Introduction to general pharmacology

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Pharmacokinetics

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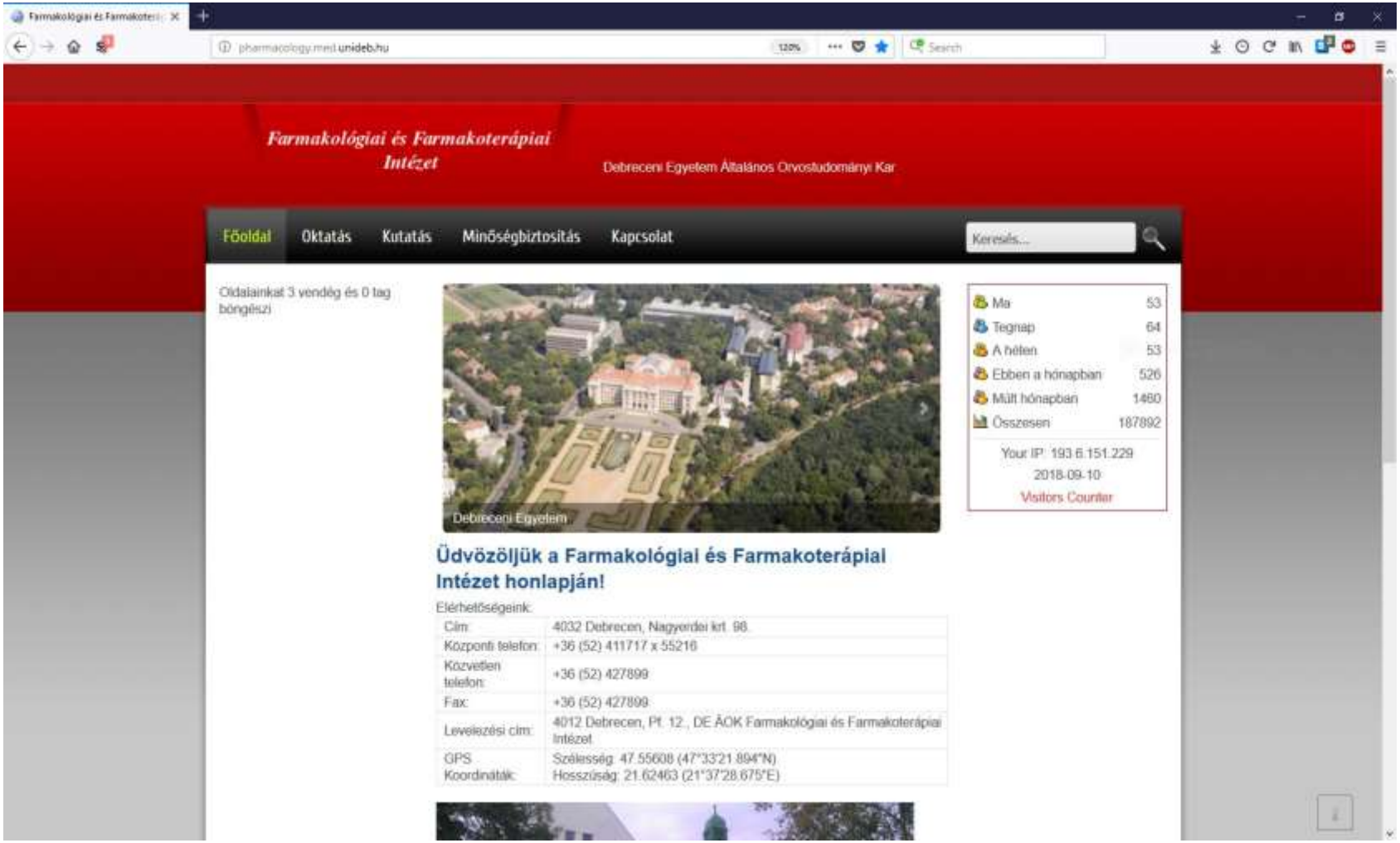
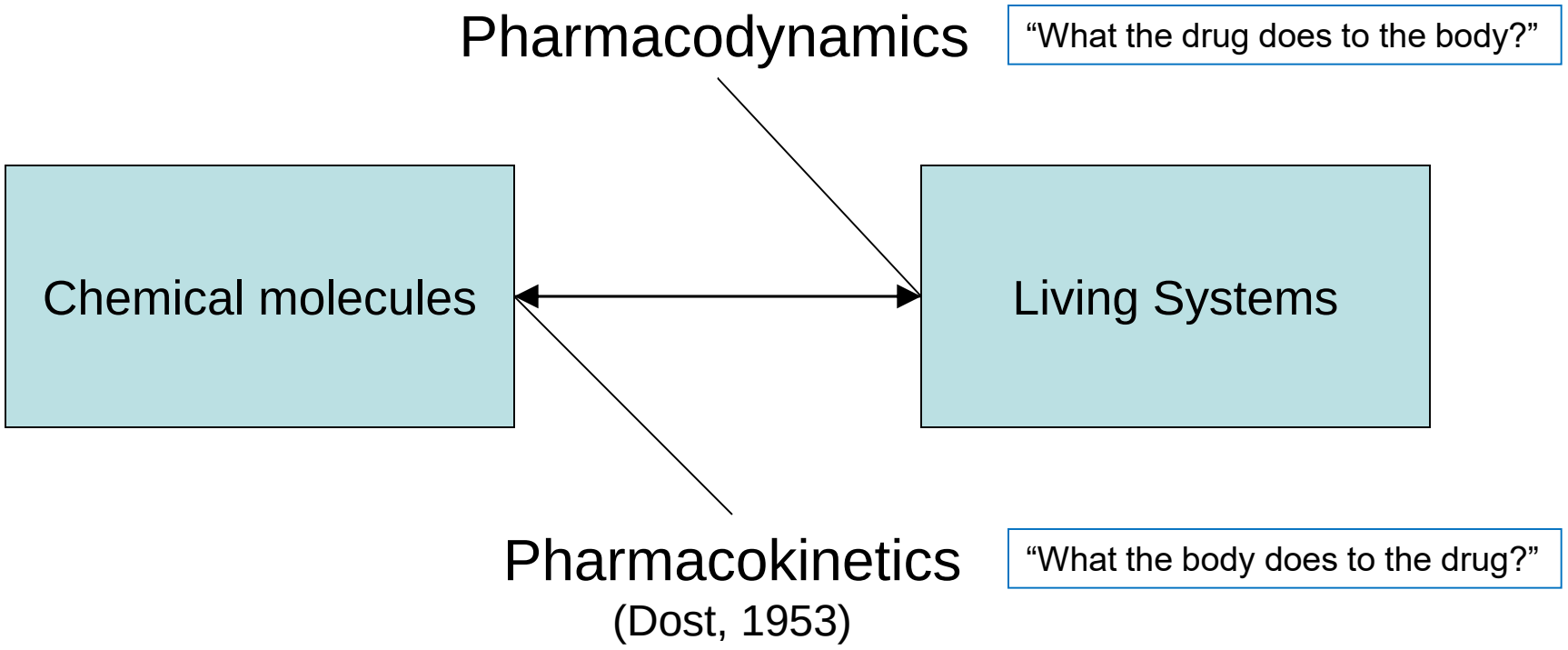
13.09.2018.



Lecture slides:

http://pharmacology.med.unideb.hu/
Oktatás – Általános orvos/General Medicine
pdf password - 12358

Pharmacology



INTERACTION

Pharmacology ≠ Pharmacy

- **Pharmacology**
  - **Medical pharmacology**
    - **Experimental pharmacology** (non-human)
    - **Clinical pharmacology** (human)
    - **Pharmacotherapy** (disease → drug)
- Pharmacy
  - physicochemical properties, incompatibilities, identification, storage …

General vs. detailed pharmacology

- General pharmacology
  - basic principles
  - generally applicable rules / laws / concepts
- Detailed pharmacology
  - specific information about individual drugs / drug groups

Drug 1.

- „drug”
  - any substance influencing the function of living systems
  - medicines, abused substances, poisons ..
- medication / medicine / approved drug
  - the purpose of application
    - **therapy**
    - prevention
    - diagnosis

chemicals that **cause** disease → toxicology

Drug 2.

- legal aspects
  - **approved medicine** (see EMA, FDA, OGYÉI)
    - approval: proof of efficacy and relative safety
    - prescription drug
    - OTC (over the counter) drug - no prescription needed
  - not approved drugs
    - no systematic proof for efficacy / relative safety
    - food additives
    - herbal products
    - vitamins
    - homeopathic drugs

Drug 3.

- artificial separation
  - scientific medicine ↔ alternative medicine
- all chemicals
  - can be harmful (toxic) – dose …
  - evaluation methods =
    - statistics …
  - proof of efficacy / safety =
    - ideally e.g. RCT (randomized controlled clinical trial)
  - natural origin ≠ safety
  - extracts, mixtures
    - chemicals = , purity ≠

therapy can be **non-pharmacologic** too

Natural origin = safety ?

- *Amanita phalloides*: α-amanitin cyclic octapeptide; median lethal dose (LD50) in mice 0.3 mg/ttkg
- *Clostridium botulinum* toxin, lethal dose in experimental animals <1 µg/ttkg. Humans are also sensitive: the oral lethal dose of botulotoxin in humans is around 10 µg, this amount can be found in approx. 0,1 ml of contaminated food (e.g. canned food, honey)

Origin of drugs

- natural
  - plants (e.g. atropine, morphine, codeine)
  - animals (e.g. adrenalin, insulin (**BUT not small molecule !!!)**)
  - minerals (e.g. aluminium-hydroxide)
- semisynthetic (e.g. methyl-homatropine, heroin)
- synthetic
  - chemical synthesis (e.g. tiotropium, metoprolol)
  - „biological synthesis” - **„biological drugs”**
    - **biotechnological production**
    - currently mostly **proteins**, molecular weight > 10 kDa
    - pl. hormones, growth factors, **antibodies**
    - origin: natural or non-natural (see. inzulin)
    - „biosimilarity” ↔ generic

„small chemicals”

Biological therapy ≠ targeted therapy

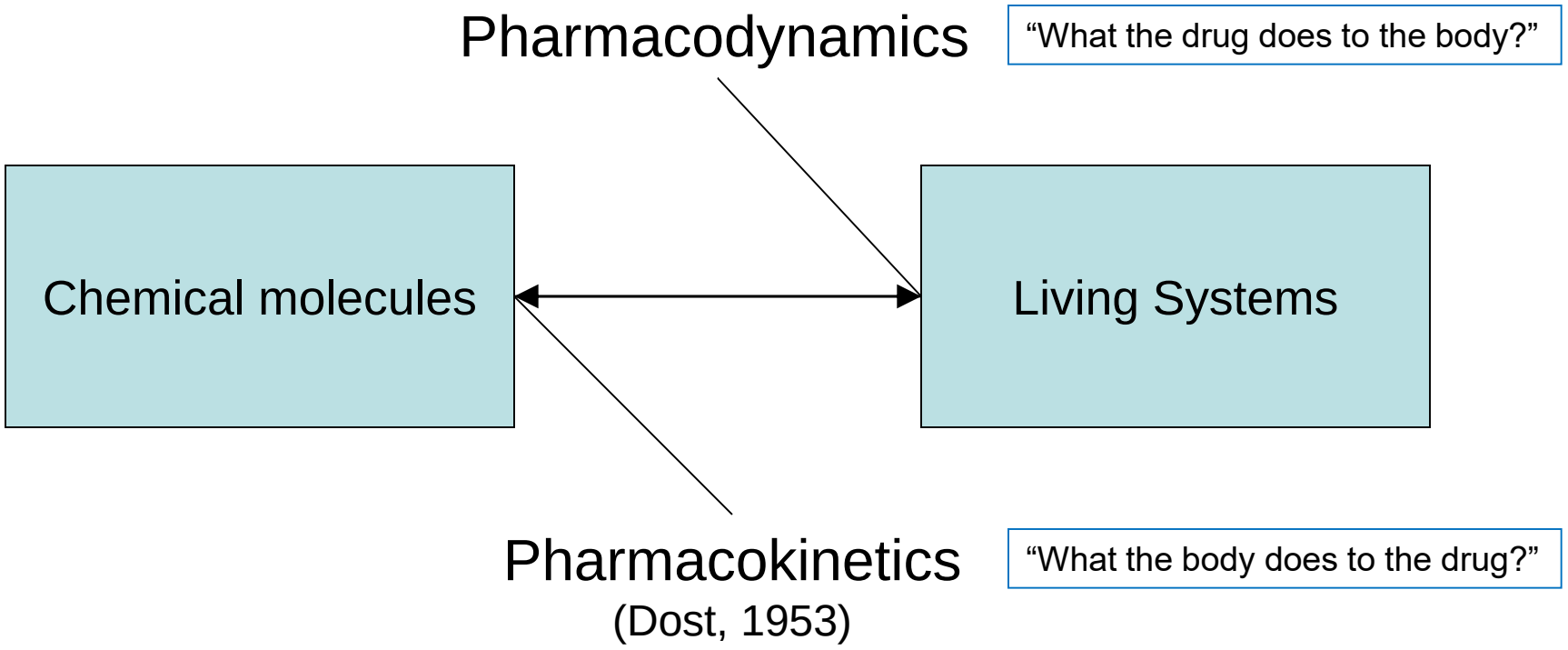
- anticancer molecularly targeted therapy
  - non-biologicals
    - tyrosine kinase inhibitors
      - e.g. imatinib, dasatinib, nilotinib (BCR-ABL kinase, CML)
    - epidermal growth factor receptor inhibitors
      - e.g. lapatinib (HER2+ breast cancer)
      - e.g. erlotinib (metastatic non–small cell lung cancer)
  - biologicals
    - epidermal growth factor receptor inhibitors
      - e.g. trastuzumab (HER2+ breast cancer)
      - e.g. cetuximab (EGFR+ metastatic colorectal cancer)
- DMARDs
  - non-biologicals
    - e.g. methotrexate, hydroxychloroquine, leflunomide
  - biologicals
    - e.g. infliximab, adalimumab, etanercept

Drug names

chemical name	generic name*	trade name
sodium N-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-N-methylaminomethanesulphonate monohydrate	metamizol (dipyrone, novamidazophen, **noraminophenazonum natrium mesylicum**)	Algopyrin Algozone …
1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline	captopril	Tensiomin Aceomel
(6R)-6-[α-D-(4-hydroxyphenyl)glycylamino]penicillanic acid	amoxicillin	Clonamox Ospamox …

*INN (International Nonproprietary Name)

Pharmacology



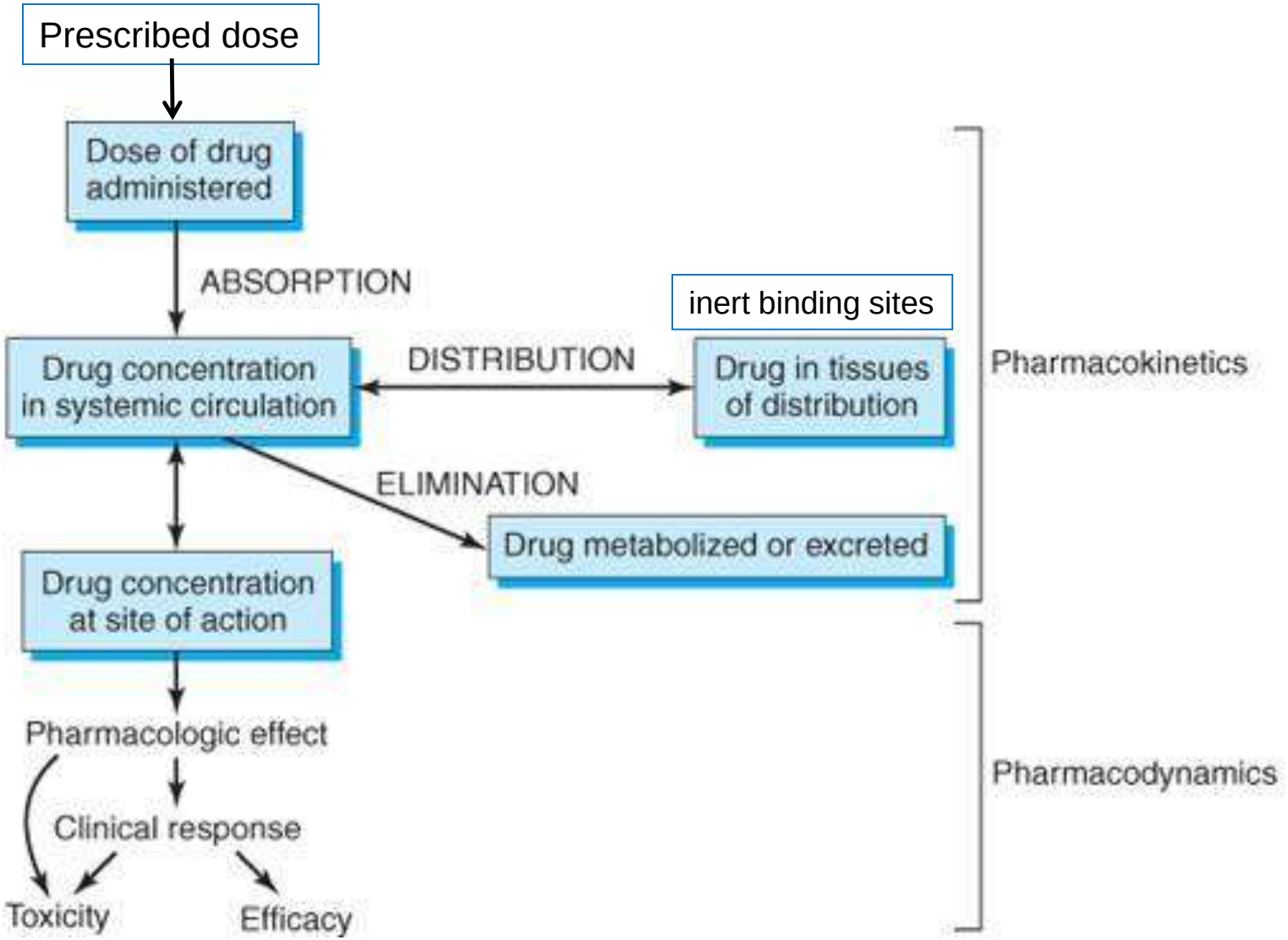
INTERACTION

- Pharmacodynamics
  - Site & **mechanism of action**
  - Drug-receptor interactions (“receptors”, inert binding sites)
  - **Dose-response relationships**

- Pharmacokinetics
  - **Absorption** – site of application → blood
  - **Distribution**
  - Biotransformation (**M**etabolism)
  - **E**xcretion

} **Elimination**

(L)ADME

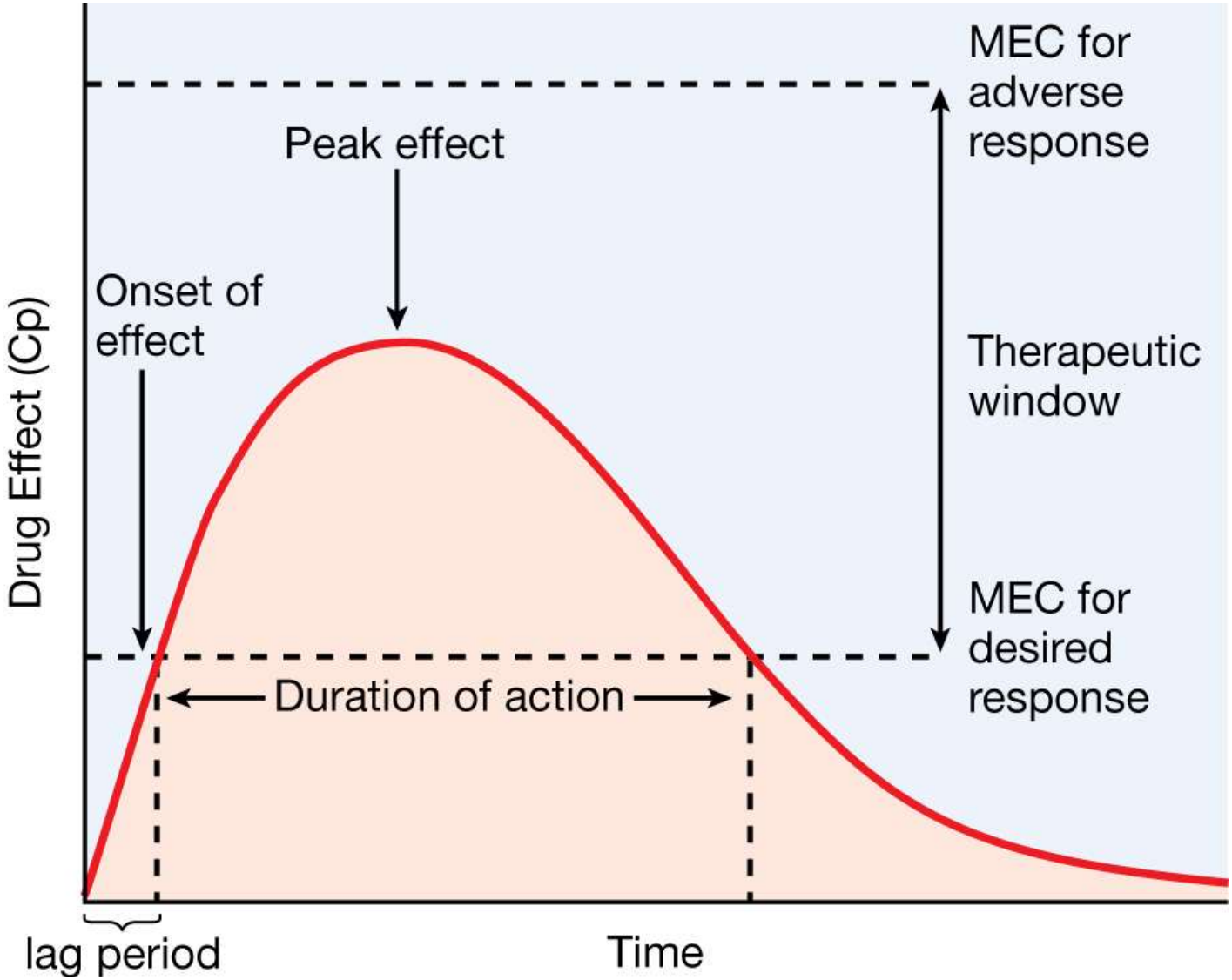


hatás (kedvező vagy toxikus) ~ koncentráció

farmakogenetika: PK/PD variáció

MEC = minimum effective concentration

plasma concentration (Cp) ~ effect



oral administration

Significance of pharmacokinetics

- for drug development
  - decide on an appropriate dosing regimen
- for drug regulation/approval
  - bioequivalence (same C_{max}, t_{max}, AUC)
- for clinicians
  - for optimal drug use - basic principles
  - drug interactions
  - therapeutic drug monitoring

Therapeutic drug monitoring in the clinics

example drugs	category
ciclosporine, tacrolimus	immunosuppressants
digoxin	cardiovascular
theophylline	respiratory
lithium, antiepileptics	CNS
aminoglycosides, vancomycin	antibacterials
methotrexate, carboplatin	antineoplastics

Limitations of pharmacokinetics

- plasma cc ≠ cc at site of action
  - intracellular target (cannot penetrate)
  - blood brain barrier (other “sanctuaries”)
- effect ≠ cc around the site of action
  - irreversible binding
  - delay
  - tolerance / physiologic adaptations

Movement of drugs through barriers

- absorption, distribution, excretion
  - crossing barriers (membranes)
- determined by
  - size
    - for most drugs MW from 100 to 1000 → lipid diffusion
    - but can be smaller / larger
      - two ends of the spectrum
      - Li+ ion (MW=7)
      - alteplase (MW=59050), antibodies (biologicals)
    - permeation can be significantly different
  - electrical charge
    - for ionizable drugs (i.e. weak acids or bases)
      - pH differences → altered ionization → altered diffusion / excretion
  - shape

Permeation of drug molecules across membranes

- **passive** (concetration gradient)
  - diffusion
    - aqueous
      - body surface: tight junctions (MW < 150, Li^+, methanol)
      - most capillaries (MW < 20000-30000, “protected sites”: e.g. brain, testes)
    - lipid
      - lipid:aqueous partition coefficient (weak acids/weak bases)
    - facilitated
      - special carriers, e.g. amino acids, peptides
      - saturable, inhibitable
- **active**
  - active transport
  - pinocytosis
    - MW >1000, vitamin B_{12}+ intrinsic factor, Fe + transferrin

Lipid diffusion

- Fick's law
  - $J=P*A*(C_1-C_2)/T$
- Ionization of weak acids and weak bases
  - Henderson-Hasselbalch equation
    - log ([protonated form]/[unprotonated form])=pK_a-pH

aspirin (weak **acid**) $C_8H_7O_2COOH \leftrightarrow C_8H_7O_2COO^- + H^+$

pyrimethamine (weak **base**) $C_{12}H_{11}ClN_3NH_3^+ \leftrightarrow C_{12}H_{11}ClN_3NH_2 + H^+$

for acids	protonated	unionized	apolar	lipid soluble
for bases	protonated	ionized	polar	water soluble

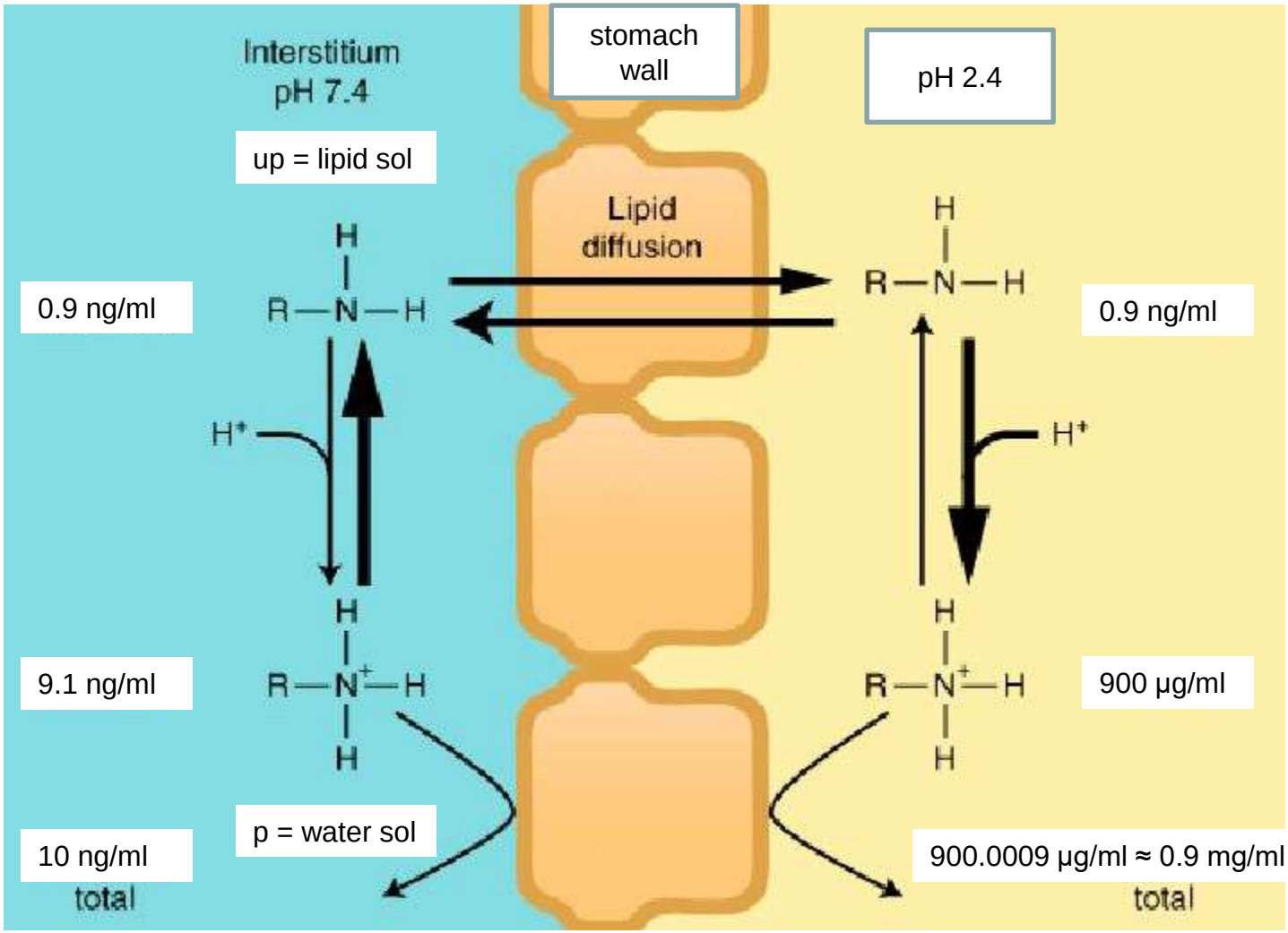
pH dependent reabsorption of a weak acid

(phenobarbital – weak acid - pK_a=7.4)

	pH=6.4	pH=7.4	pH=8.0
pK_a-pH=7.4-pH	1	0	-0.6
antilog(pK_a-pH)=$10^{(pKa-pH)}$	10	1	0.25
ratio of protonated/unprotonated (i.e. reabsorbable/non-reabsorbable)	10/1	1/1	1/4
reabsorption from tubule	faster		slower
excretion in urine	slower		faster

The „ion trap”

log [p]/[up] = pK_a – pH = 8.4 -7.4 = 1
[p]/[up]=10^1=10
[p]=10 x [up]



log [p]/[up] = pK_a – pH = 8.4 – 2.4 = 6
[p]/[up]=10^6= 1000000
[p]=1000000 x [up]

Major pharmacokinetic parameters

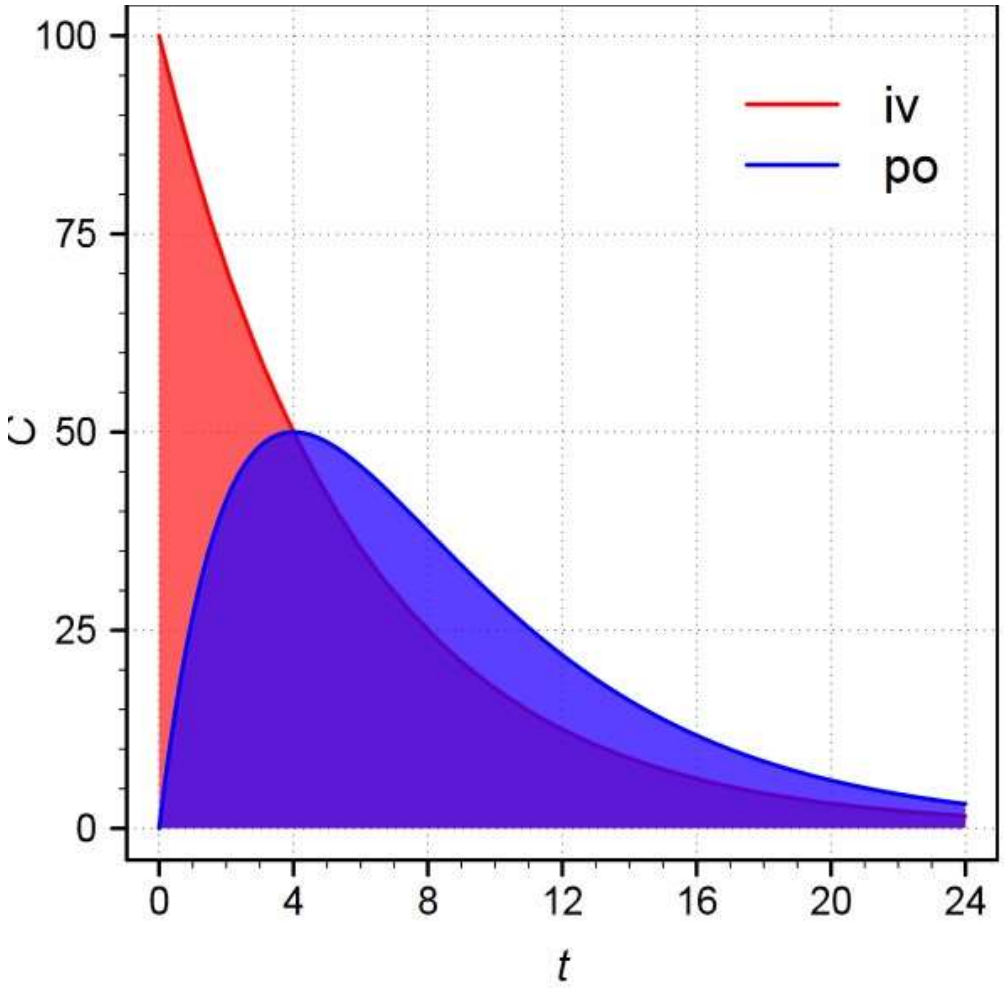
- for **clinically useful** quantitative characterization of drug concentrations in blood / plasma

- **bioavailability** → absorption
- **apparent volume of distribution** → distribution
- **clearance** → elimination

Bioavailability (F)

- The fraction (or percent) of drug reaching the systemic circulation without chemical modification
  - $0 \leq F \leq 1$ (see **iv.** administration and **prodrugs**)
- depends on
  - site of application – see route of administration
  - absorption
    - e.g. drug formula, lipid solubility, transporters (e.g. P-gp), metabolism in the wall of the gut
  - **first pass effect**
    - metabolism in liver or portal blood, biliary excretion

Measuring bioavailability



if doses are equal

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

if doses are not equal

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

unit of AUC: mg/l h

Oral bioavailability of some drugs

drug	oral bioavailabilty (%)
lidocaine	35
atropine	50
captopril	65
digoxin	70

Lidocaine is NOT available for oral admininstration!

$$C = \frac{F * D}{V}$$

Distribution

is a function of time and determined by

- **Permeation** through membranes
  - size, shape, ionization
  - properties of the barrier (e.g. HEB, placenta)
- **Affinity** to tissues
  - lipophilic molecules (CNS, adipose)
  - specifc binding (I – thyroid, As – epidermis, nails, hair)
- **Blood flow**
  - e.g. thiopental (see iv. general anesthetics)
- Plasma **protein binding**
  - only free drug
    - can interact with receptors – effect
    - can cross membranes – distribution / elimination

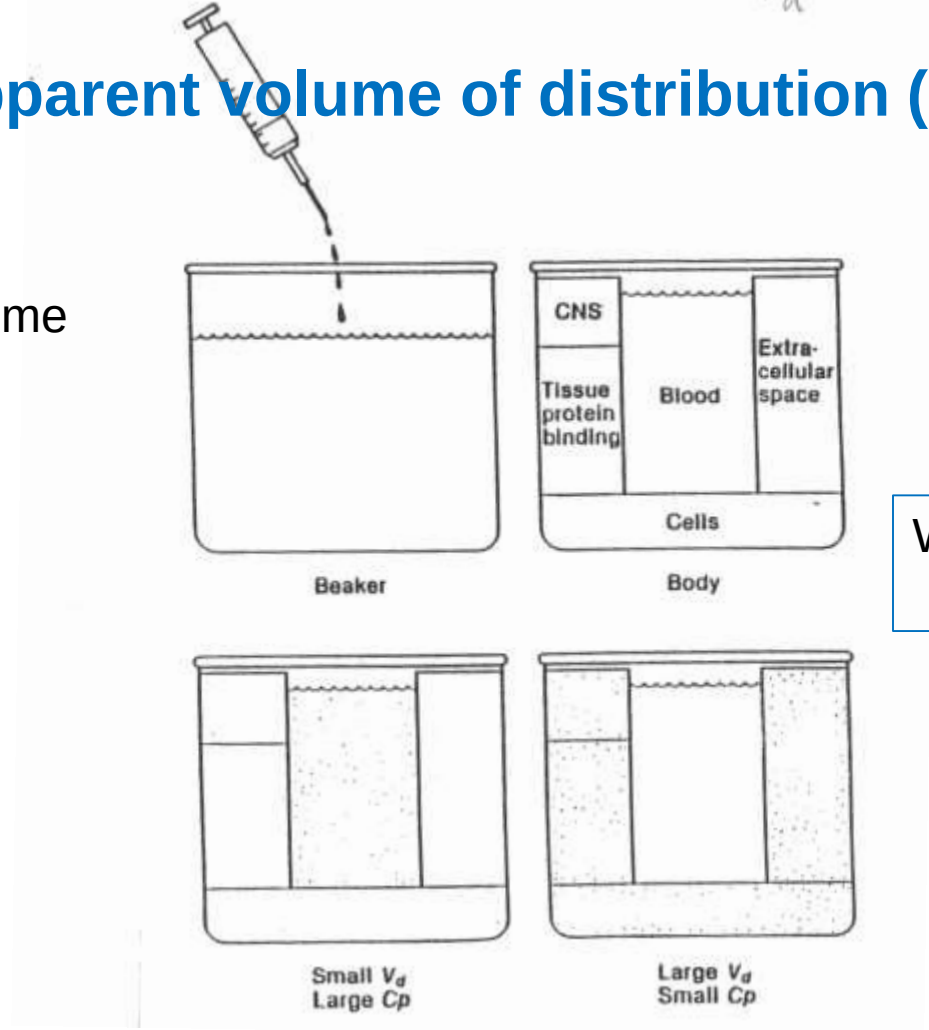
Accumulation of a drug in a tissue does not necessarily indicate its site of action!

Apparent volume of distribution (V_d)

conc. = dose / volume

$$C = \frac{D}{V_d}$$

$$V_d = \frac{D}{C}$$



Where C is measured?
in blood or plasma?

apparent volume of distribution

distribution is
not restricted to blood / plasma
not homogenous

Apparent volume of distribution (V_d)

Blood ~ 0.08 l/kg

Plasma ~ 0.04 l/kg

Total body water ~ 0.6 l/kg

Extracellular water ~ 0.2 l/kg

Drug	Volume of distribution (L/70 kg)
Chlorpropamide	6.8
Furosemide	7.7
Valproic acid	9.1
Warfarin	9.8
Morphine	230
Digoxin	500
Nortriptyline	1300
Imipramine	1600
Fluoxetine	2500
Chloroquine	13000

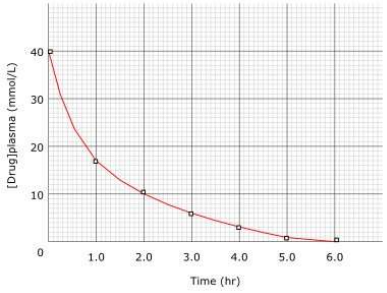
an apparent volume if in which the **same amount** of drug would be distributed **homogenously** then the concentration would be the same as the concentration measured in the plasma/blood

Clinical utility of V_d

- If
  - target concentration (C_0)
  - apparent volume of distribution (V_d)
- is known then

$$D = C_0 * Vd$$

- single iv. bolus administration of a D dose will result in a peak concentration of C_0

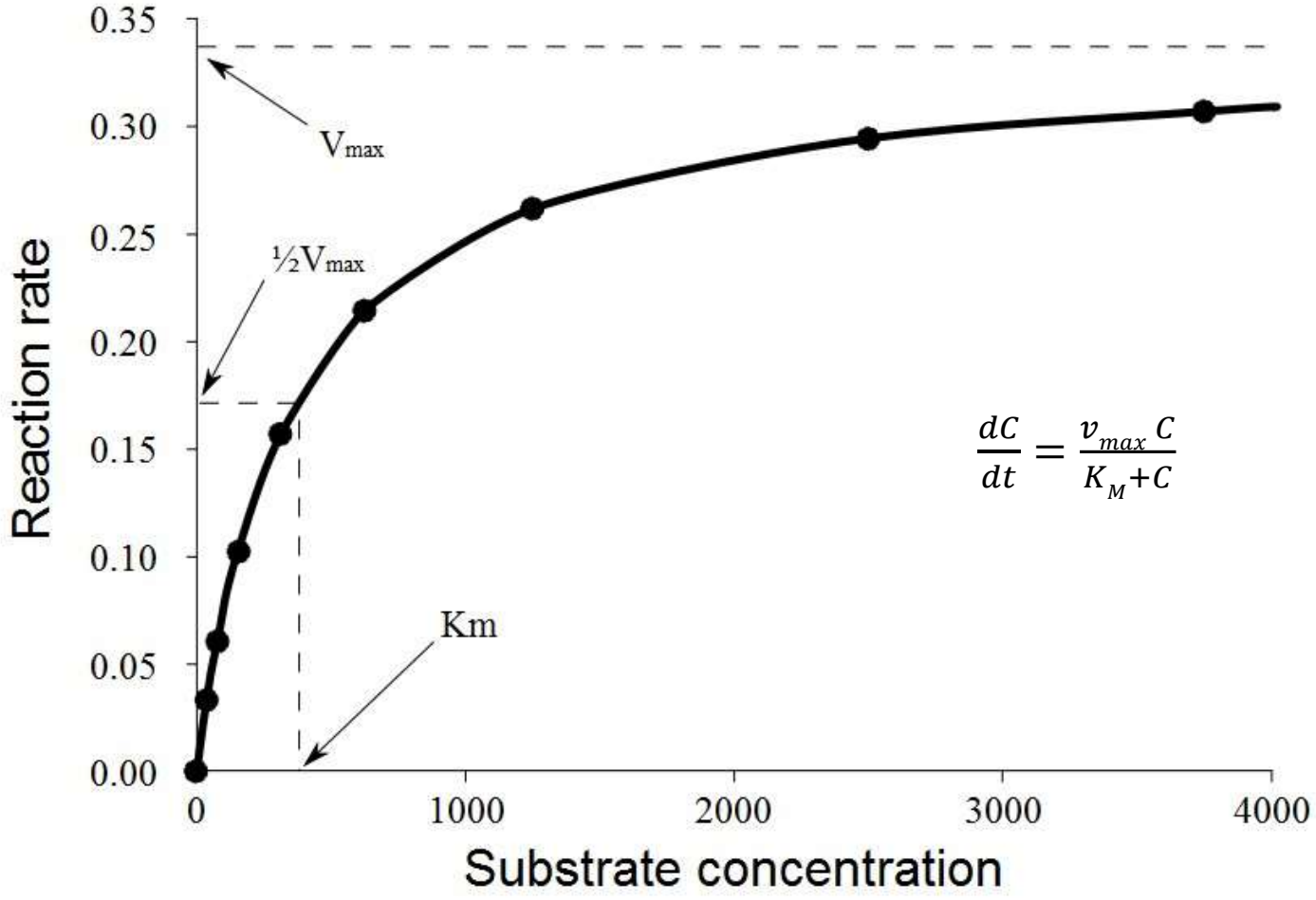


loading dose – to reach therapeutic concentration "promptly"

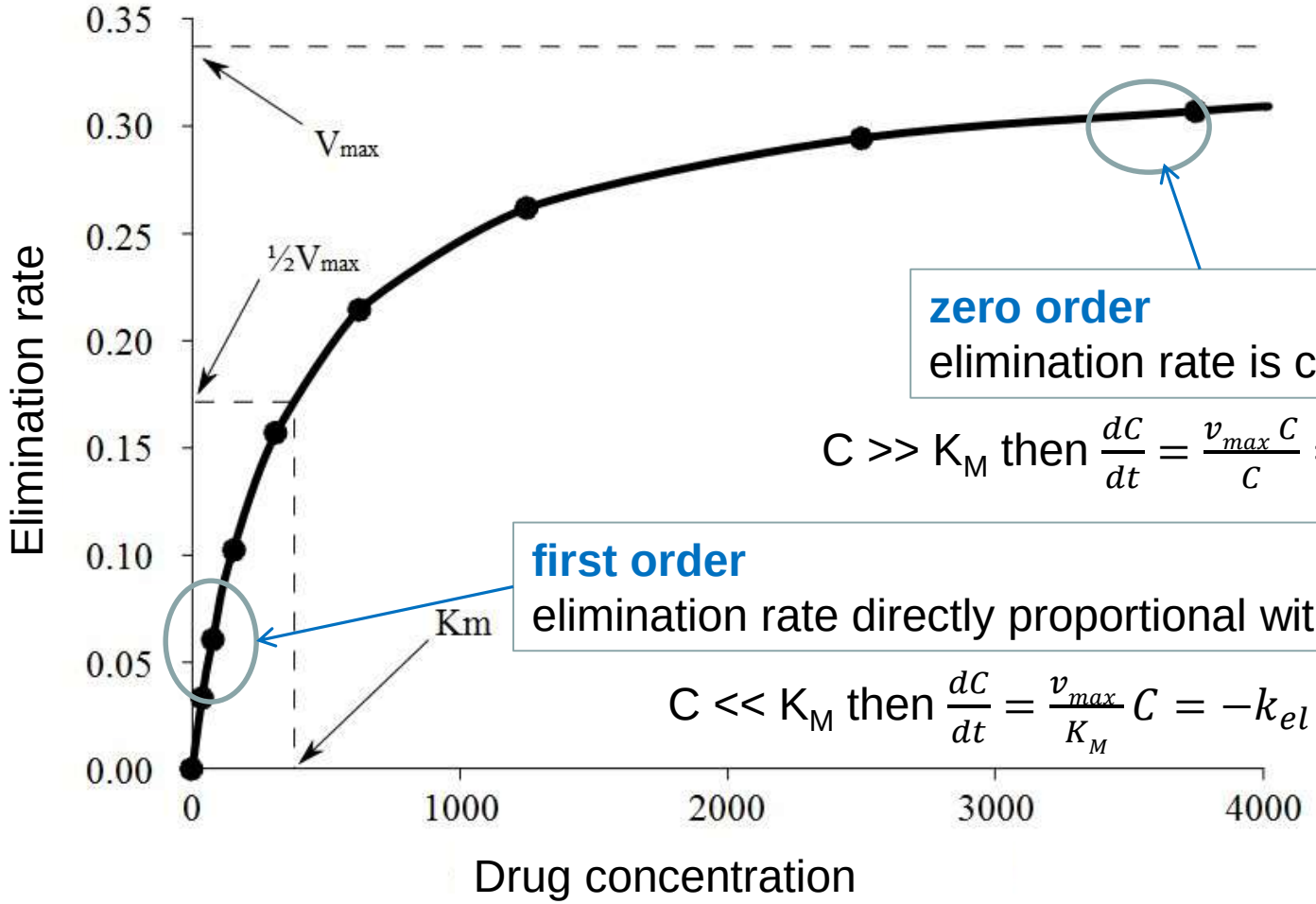
Elimination

- any process reducing the amount (concentration) of a drug
  - biotransformation (= metabolism)
  - excretion
    - sites: **kidney** (filtration – secretion – reabsorption) ***/*** liver / GI-tract / lung / sweat glands / mammary glands
- can be
  - **saturable** (e.g. biotransformation by enzymes / active secretion)
  - non-saturable (e.g. glomerular filtration)

Enzyme reaction kinetics



Saturable elimination



zero order
elimination rate is constant

C >> K_M then $\frac{dC}{dt} = \frac{v_{max}\,C}{C} = v_{max}$

first order
elimination rate directly proportional with conc.

C << K_M then $\frac{dC}{dt} = \frac{v_{max}}{K_M} C = -k_{el}\,C$

First order elimination kinetics

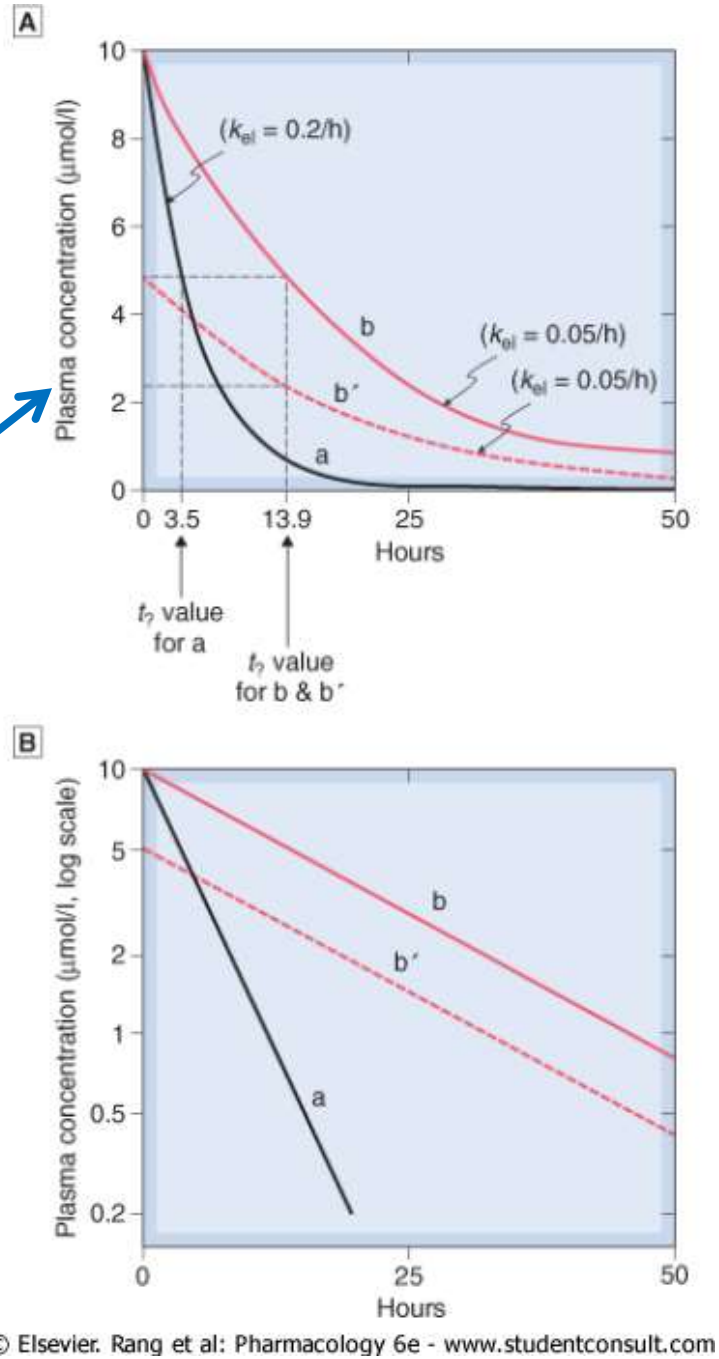
$$C_t = C_0\, e^{-kt}$$

C_t – blood/plasma concentration at time t
C_0 - blood/plasma concentration at time 0
e – base of the natural logarithm
k – elimination rate constant
t – time

Linear graph (C vs. t)

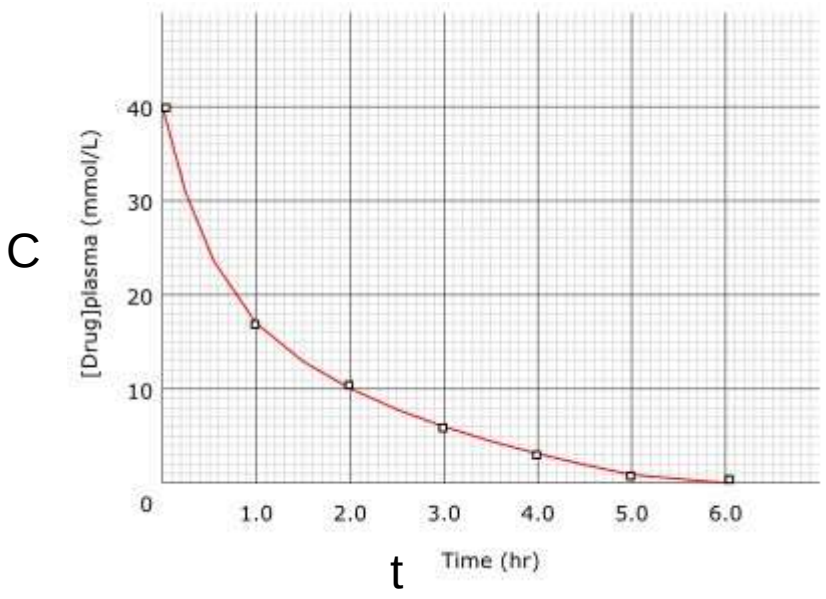
half life is constant

Semilogarithmic graph (ln C vs. t)



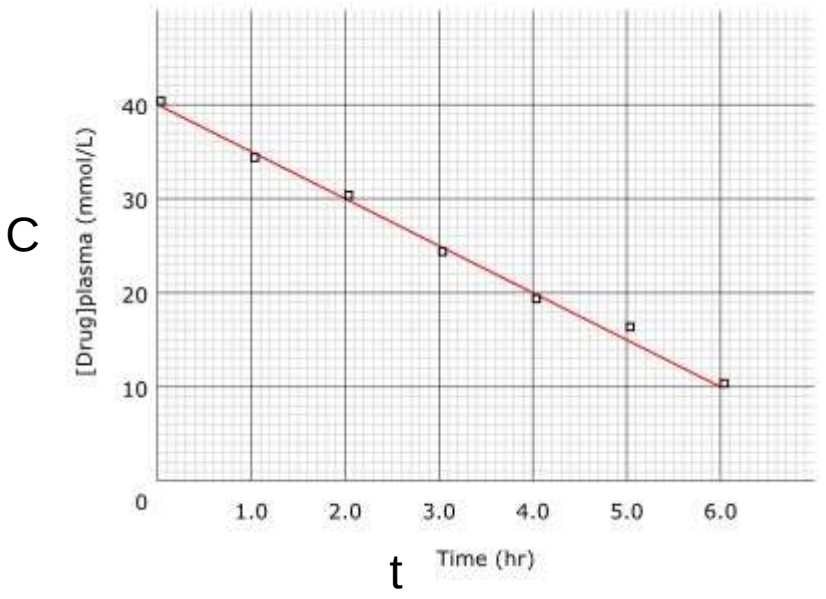
Elimination kinetics

First order



for most drugs
elim. non-saturated
half-life is constant

Zero order



for e.g. ethanol / phenytoin / Aspirin
elim. saturated
half-life is NOT constant

Clearance

- For renal clearance: CL = (U * V) / P
  - U : urinary concentration (mg/ml)
  - V : urine flow rate (ml/min)
  - P: plasma concentration (C_p) (mg/ml)
  - U * V = rate of elimination (mg/min)
- **CL = rate of elimination / C_p** (ml/min)
- For non-saturated elimination (i.e. 1st order)
  - rate of elimination = $k_{el} * C * V_d$
  - CL = $(k_{el} * C * V_d) / C = k_{el} * V_d = (\ln 2 / t_{1/2}) * V_d$

Measurement of clearance

- $clearance = \frac{rate\ of\ elimination}{concentration}$

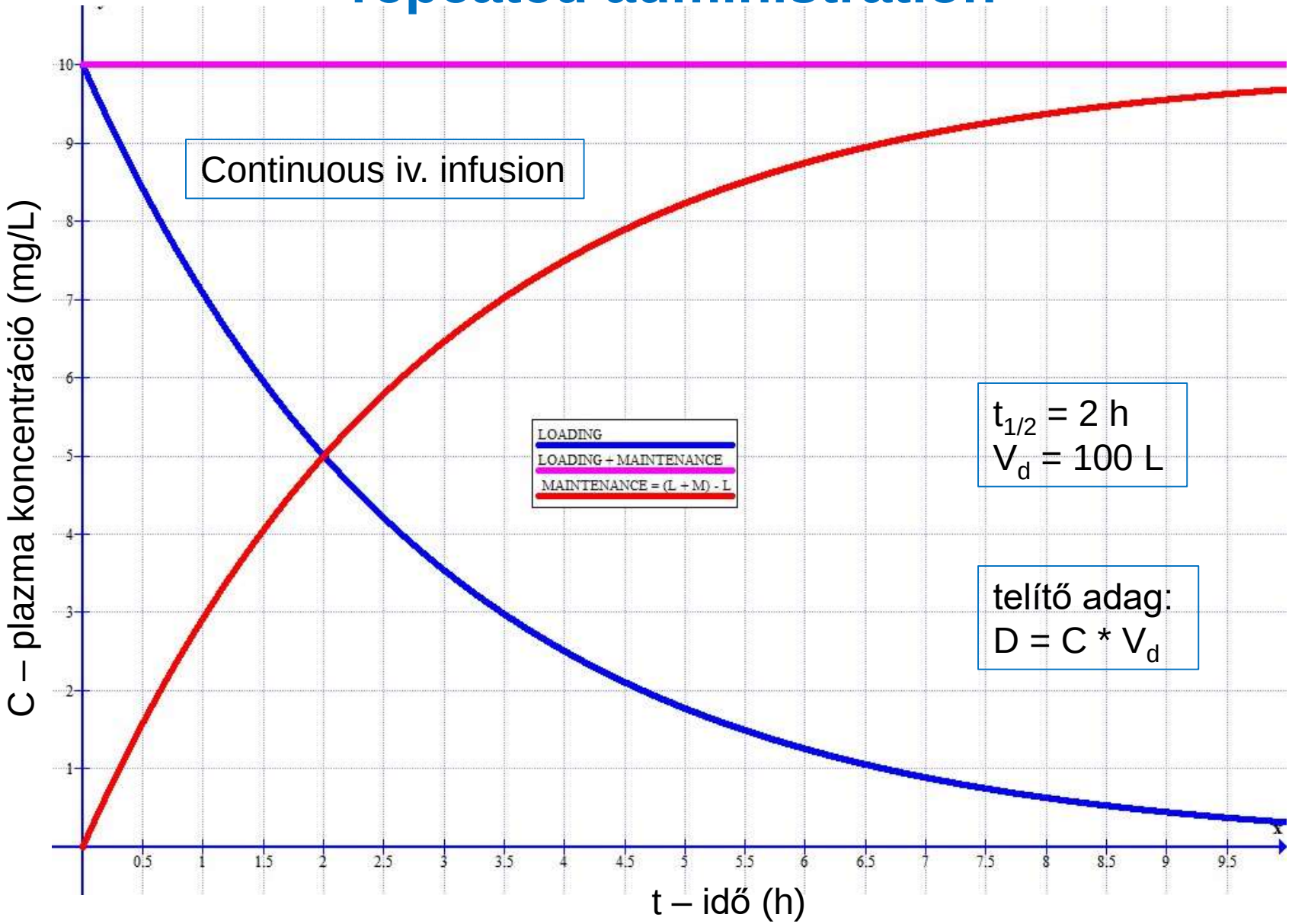
- $CL = \frac{k_{el}\, V_d\, C}{C} = k_{el}\, V_d = \frac{\ln 2}{t_{1/2}}\, V_d \approx \frac{0.693}{t_{1/2}}\, V_d$

- $CL = \frac{dosing\ rate}{steady\ state\ concentration} = \frac{DR}{C_{ss}}$ **at SS**

- $CL = \frac{D}{AUC}$

Clinical utility of clearance

repeated administration



Clinical utility of clearance
repeated administration

- At constant infusion rate **when steady state is reached** (C_{ss}) ? – **depends only on half life ($t_{1/2}$)**
  - 1x $t_{1/2}$ – 50% of C_{ss}
  - 2x $t_{1/2}$ – 75% of C_{ss}
  - 3x $t_{1/2}$ – 87.5% of C_{ss}
  - **4x $t_{1/2}$ – 93.75% of C_{ss}**
  - **5x $t_{1/2}$ – 96.88% of C_{ss}**
- **How large will be C_{ss}** at a given constant infusion rate (dosing rate = DR) ?
  - C_{ss} = DR / **CL**
- **What dosing rate** can maintain a given appropriate C_{ss} (**target concentration**)?
  - DR = C_{ss} * **CL**

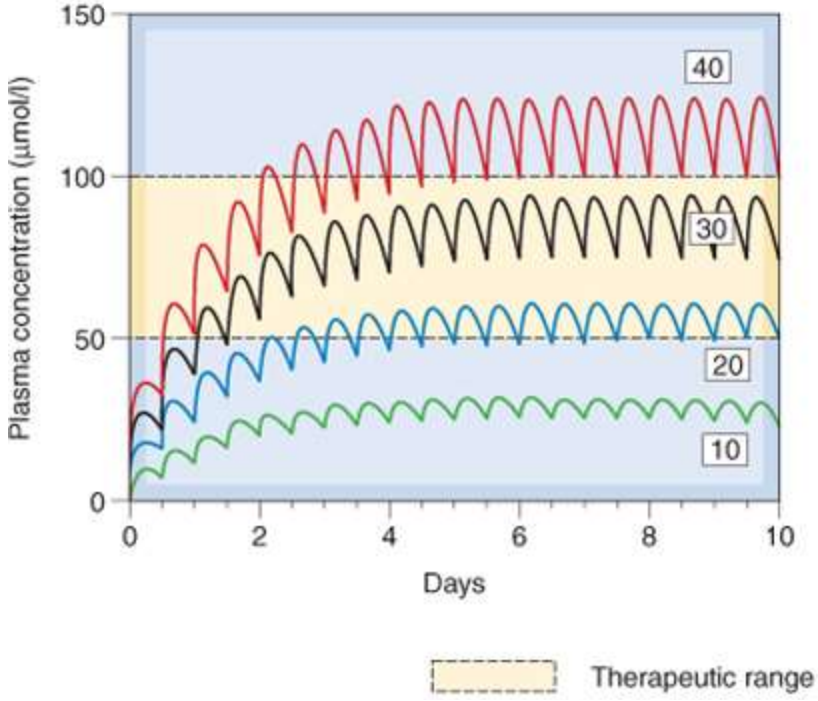
$$CL = \frac{rate\ of\ elimination}{C}$$

at steady state: rate of elimination = dosing rate (DR)

$$CL = \frac{DR}{C_{ss}} \qquad \rightarrow DR = CL * C_{ss}$$

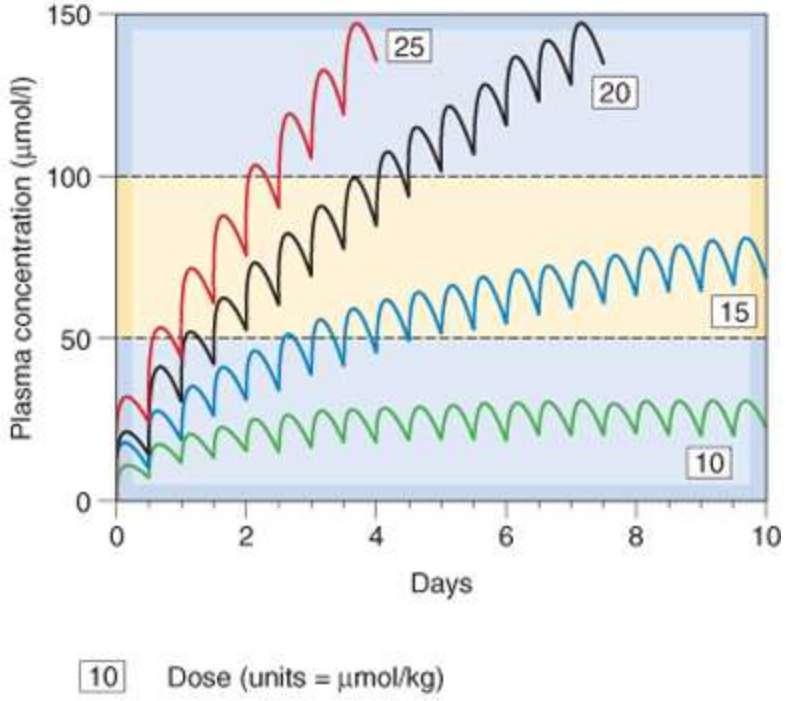
$$\rightarrow C_{ss} = \frac{DR}{CL}$$

First order elimination kinetics



Linear pharmacokinetics

Zero order elimination kinetics



Non-linear pharmacokinetics

Summary 1.

Introduction

- What is **pharmacology**?
- What is a **drug**?
- What is “**biological therapy**”?
- The meaning of **pharmacodynamics / pharmacokinetics**?

Summary 2.

Pharmacokinetics

- Drug **permeation** through membranes.
  - Mechanism and significance of **ion trap**.
- Concept and clinical utility of
  - **bioavailability**
  - **apparent volume of distribution**
  - **clearance**
- Elimination kinetics
  - non-saturated (**first order** / linear PK)
  - saturated (**zero order** / non-linear PK)
- Conc. - time curves after continuous infusion
  - time to C_{ss} ($4 * t_{1/2}$)
  - C_{ss} calculation ($C_{ss} = DR / CL$)