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PHARMACOKINETICS

Notes for Students

This study material is exclusively for students of general medicine and stomatology in Pharmacology I course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.

Basic principles of pharmacokinetics

Pharmacokinetics is aimed on this processes:

- absorption
- distribution
- biotransformation
- excretion of drugs

and their relation to pharmacologic (therapeutic or toxic) effects

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Pharmacokinetics

absorption	**A**	**invasion**	**“ADME“**
distribution	**D**		
metabolism	**M**	**elimination**	
excretion	**E**		

- processes of **ADME**

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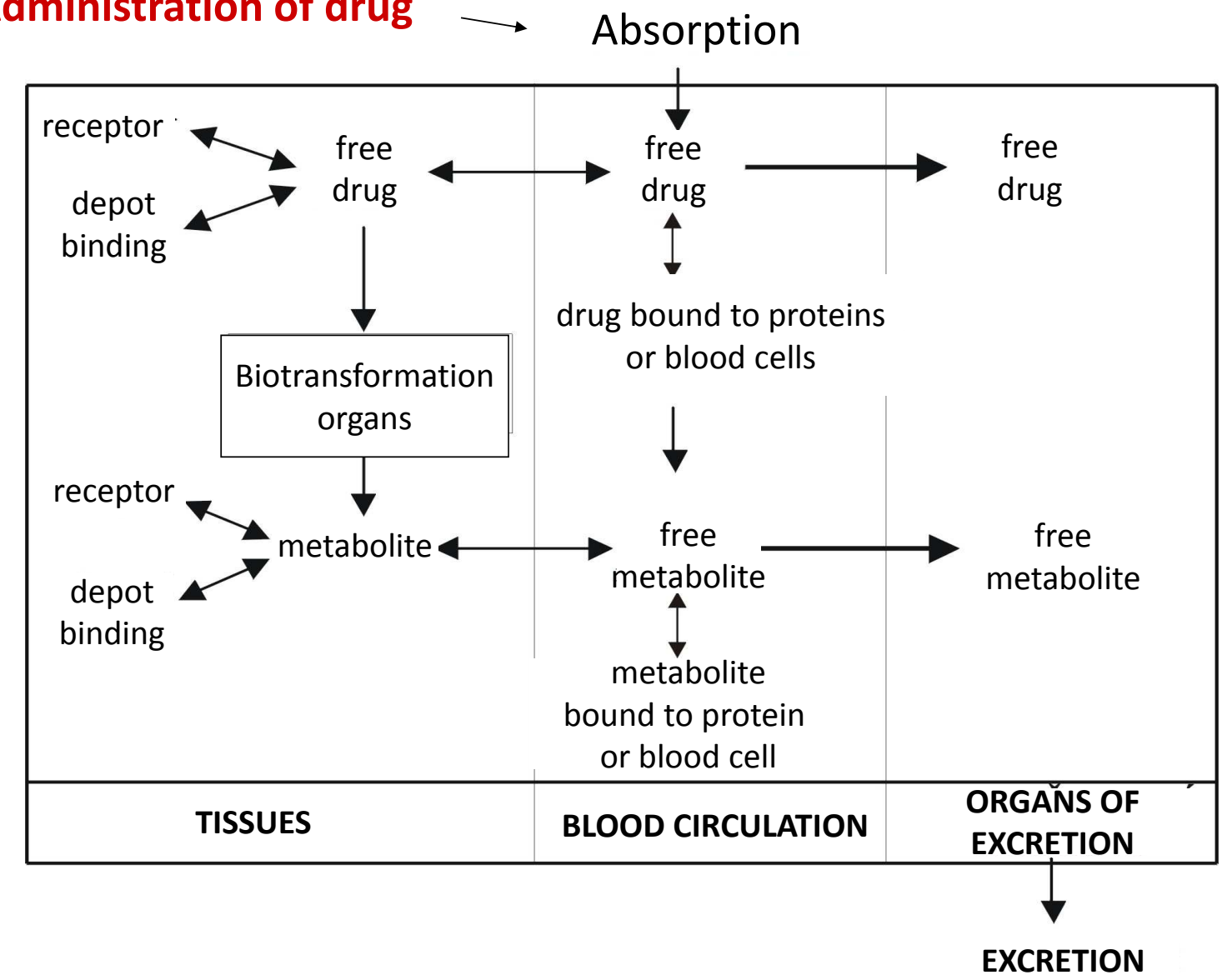
Administration of drug



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General rules for drug movement

1. **Physical-chemical characteristic of drug**
   - lipophilic vs hydrophilic, size, charge, pKa, solubility
2. **Drug transmission through biological barriers**
   - lipophilic - pasive diffusion
   - hydrophilic- pore transmission
   - active transport
   - vesicular transport – pinocytosis, phagocytosis
3. **Drug binding**
   - plasmatic proteins
   - blood cells
   - tissue binding
   - receptor binding
4. **Tissue perfusion**
   a) brain, heart, liver and kidney
   b) adipose tissue

http://icp.org.nz/icp_t11.html

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Absorption – routes of administration

- penetration of dissolved drug from the site of administration to blood (systemic circulation) – necessary for general effect**– systemic effect**
- **Local effect:**
  - on skin, mucosas or ventricles
  - absorption is undesirable – possible AE
  - ie. local corticoids, local anesthetics

Speed and **extent** of absorption are described by P-kinetic parameters:

C_{max} max. concentration of drug in plasma after single dose

T_{max} time, when drug reach c_{max} (speed)

F bioavailability (extent)

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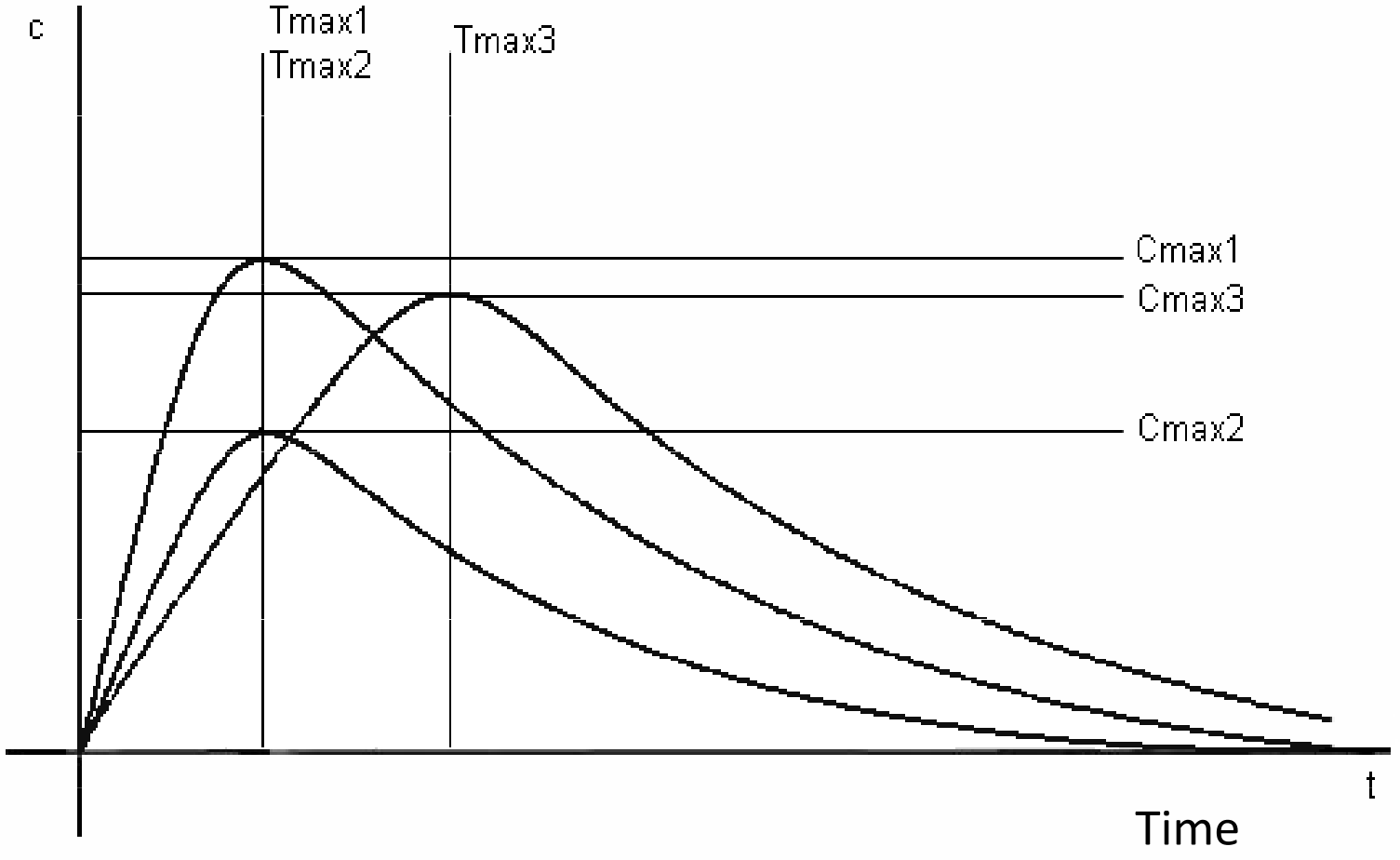
Concentration of drug



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Bioavailability- F

- **how much from the administered dose get to circulation**

extravascular administration - 0-100% (resp. 0-1)

intravenous (intravascular) - 100% = 1

- if F is < 20 % = 0 - 0,2 – it not worth to administer the drug by this way

(some of them are administered through that - SET, bisfosfonates)

- the measure of bioavailability is the **area under the curve** (AUC)

http://icp.org.nz/icp_t6.html

- AUC_{po}

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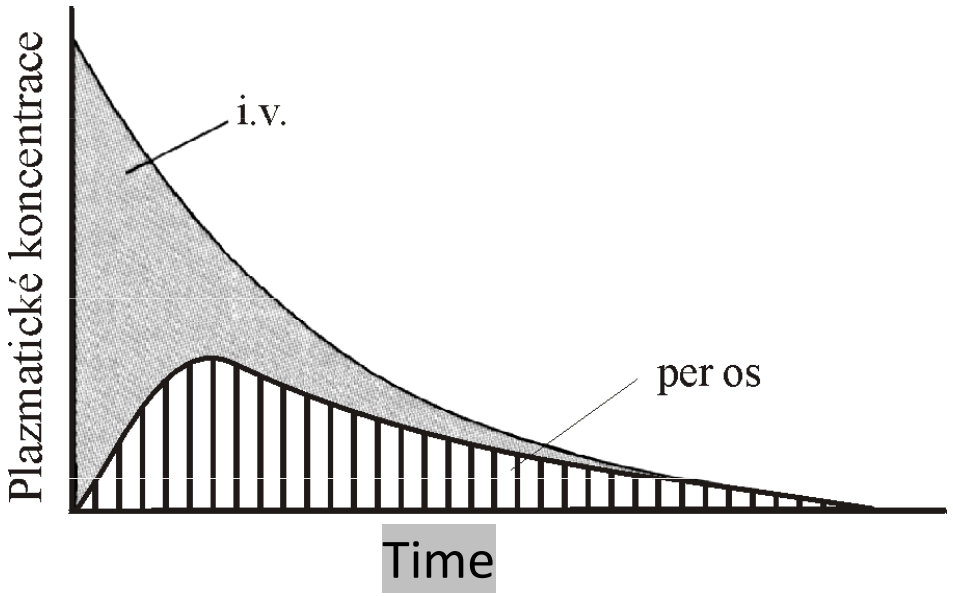
AUC – area under the curve



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Bioavailability- F

- **Absolute bioavailability**
  - comparing the AUC of administered drug in the test dosage form and the AUC after i.v. drug administration

- **Relative bioavailability**
  - assess the expected biological equivalence of two preparations of a drug
  - if the relative bioavailability = 1 (100%) → tested preparation is bioequivalent to the reference

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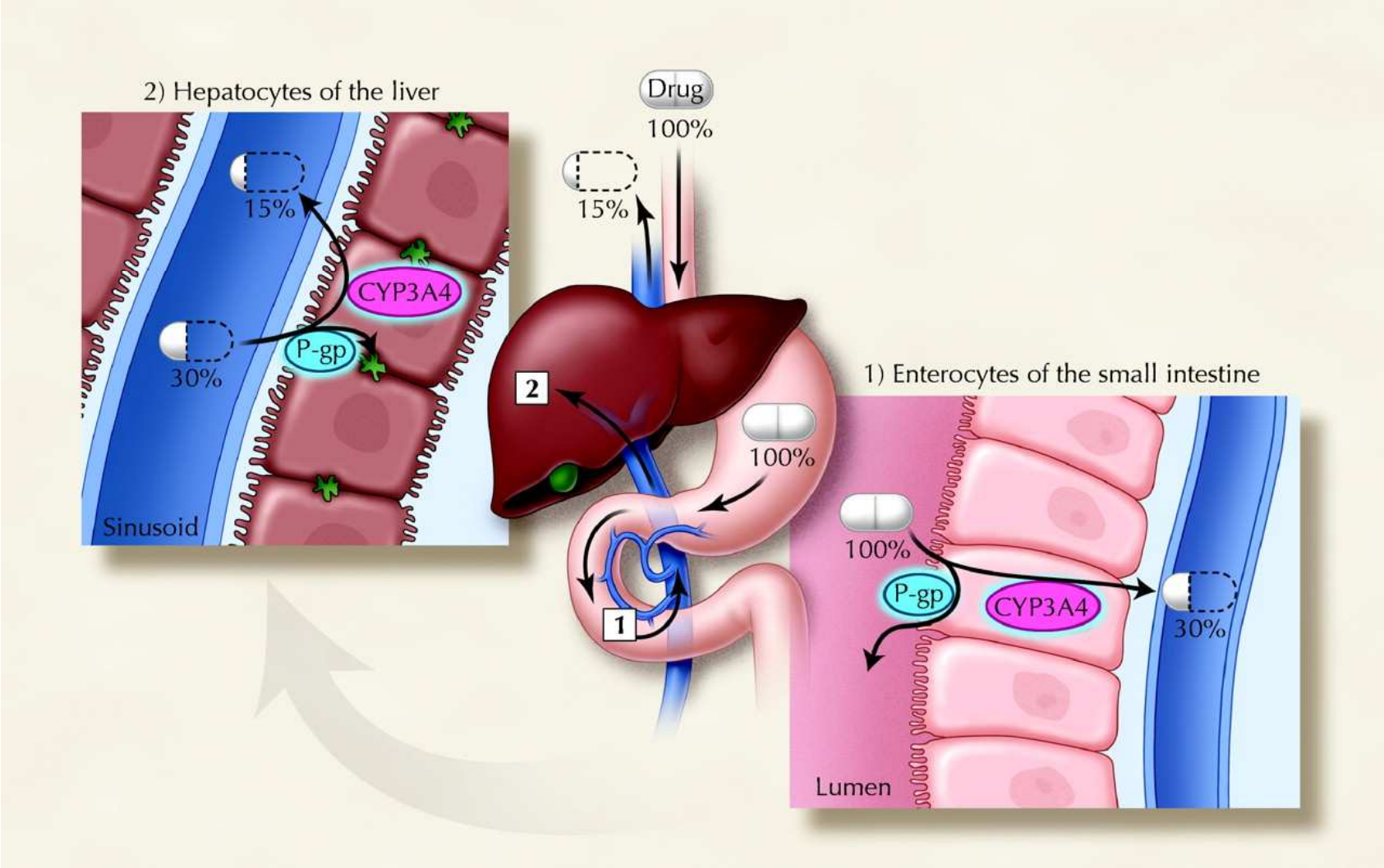

David G. Bailey, and George K. Dresser CMAJ 2004;170:1531-1532

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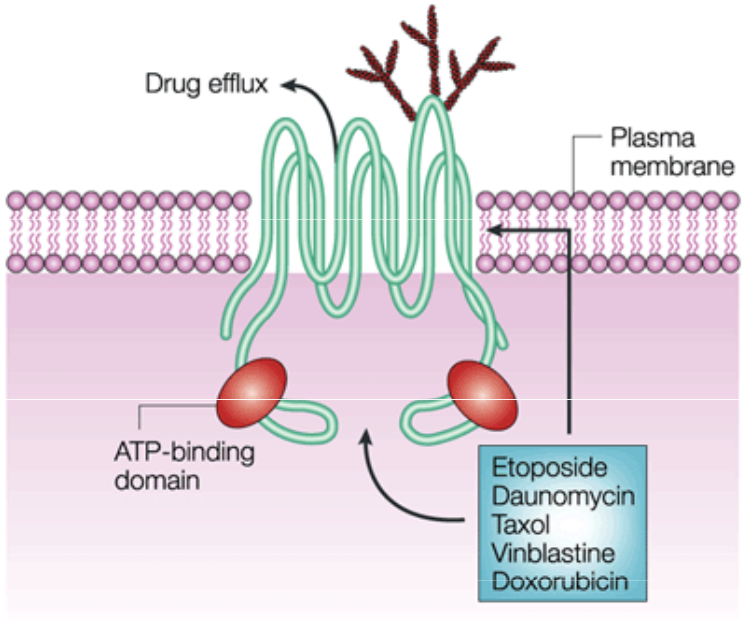
P-glycoprotein

- transmembrane pump encoded by *MDR1, ABCB1*
- drug efflux pump for xenobiotics
- multidrug resistence to chemotherapeutics



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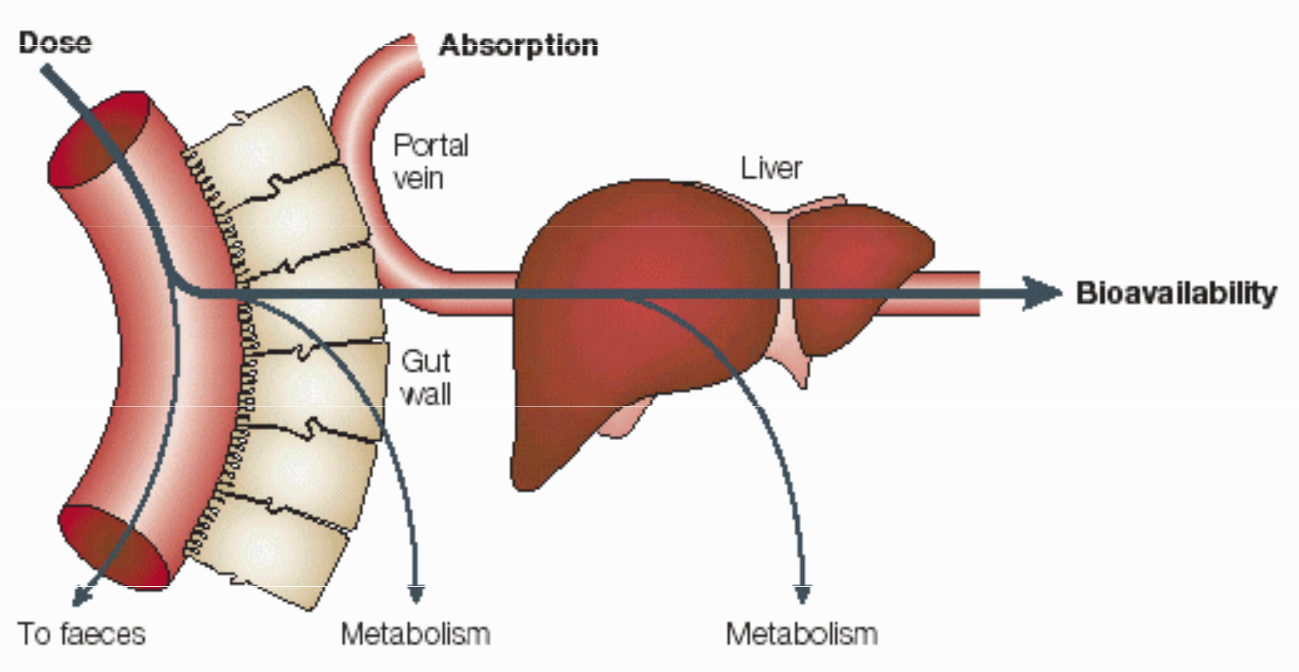
Presystemic elimination

First pass effect



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Other factors influencing drug absorption

- gender, weight, plasmatic volume, speed of gastric discharging
- age - pH, bile, enzymes
- pathophysiological defect – diseases of liver, inflammation ...
- body constitution (BW/LBM)
- diet
    - acceleration/ decceleration
    - chemical incompatibilities
    - GIT functionality

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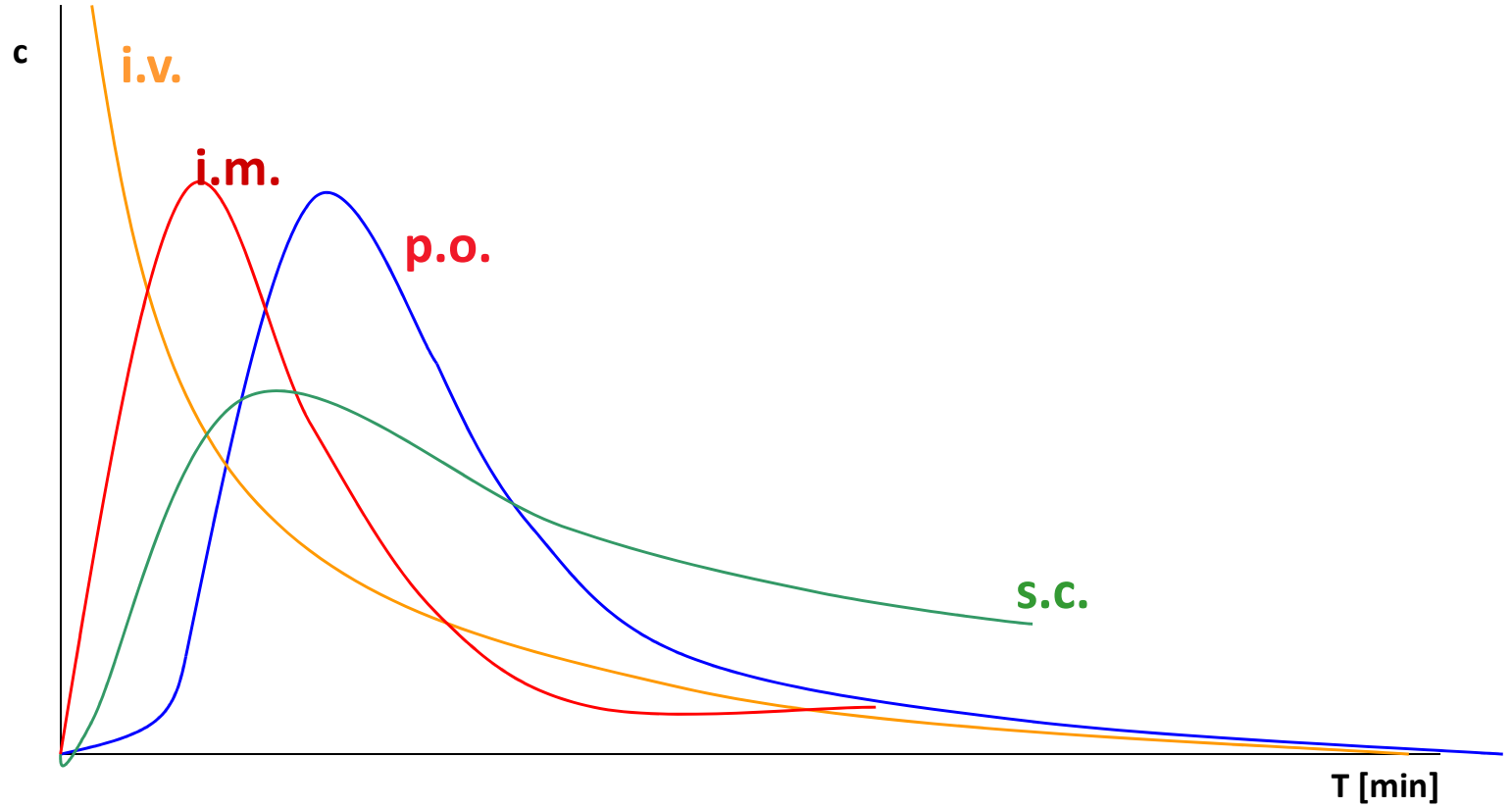

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Distribution

- Penetration of drug from blood to tissues, dynamic proces where we are interested in:

  speed of distribution- depends on:

  bindings

  membrane penetration

  organ perfusion

  status- distribution balance, free fractions of drug are equal in blood and tissue

Volume of distribution V_d

- hypothetic, theoretical volume
- rate between amount of drug in organism and plastmatic concentration

$$Vd = \frac{D \cdot F}{C_0} [l]$$

http://icp.org.nz/icp_t3.html?htmlCond=0

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The apparent volume of distribution, *V*d, is defined as the volume that would contain the total body content of the drug at a concentration equal to that present in the plasma

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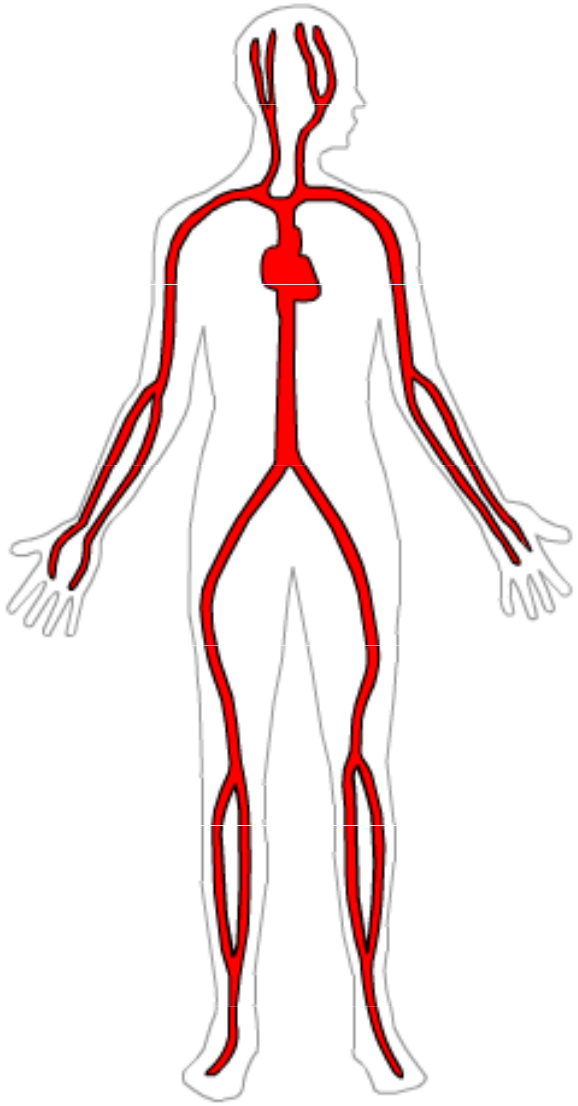

Vd

5 L

Drug concentrated
in blood stream

Drug in blood and
extracellular space

Drug equally distributed
in blood and tissues

Drug moderately
concentrated in tissues

Drug highly concentrated
in tissues
(usually adipose)

10,000 L

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

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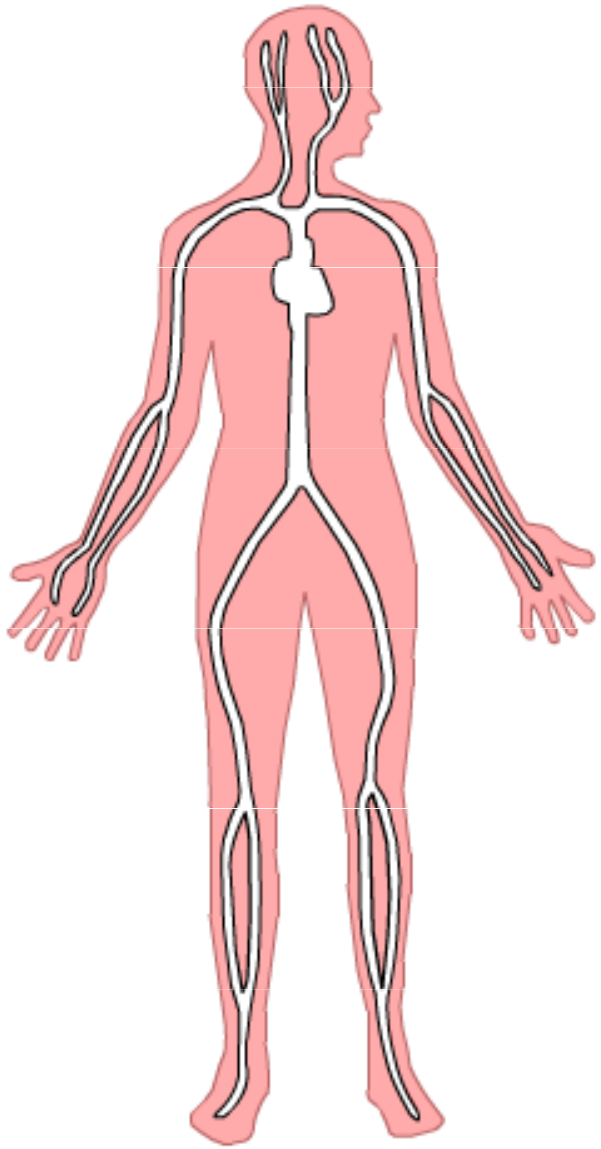

Vd

5 L

Drug concentrated in blood stream

Drug in blood and extracellular space

Drug equally distributed in blood and tissues

Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

10,000 L

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

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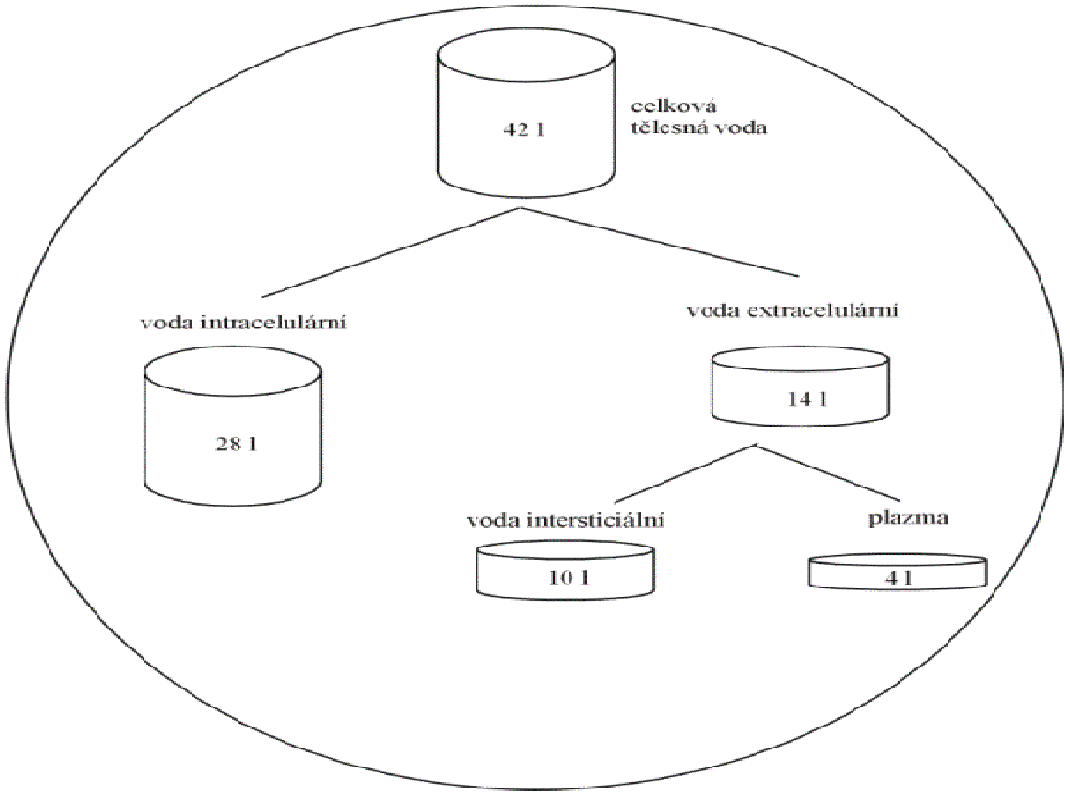
Vd = **hypothetical volume**,

Final value of Vd can be even 50000 liters (antimalarial drugs).
What does this value tell us:

We can assess distribution of the drug in the body.



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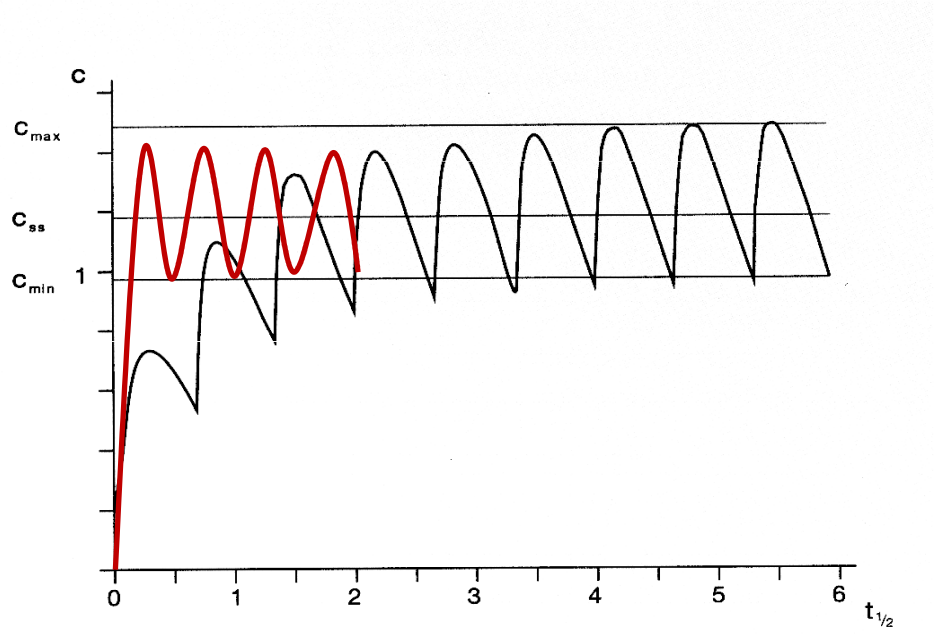
Distribution

Distribution volume - use:

Calculation of initial dose:

$$D = Vd \cdot c_T$$



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Distribution

Estimate the amount of drug in the body

$$M = Vd \cdot C$$

Assessment of the effect of hemodialysis and hemoperfusion

- drugs with higher Vd can not be eliminate from the body by these technics

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Elimination of drugs

First-order elimination

- Elimination speed is influenced by plasmatic concentration
- Linear kinetics

Zero-order elimination

- Elimination speed is not influenced by plasmatic concentration
- Non-linear kinetics

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Biotransformation - metabolism

- Predominantly in liver, but also in other organs and parts of body

Enzymatic processes

- **bioactivation (prodrug**)

  tamoxifen – endoxifen

  cyclophosphamide – phosphoramide

- **biodegradation**

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Biotransformation - metabolism

1. **Phase:**
   - oxidation, hydrolysis → drug is still partly lipophilic
   - cytochromes P450, dehydrogenases
2. **Phase:**
   - conjugation → molecules becomes hydrophilic

Metabolites

- effective („more/less“)
- inneffective
- toxic

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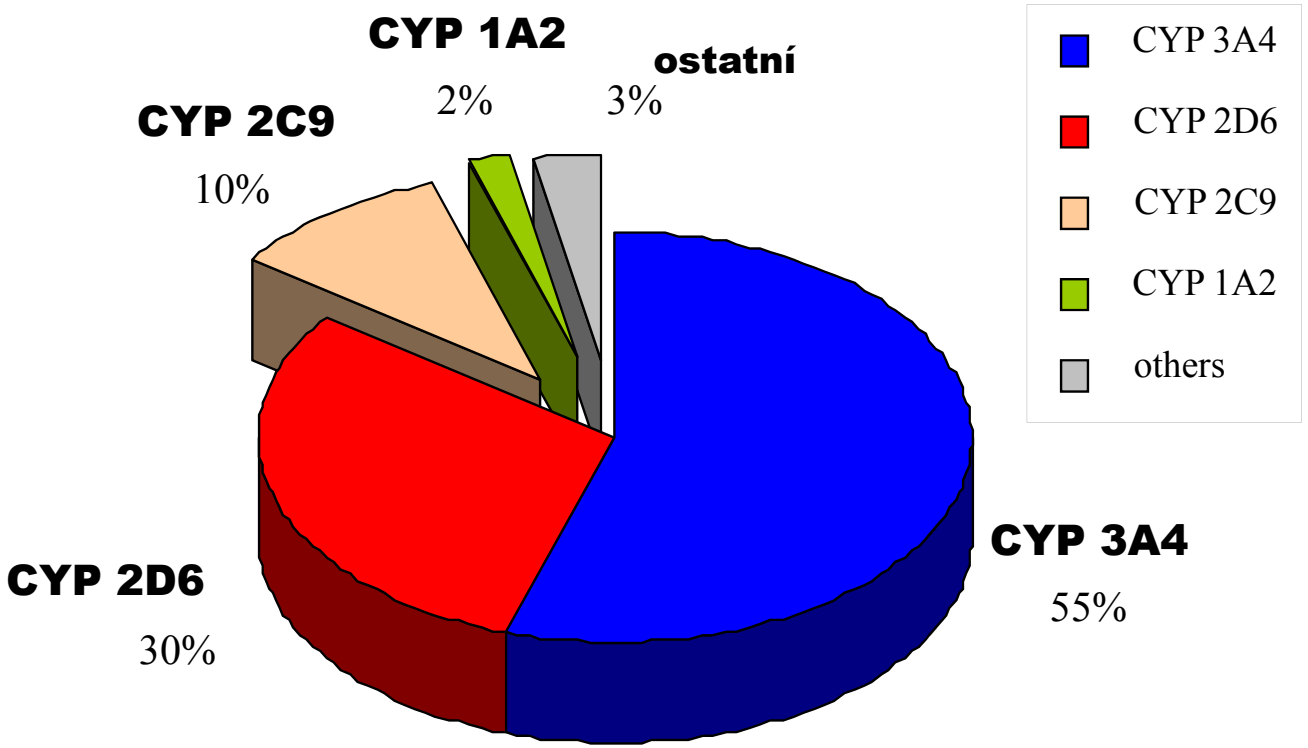
CYP 1A2
2%
ostatní
3%
CYP 2C9
10%
CYP 2D6
30%
CYP 3A4
55%
CYP 3A4
CYP 2D6
CYP 2C9
CYP 1A2
others

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Inducers of CYP450

- dexametazon
- fenobarbital
- rifampicine
- fenytoin
- St. John´s worth (Hypericum *perforatum)*
- Maidenhair Tree *(Ginkgo biloba)*

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Inhibitors of CYP450

- antidepressants (fluoxetin, fluvoxamin, paroxetin)
- chinin, chinidin
- chloramphenicol, erytromycine
- ketokonazol, itrakonazol
- grapefruit juice

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Excretion

kidneys

bile

lungs

Saliva, skin, hair, milk…

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Excretion by kidney

- MW < 60.000 D (MW of albumin = 68.000 D)
- glomerular filtration
- tubular secretion
  - organic acids
    - furosemide
    - thiazide diuretics
    - penicilins
    - glukuronids
  - organic bases
    - morfin
- tubular reabsorption
  - diazepam

alkalization

natrium hydrogencarbonate

acidification

ammonium chloride

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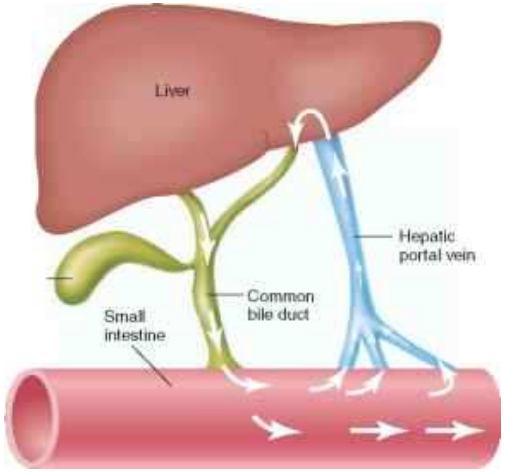
Excretion by liver

- Substances permeate through 2 membranes of hepatocytes – basolateral and apical (canalicular)
- Metabolites are excreted primary by **pasive diffusion**, further by **active transport** (glucuronides, bile acids, penicillins, tetracyclines, etc.)
- Metabolites can be deconjugated by bacterial enzymes in intestine → release of lipophilic molecule → **re-absorption**

= ENTEROHEPATIC CIRCULATION



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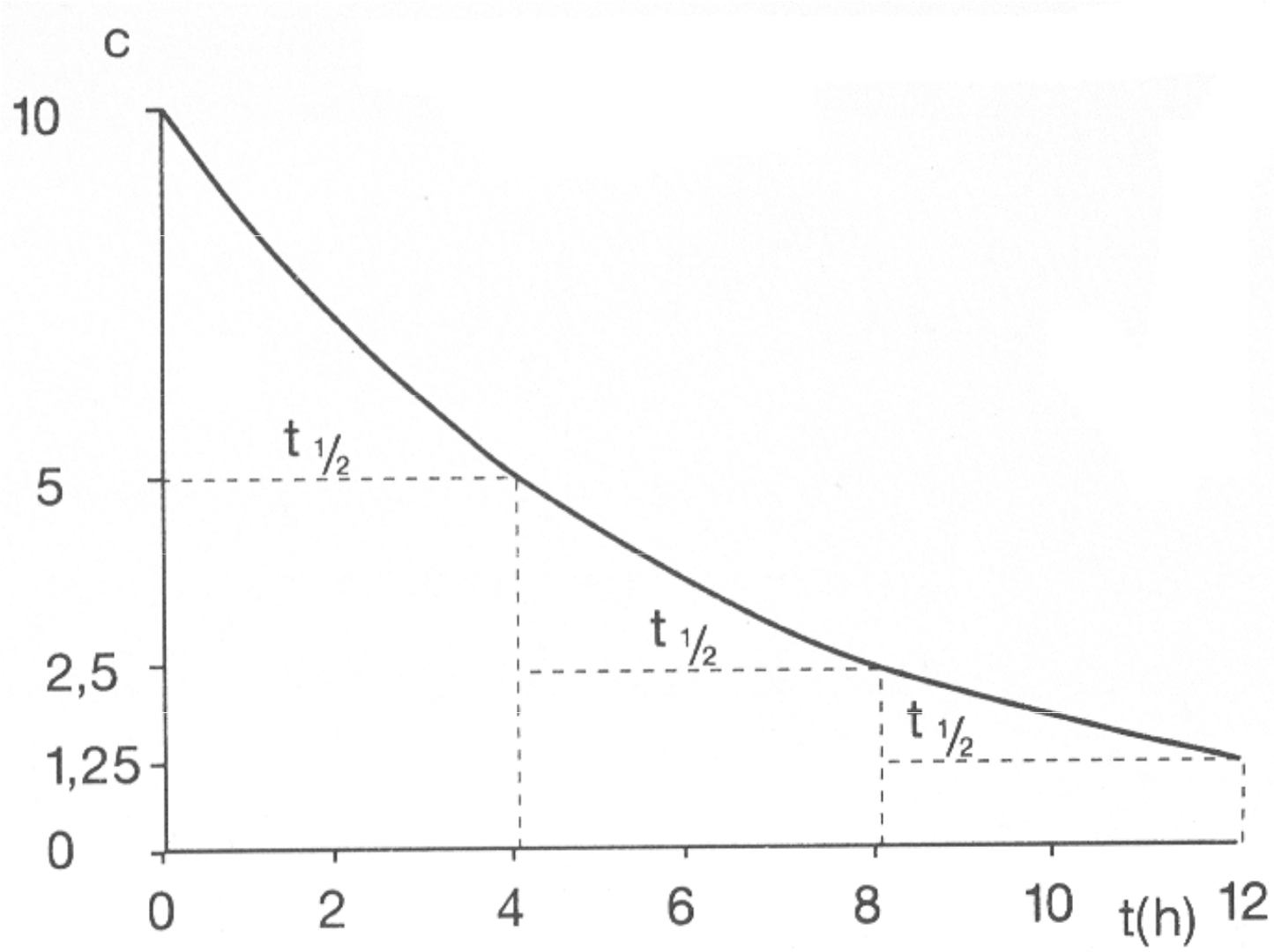

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Pharmacokinetic parameters

Mathematic description of pharmacokinetic processes and its use in drug dosage

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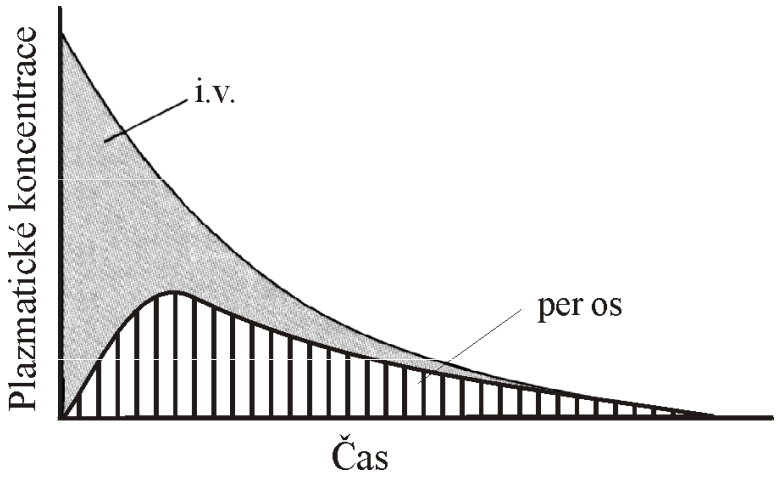
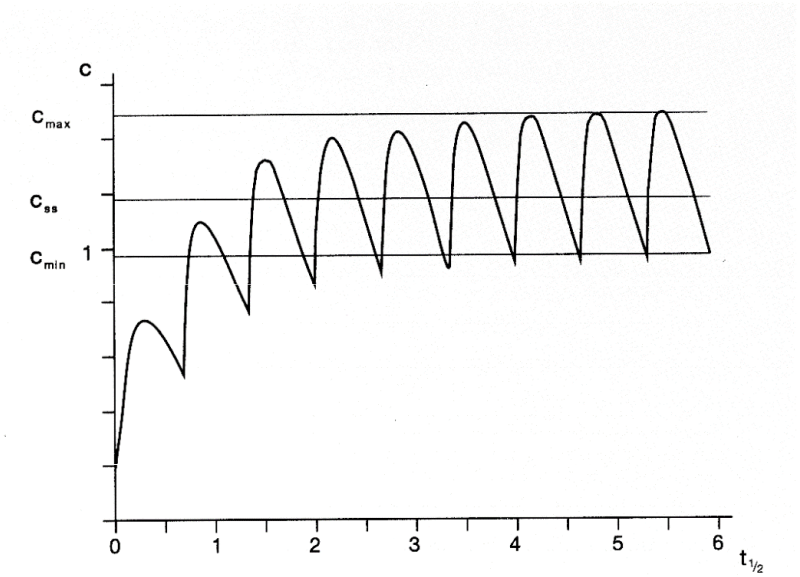
The guide for evaluation of pharmacokinetics in clinical practise is **plasma concentration/time curve** – problems with measuring in vivo





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- In accordance with concentration-time curves we determine **pharmacokinetic parameters** – model values, which provides us to describe P-kinetic processes
- There are three possible manners of drug administration with regards to concentration-time curves:

  single dose

  continuous administration

  repeated dose

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Single dose

Invasion phase

C_{max}

T_{max}

Bioavailability - F

$$F = \frac{AUC_{po}}{AUC_{iv}}$$

Volume of distribution - Vd

$$Vd = \frac{D \cdot F}{C_0}$$

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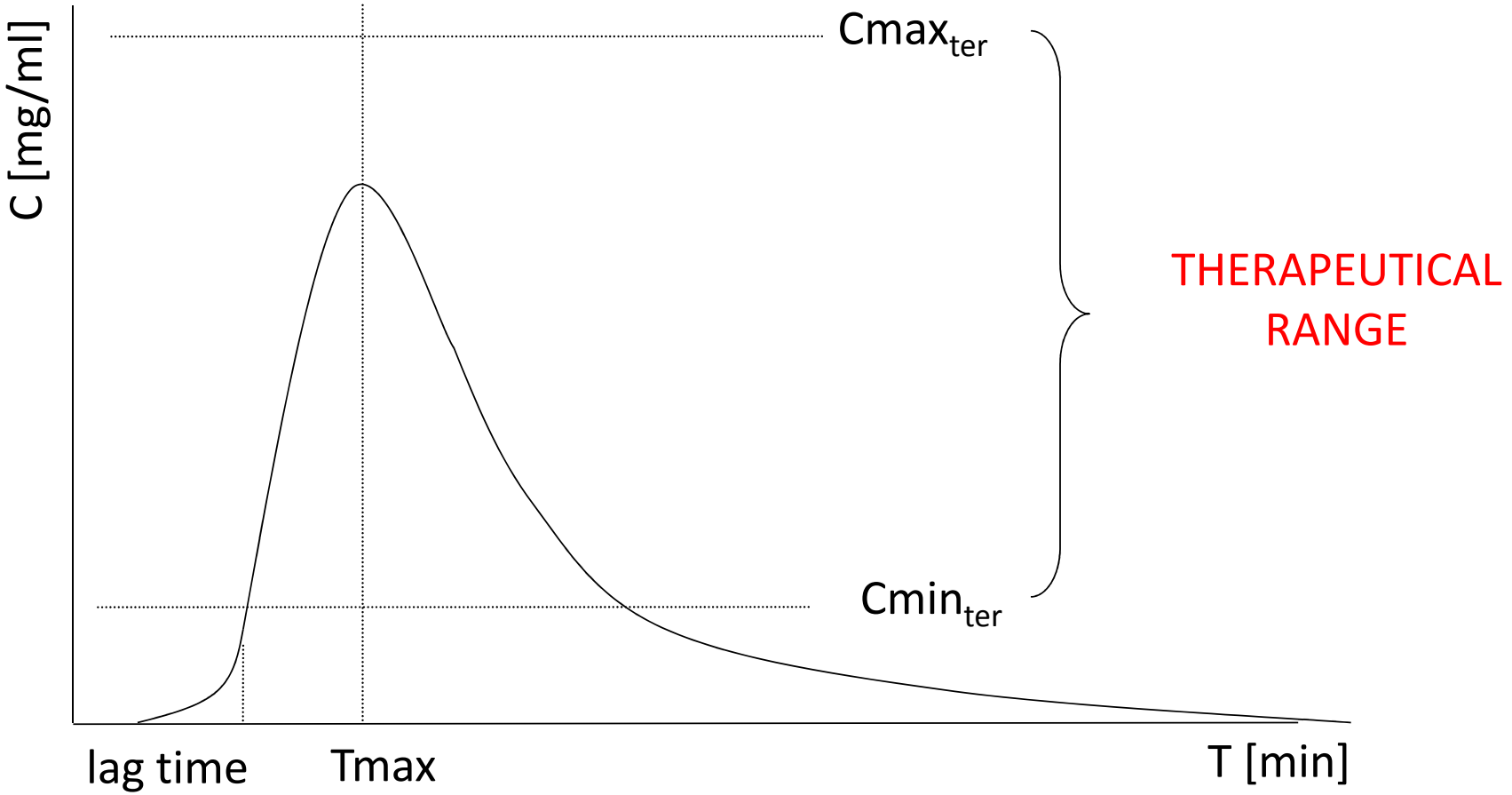
Relationship of plasmatic conc. on time



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Single dose

Elimination phase

- Drug is eliminated from the organism with speed determined by:

Elimination rate constant:

$$k_e = \frac{\ln c_1 - \ln c_2}{t_2 - t1}$$

Biological halftime – drug is totally eliminated after 4-5 halftimes

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0,7}{k_e}$$

Clearance

= volume of plasma, which is fully cleaned from drug at time unit[l . h^{-1}]

$$Cl_{TOT} = \frac{D}{AUC} = ke \,.\, Vd = Cl_{REN} + Cl_{HEP} + Cl_{PUL} \ldots$$

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Compartment models

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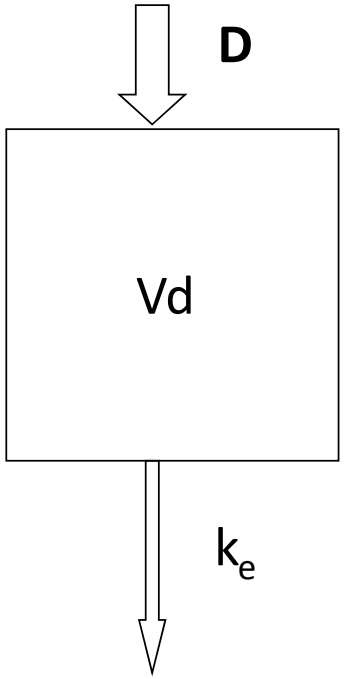
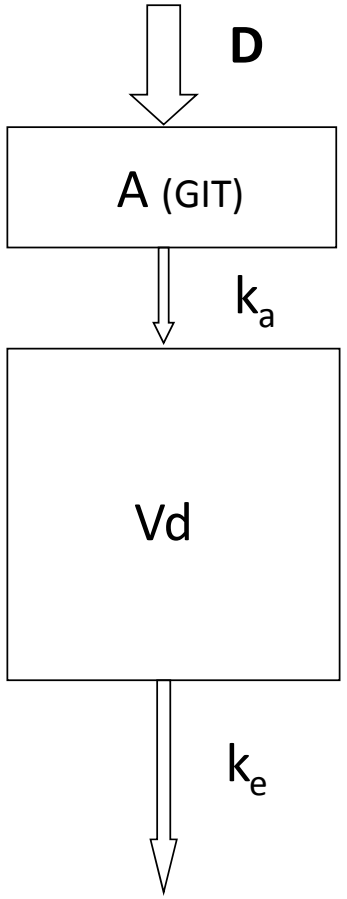
Compartment models– block schema

1- compartment model

i.v.
intake





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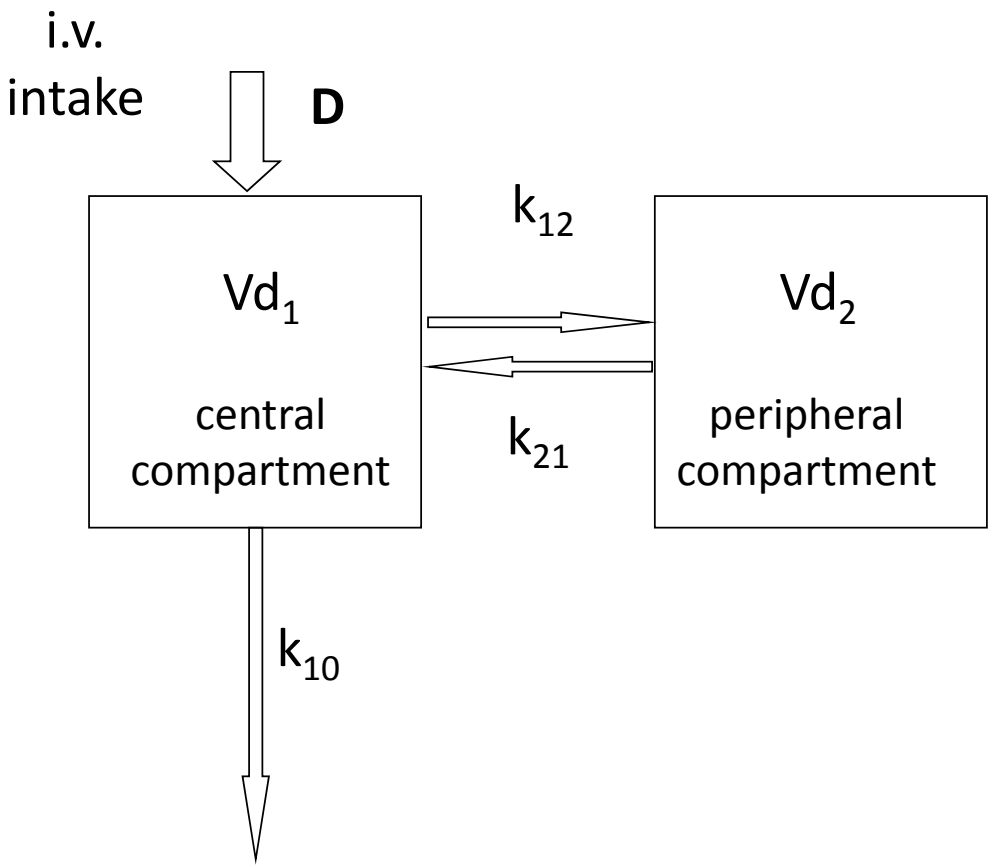
Compartment models– block schema

2- compartment model



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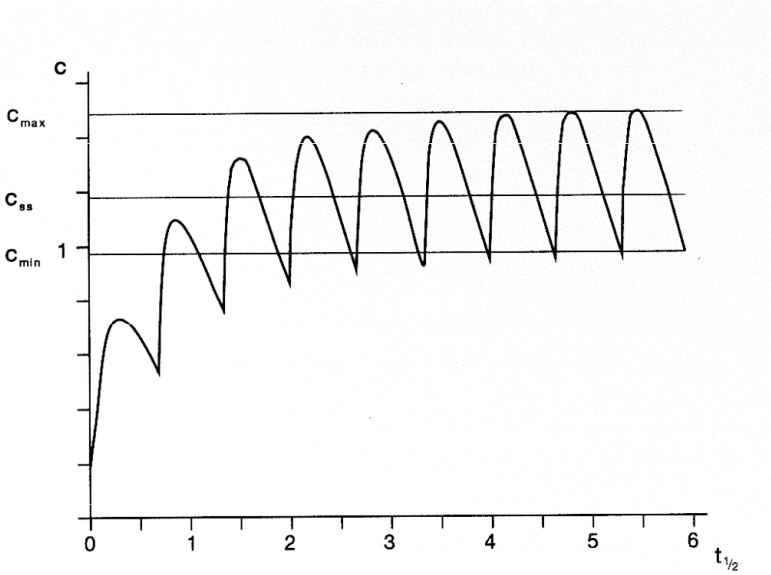
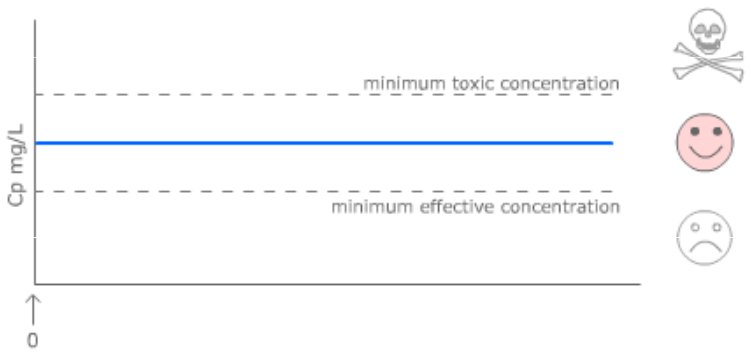
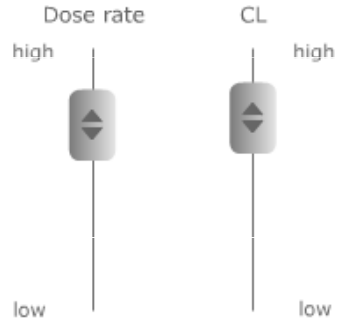
Continuous and repeated administration of drugs







$$Cpss = \frac{\text{Dose rate}}{CL}$$

$$\text{Dose rate} = Cpss \times CL$$

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Continuous administration

- **Intravenous** (e.g. by infusio pump), **transdermal** (TTS), **implant** → administration of drug with constant speed (mg/min)

- If duration of infusion is long enought, concentrations are increasing until the speed of elimination and inflow are the same – plato state is reached (concentration of plato is expressed as **Css**)

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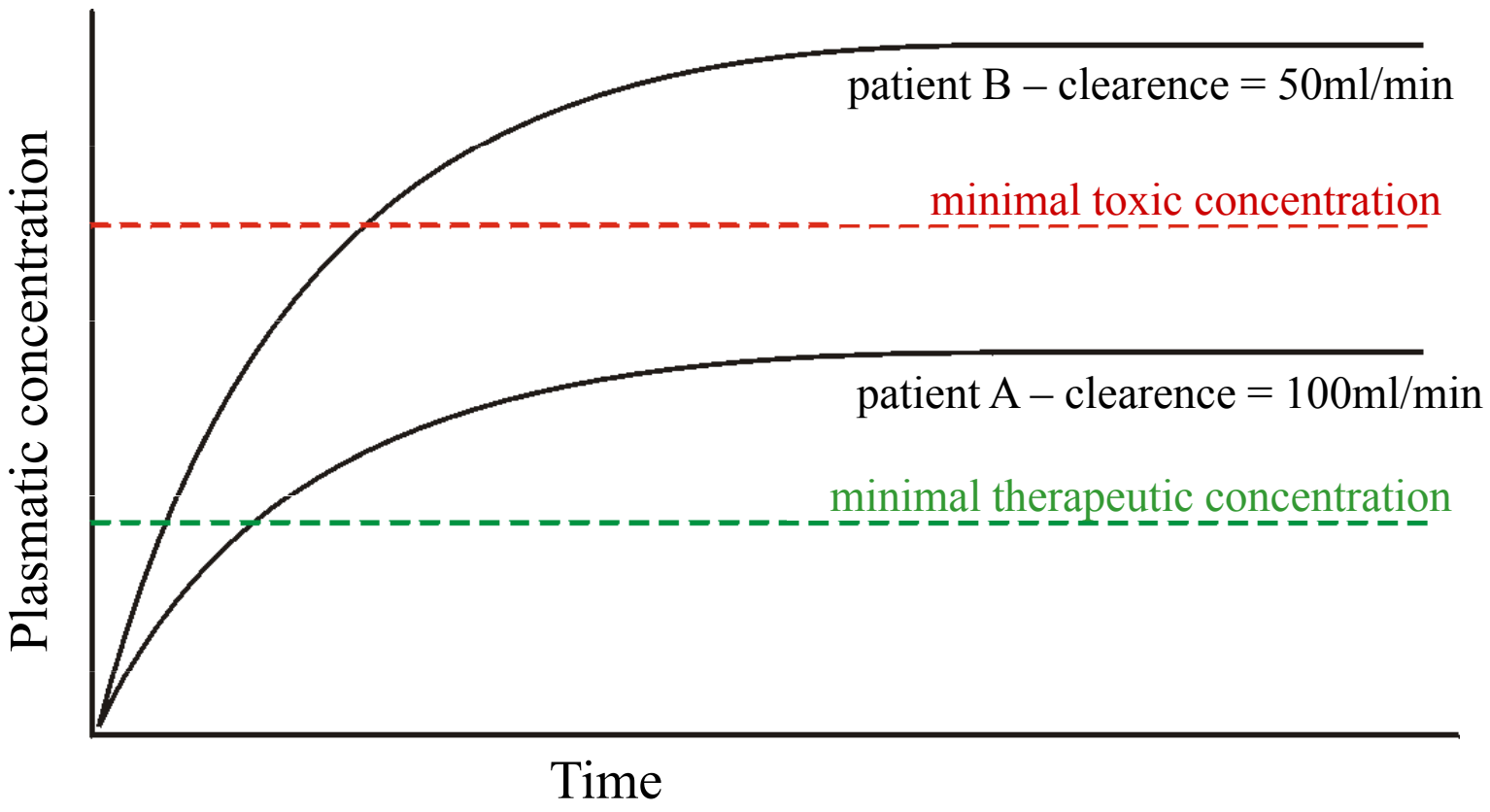
Continuous administration



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Continuous administration

In plato:

- Drug is binded to all binding sites, which can be occupied (distribution is finished)
- constant infusion speed **supplements amount, which is eliminated from organism in same**
- **speed of inflow [mg/min] = speed of elimination [mg/min]**

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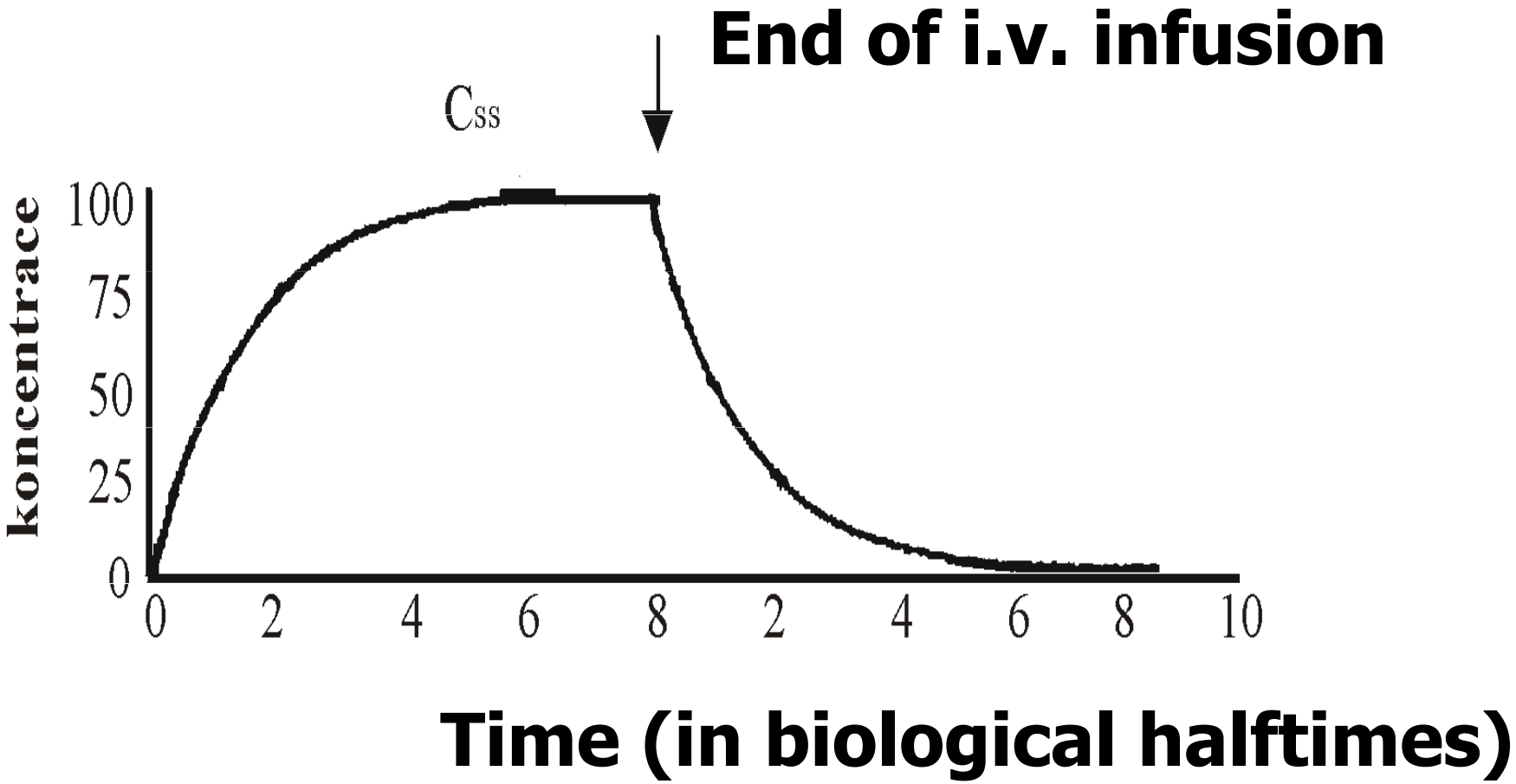
Continuous administration



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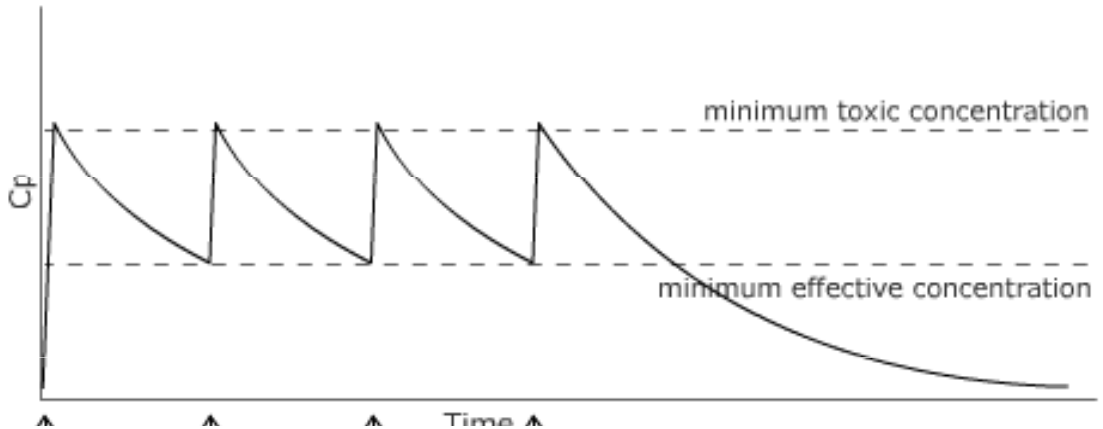
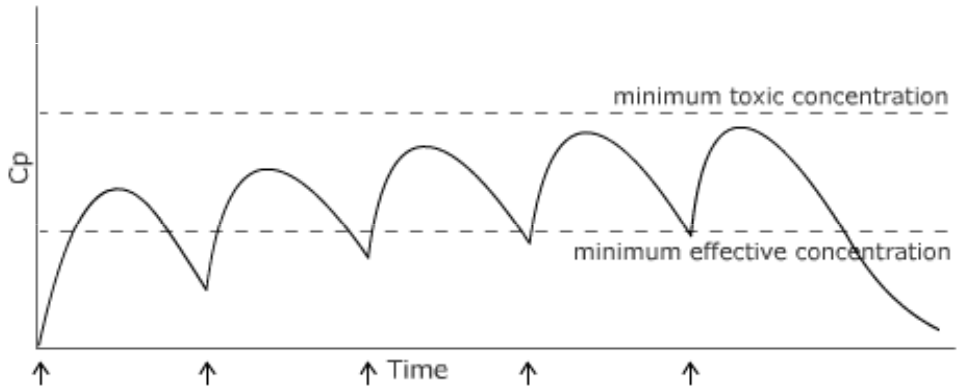
Repeated administration

intra- (repeated intravascular injection) or **extravascular** (i.e. per os)





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Repeated administration

- If doses are administered so close that first of them is not fully eliminated, **cumulation** starts or **plato** is reached
- Instead of css, $\mathbf{css_{plato}}$ is described and it is an average concentration from all concentrations meaured during one dosage interval

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Repeated administration

1) F – bioavailability – repeated administration is typical for p.o. administration

2) τ – dosage interval – plasmatic concentrations are fluctuating among minimal and maximal numbers – after reaching steady state this fluctuation is stabilized between $Cmax_{plato}$ and $Cmin_{plato}$

$$\frac{D \cdot F}{\tau} = Cl \cdot css_{plato}$$

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Basic pharmacokinetic parameters (+computations)

c_{max} = maximal plasmatic concentration

t_{max} = time when c_{max} is reached

k_e = elimination rate constant $k_e = \frac{\ln c_1 - \ln c_2}{t_2 - t1} \; [h^{-1}]$

$t_{1/2}$ = biological halftime $t_{1/2} = \frac{\ln 2}{k_e} = \frac{0,7}{k_e} \; [h]$

V_d = volume of distribution $Vd = \frac{D \,.\, F}{C_0} = \frac{F.D}{AUC \,.\, ke} \; [l]$

Cl = clearence $Cl_{TOT} = \frac{D}{AUC} = ke \,.\, Vd = Cl_{REN} + Cl_{HEP} + Cl_{PUL} \; \ldots [l.h^{-1}]$

AUC = area under the curve $AUC = \frac{D}{Cl} = \frac{c_0}{k_e} = \frac{D}{k_e \,.\, Vd} \; [mg \,.\, l^{-1} \,.\, h]$

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