg/L x 1.47L/h x 24h = 529mg/day

Thank you!