Semester I.
Seminar 5.

Dr. Balázs Varga
University of Debrecen, Faculty of Medicine,
Department of Pharmacology and Pharmacotherapy

Exam titles 9-10

9.

- Distribution of drugs in the body: the apparent volume of distribution (Vd)
- General description of sympathetic nervous system from pharmacological point of view (neurotransmitters and receptors)
- Characterization of quinidine, lidocaine, and amiodarone

10.

- Elimination of drugs: the half-life (T1/2)
- Pharmacological tools to influence the sympathetic neurotransmission
- Expectorants and antitussives

Distribution of drugs in the body: the apparent volume of distribution (Vd)

Pharmacokinetics

- „Effect of the body on the drug”
- Fate of the drug is divided into 4 stages designated by the acronym ‘ADME’:

- • Absorption from the site of administration
- • **Distribution within the body**
- • Metabolism
- • Excretion

Invasion

Elimination

Drug Distribution

BLOOD → organs, tissues, cells
(Site of effect)

- Distribution lasts until a dynamic balance is reached between free concentration of drug in plasm and in tissues.

- Tissue concentration does not always correlate with effect

(e.g.: concentration of halothan is higher in adipose tissue than in brain, where it exerts its effect)

Primary distribution and secondary distribution

First Phase

Following administration distribution is determined by blood supply of tissues:

1. Central compartments: kidneys, liver, lungs, heart, brain
2. Peripheral compartments: adipose tissues, skin, skeletal muscles at rest
3. Deep compartments: bone, cartilages, joint cavities

(elimination, however, is inversely proportional!)

Second phase

(redistribution)

Determined by affinity of drugs to tissues or organs.

First the drug goes where blood supply is high. But later it may accumulate in e.g. adipose tissue. A new balance develops (with adipose tissue accumulation) = redistribution.

Binding to plasm proteins

- Albumin!
- A few binds to globulin (steroids, thyreoid hormones)
- Bond: reversible (ionic, H-bond, van der Waals forces)
- Increases elimination halftime of drugs
- Bound drugs are inactive! (e.g.: nalidixic acid 99,9%)
- There is a continuous balance between free and bound form.
- Binding is saturable ➔ After saturation concentration of free form rises rapidly ➔ danger
- Liver produces plasm proteins ➔ hepatic disease ➔ decrease ➔ free drug level increases
- Binding places are not specific
  In case of simultaneous use of 2 drugs **competition** may happen

↓

They push each other off, increasing concentration of free (effective) form of drug

←

E.g.: if a drug is 97 % protein-bound, and another pushes off 3 %, it is still 94 %... BUT
Free form increases from 3% to 6%, which is 100% change, increased effect

Role of particular organs and tissues in distribution Selective accumulation

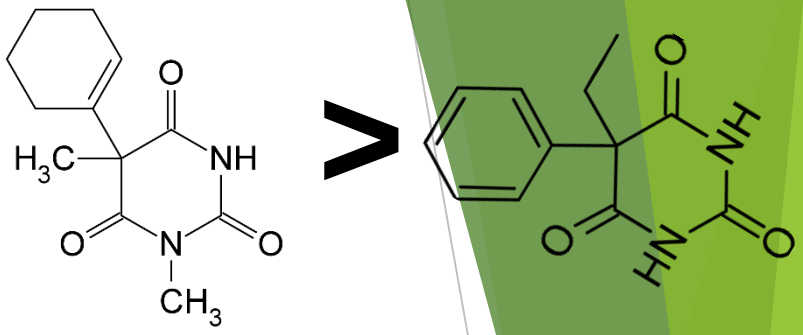
LIVER

- Wall of hepatic sinusoids are relatively easily permeable
- Storage function (e.g. glucose, lipid soluble vitamins, but xenobiotics may accumulate as well)

CNS

- Entering Liquor cerebrospinalis is difficult for drugs
- wall of brain capillaries is the least permeable: endothel cells are tightly connected, basement membrane of capillaries are thick, which is covered by projections of glial cells („blood-brain barrier”)

Blood-brain barrier



- Lipid-solubility is a decisive factor (e.g. hexobarbital > phenobarbital)
- Most chemoterapeutic agent can not enter
- At the site of area postrema the barrier is not perfect (many drugs cause emesis)
- Ionised drug-forms can not get in (e.g. neostigmin or tubocurarine)
- In case of inflammation (e.g. meningitis) permeability increases
- Even sugars, aminoacids and analogs get in by carrier-mediated transport

- Other barriers:
  - Blood-placenta barrier
  - Blood-testicle barrier
  - Blood-retina barrier

Role of particular organs and tissues in distribution

Adipose tissue

- Variable, 4-32 % of body mass
- Low blood supply
- Pharmacokinetics of lipophilic substances: slowly accumulate in adipose tissue, and slowly eliminated,
  sudden weight loss ➔ drugs into systemic circulation ➔ toxic symptoms

Bones

- Tetracyclines, lead, strontium etc. may accumulate
- xenobiotics eliminated slowly from here

Placenta

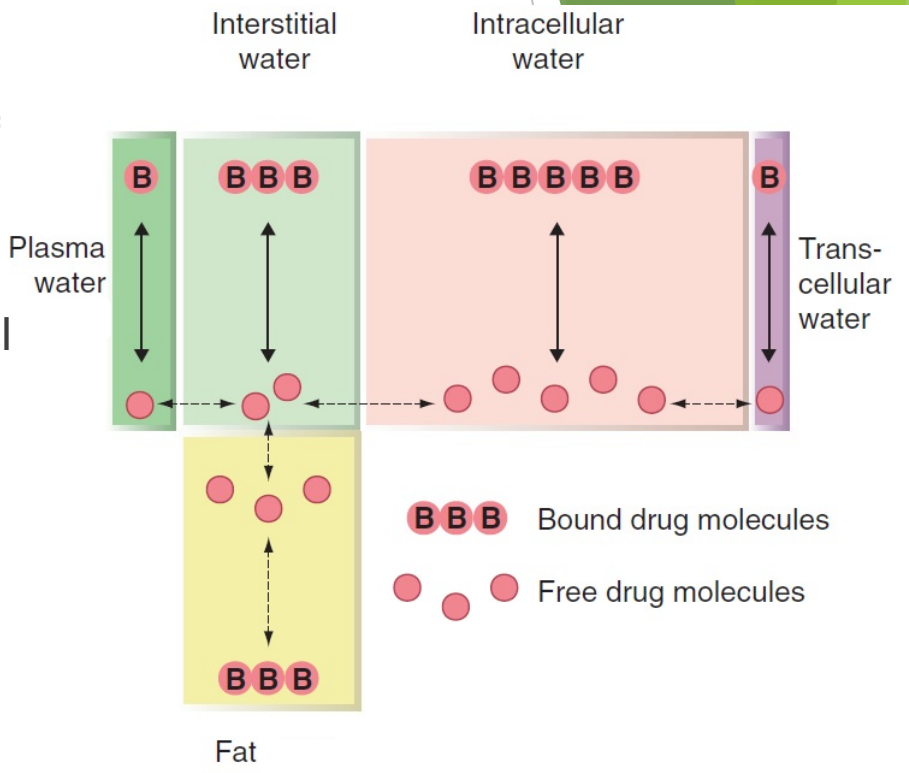
- Even at the end of pregnancy only gets 5-10% of maternal cardiac output
- Capillary wall thickness at start of pregnancy 25 μm, at the end 2μm
- Lipophilic substances may easily get through
- Ethanol and some drugs are metabolised by placenta
- Does not protect against chronic use

Retina

- Phenothiazines, chloroquine binds to pigment of retinal pigment epithelium (melanin) with high affinity --> visual disturbances

Aqueous (fluid) compartments of the body

- a. **Total volume**: at about 60% of body mass
(in a 70 kg person approx**. 42 l**) – less in women
- b. **blood**: approx. 12% of total (in case of 42 l **approx. 5 l**)
important, we can measure drug concentration in this
- c. **interstitial space**: approx. 25% of total (in case of 42 l approx. **10 l**)
- d. **intracellular space**: approx. 50% of total (in case of 42 l approx. **20 l**)
- e. **adipose tissue**: very variable amount, usually most of the remaining part (approx. 12% of total; in case of 42 l approx. **5 l**)
- f. **transcellular space: the remaining approx. 1% (max 2 l).**
Cerebrospinal, peritoneal, pleural, synovial liquids, aqueous humor of the eye, digestive fluids belong to this category.



Apparent volume of distribution V_d

theoretical volume of fluid required to contain the total amount of drug at the same concentration as present in the plasma:

$$V_d = \frac{Q}{Cp}$$

i.v. administered **drug amount** divided by **plasmal level** at a time, when distribution equilibrium is achieved

Vd: Apparent volume of distribution (liter)

Q: total amount, dose (mg)

Cp: plasmal concentration (mg/L)

Apparent volume of distribution V_d

- It is virtual, **not a realistic feature**, upon calculating it we assume no metabolization, no excretion of the drug, and that the distributional equilibrium is achieved (i.v. bolus)

conclusions:

- If V_d is smaller than 5 L the drug is distributed only in blood (may reflect strong protein-binding)
- If the value is e.g. 12 L, the drug got into the extracellular space as well
- If higher than 15 L, it got into intracellular compartment as well
- But what if V_d is higher than the total volume of fluid compartments in the body……?
- ➔ accumulation occurs in a compartment

One possible use of apparent volume of distribution V_d

- Some pharmacology books list Vd values of drugs. With this knowledge total drug amount in the body can be estimated.
- Vd = Q/Cp ➔ Q=Vd*Cp

75 kg patient took an unknown amount of paracetamol, 4 hours after ingestion plasmal concentration of paracetamol is 200 mg/l. (Vd= 1 L/kg)

Q= 1L/kg * 75 kg * 02 g/L, so 15 g

(hepatotoxic amount)

Apparent volume of distribution V_d for some drugs

Agent	V_d (L/kg)	Possible distributional volume
Dextran	0,04	Plasm
Acetyl-salicylic acid	0,15	Extracellular fluid compartment
Insulin	0,17	Extracellular fluid compartment
Gentamycin	0,28	Intracellular fluid compartment
Ethanol	0,57	All fluid-compartments
Diazepam	1,1	Tissue cummulation
Thiopental	3	Tissue cummulation

72 kg patient:
Dextran: 0.04*72= 2.88 L ➔ distributed only in blood

Acetyl-salicylic acid: 0.15*72→10.8 ➔ >5L
Insulin: 0.17*72= 12.24 ~ 12 L

Gentamycin: 0.28*72= 20.16 ➔ >15

Ethanol: 0.57*72= 41.04 ~ 42L

Diazepam: 1.1*72= 79.2 ➔ >42L
Thiopental: 3*72 =216 >>> 42L ➔ tissue cummulation

Factors affecting distribution

Factors affecting the drugs getting from the systemic circulation to the tissues.

- Capillar permeability.
- Blood supply of the tissues, velocity of perfusion.
- Plasmal and histic binding of drugs.
- Local pH differences.
- Types of transport mechanisms.
- Permeabilitical properties of the various tissue membranes.

Elimination of drugs: the half-life ($t_{1/2}$)

Elimination of drugs and the half-life ($t_{1/2}$)

- Elimination of drugs: is the process, during which the drugs are metabolised and/or excreted from the body, by which their effect eventually ceases.
  (discussed in details on later seminars)

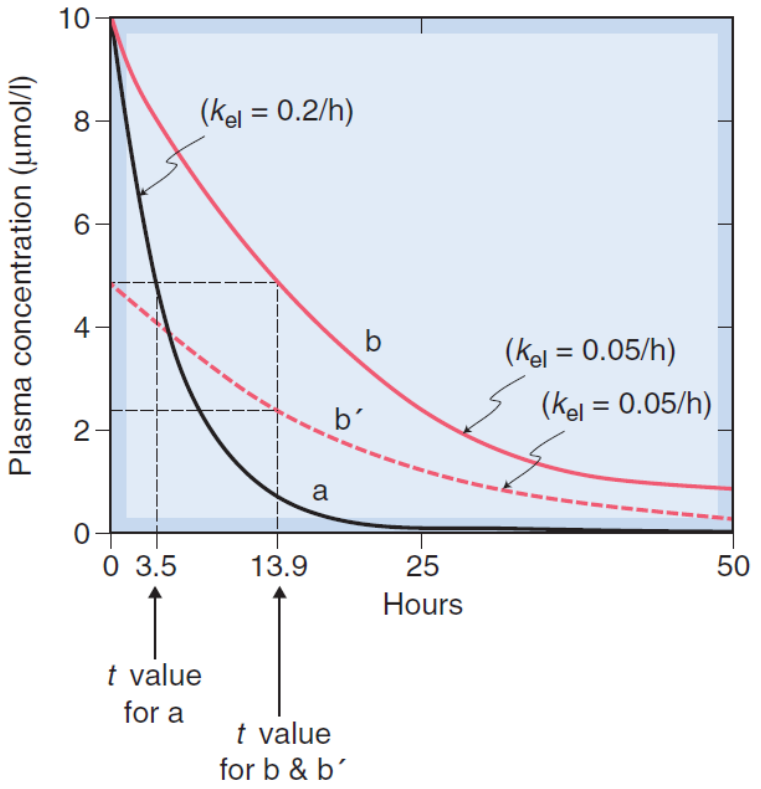
- Half-life (elimination half-life): The time during which plasmal drug concentration decreases to 50%.
  - half-life is directly proportional to V_D, and inversely proportional to clearance (latter see next seminar)

Elimination half-Life ($t_{1/2}$)

- $C = C_o \ e^{-k_{el} t}$ ← exponential decline
- if $C/C_o = 0.50$ ← half of the starting amount then $t = t_{½}$
- $0.50 = e^{-k_{el} t_{½}}$

taking logarithms:

- $\ln 0.50 = -k_{el} \ t_{½}$
- $-0.693 = -k_{el} \ t_{½}$
- $0.693 = k_{el} \ t_{½}$
- $t_{1/2} = 0.693 \ / \ k_{el}$



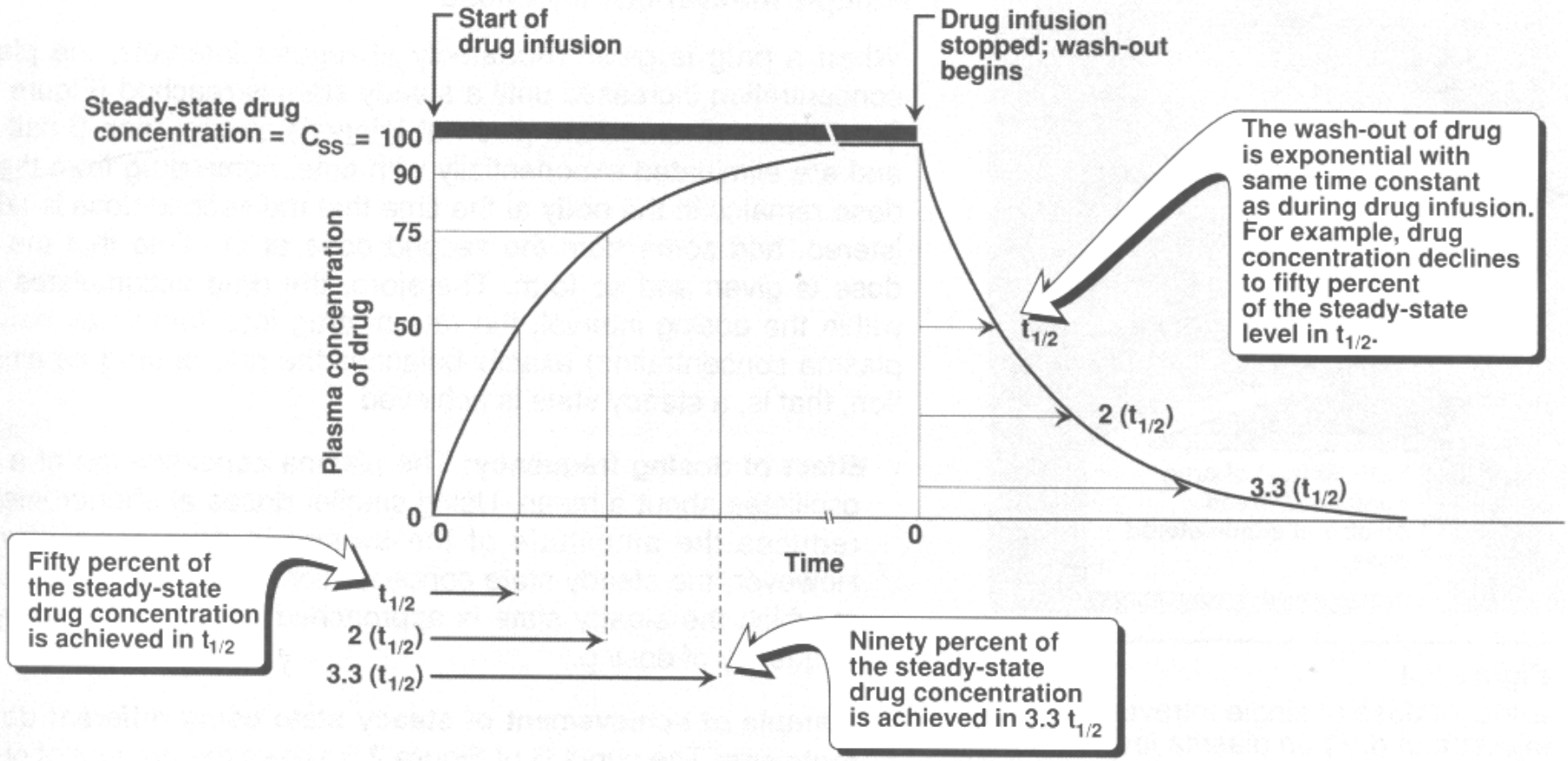
e = Euler-number, a mathemathical constant (2.718281828459)
k_{el} = elimination constant (characteristic to a given drug)
ln = natural logarithm OR logarithm to the base *e*

Use of elimination half-Life ($t_{1/2}$)

- From $t_{1/2}$ value it can be estimated, how much time is needed for the body to almost completely eliminate the drug (this is 4-5 half-life)
  - during one $t_{1/2}$ ➔ concentration will decrease by 50%, (to half of orig. conc)
  - two ➔ by 75 % (to one-quarter of the original conc)
  - three ➔ by 87,5% (to one-eighth of the original conc)
  - four ➔ by 93,75 %
  - five ➔ by 96,875 %…
- $t_{1/2}$ informs about the increase in duration of action upon doubling the dose (which is +$t_{1/2}$)
- even more (next slide)

Drug Half-Life

- during chronic drug administration the longer the half-life, the longer it will take for the drug to achieve its steady-state level:
- one half-life to reach 50% of the steady-state value,
- two to reach 75%,
- three to reach 87.5% and so on.



Drug Half-Life

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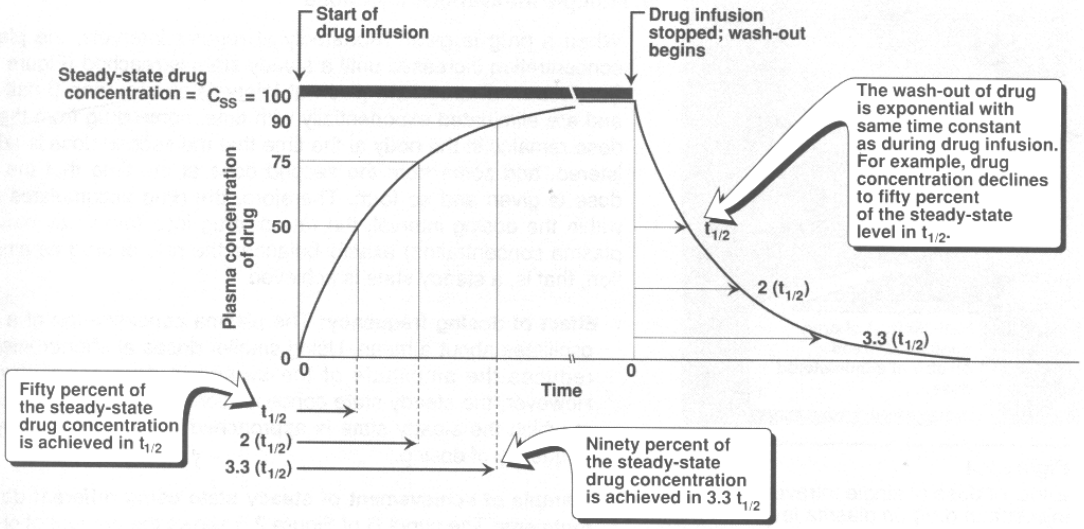

- Mathematically: imagine that we administer injection boluses (its easier to calculate with this but the result is the same with continuous infusion
- First we give 1 dose (100%)
- during one $t_{1/2}$ ➔ concentration will decrease by 50%, (to half of orig. conc)
- But we give again 1 dose (100%) so we have in the system 100% + 50% (the remaining)
- During the next $t_{1/2}$ ➔ concentration will decrease by 50% ➔ 150/2 = 75%
- +1 dose ➔ 100% + 75% = 175%
- During the next $t_{1/2}$ ➔ 175/2 = 87,5% etc. Same numbers as in the case of elimination!

Use of $t_{½}$ and k_{el} data in drug development

- If drug has short duration of action, design drug with larger $t_{½}$ and smaller k_{el}

- If drug too toxic, design drug with

  smaller $t_{½}$ and larger k_{el}

Prescriptions for the exam

Practice

Prescribe Belladonnae folii extractum siccum normatum, Papaverini hydrochloridum and Metamizolum natricum in rectal suppositories

Ingredients for 1 suppository:

Belladonnae folium extractum siccum normatum 0,05 g

Papaverinum hydrochloridum 0,1g

Metamizolum natricum 0,5g

Vehiculum ?

Dispensed form:

Rp./

Belladonnae folii extracti sicci normati

centigrammata quinque (g 0,05)

Papaverini hydrochloridi

centigrammata decem (g 0,10)

Metamizoli natrici

gramma semis (g 0,5)

Vehiculi

quantum satis (qu.s.)

Misce fiat suppositorium.

Dentur tales doses No. X (decem)

Detur ad scatulam

Signetur: Rectal suppository! Keep at coll place! In case of pain apply 1 rectally!

Prescribe Belladonnae folii extractum siccum normatum, Papaverini hydrochloridum and Metamizolum natricum in rectal suppositories

Ingredients for 1 suppository:

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Metamizolum natricum 0,5g

Vehiculum ?

Divided form:

Rp./

Belladonnae folii extracti sicci normati

gramma semis (g 0,5)

Papaverini hydrochloridi

gramma unum (g 1,0)

Metamizoli natrici

grammata quingue (g 5,0)

Vehiculi

quantum satis (qu.s.)

Ut fiant suppositoria.

Divide in doses aequales No. X (decem)

Detur ad scatulam

Signetur: Rectal suppository! Keep at cool place! In case of pain apply 1 rectally!