Semester I.
Seminar 7.

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Exam titles 13-14

13.

- Absorption of drugs and ion trap
- Comparison of elimination of acetylcholine (Ach) and norepinephrine/noradrenaline from the synaptic cleft and the possibilities of pharmacological modulation
- Therapeutic importance of diuretics, mode of action and classification. Antialdosterone compounds and other potassium-sparing diuretics

14.

- Bioavailability. AUC
- Compare the effects of norepinephrine/noradrenaline, epinephrine/adrenaline and isoprenaline
- Inhibitors of carboanhydrase enzyme, thiazides and other sulfonamide type diuretics, high-ceiling diuretics (loop diuretics) and antidiuretics

Absorption of drugs and ion trap

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 absorption and routes of administration

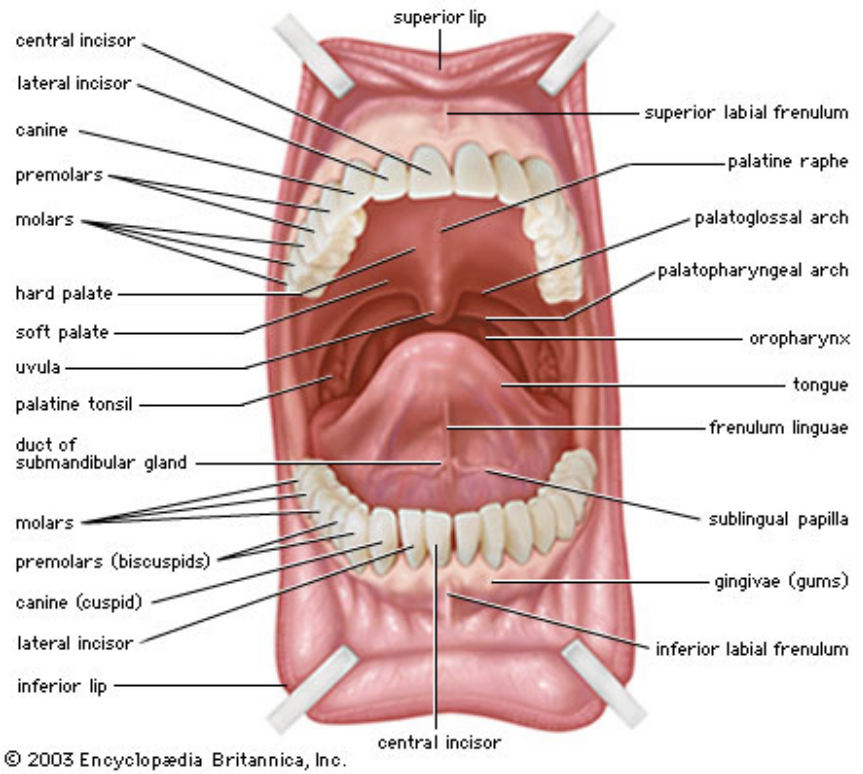
Absorption is defined as*:
the passage of drugs from the site of administration into the plasma
(➔ intravenous administration = NO absorption!)

The *main* routes of administration are:

- oral
- sublingual (oral mucosa)
- rectal
- inhalation
- Injection
- application to other epithelial surfaces
  - e.g. skin, cornea, vagina, and nasal mucosa

*This definition only apllies to systemic application. In case of local application (e.g. topical cream, bronchodilator aerosol) reaching the plasm is not necessary. (Indeed this produces side-effects.)

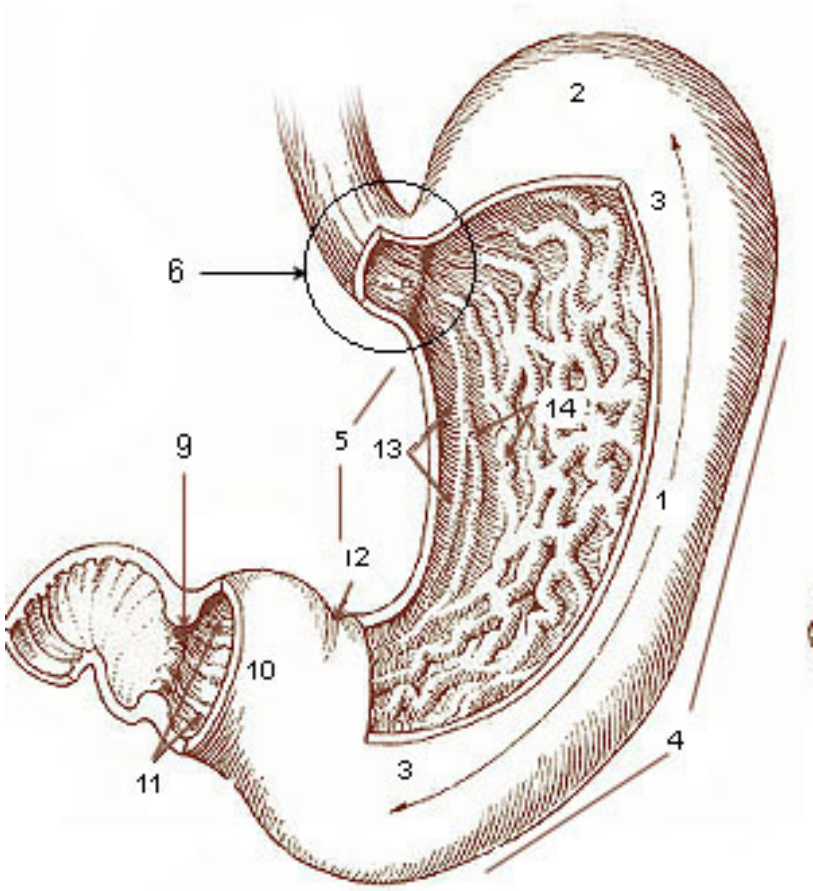
Absorption from mouth cavity - sublingual administration



- Well supplied with blood.
- Thin epithelium.
- pH = 6
- Sublingual administrative form
  - Drug gets immediately into systemic circulation, avoiding the portal system and thus the liver.
    ➔ and so it escapes first-pass metabolism by enzymes in the gut wall and liver
  - Useful when the drug is either unstable at gastric pH or rapidly metabolised by the liver.
  - E.g.: Glyceryl trinitrate
    (antianginal sublingual tablet or spray)

Oral administration – Stomach

- Moderately large surface.
- Well supplied with blood.
- pH= 1-2
- Most drugs become ionizated here and their lipid-water distributional ratio decreases.
- Absorption is influenced by:
  - Gastric motility,
  - gastric contents,
  - position of the body etc.
- Drugs of acidic character are absorbed well from stomach contrasted with public belief.
- „Ion trapping”!

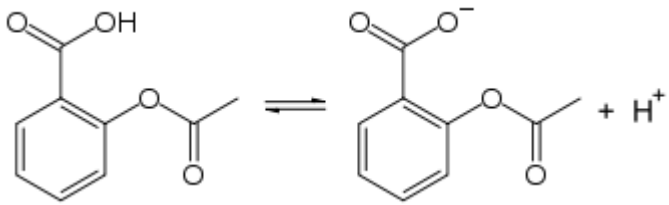


1. Body of stomach
2. Fundus
3. Anterior wall
4. Greater curvature
5. Lesser curvature
6. Cardia
9. Pyloric sphincter
10. Pyloric antrum
11. Pyloric canal
12. Angular notch
13. Gastric canal
14. Rugal folds

The effect of pH on absorption

Drugs are mainly organic electrolites (most of them are weak bases),

they dissociate only partially in aquous environment on the pH of the organism.



dissociation of acetylsalicylic acid

The amount of the ionizated and the non-ionizated drug may be calculated from the *dissociation constant* (K_d) and the *pH* of the environment.

The relationship between pH and pK is supplied by the Henderson-Hasselbalch equation.

Henderson-Hasselbalch equations

$$pK_d - pH = \lg \frac{C_{\text{non ionized}}}{C_{\text{ionized}}} \quad \text{(organic acid)}$$

$$pK_d - pH = \lg \frac{C_{\text{ionized}}}{C_{\text{non ionized}}} \quad \text{(organic base)}$$

K_d = dissociation constant

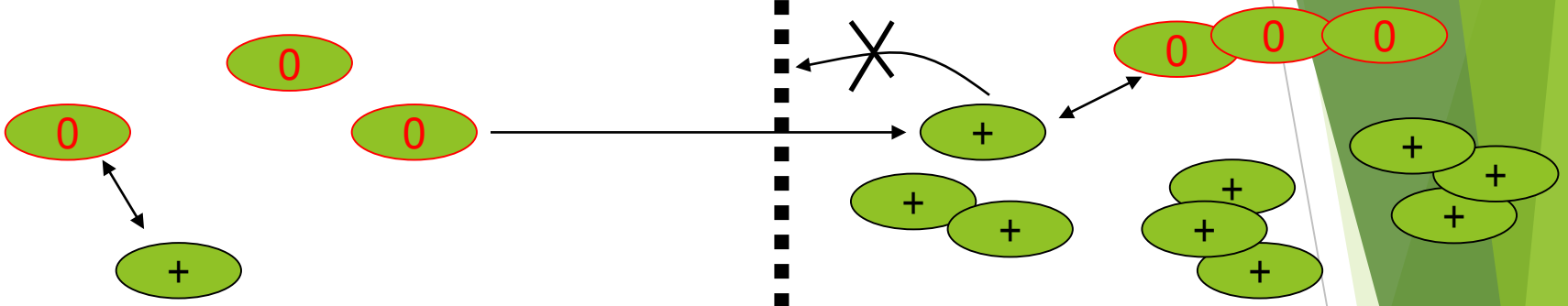
Ion Trapping

administered i.v.

Basic drug molecule

vascular lumen pH7.4
e.g. 75% of the basic drug is non-ionized

lumen of stomach pH1-2
e.g. 25% of the basic drug is non-ionized

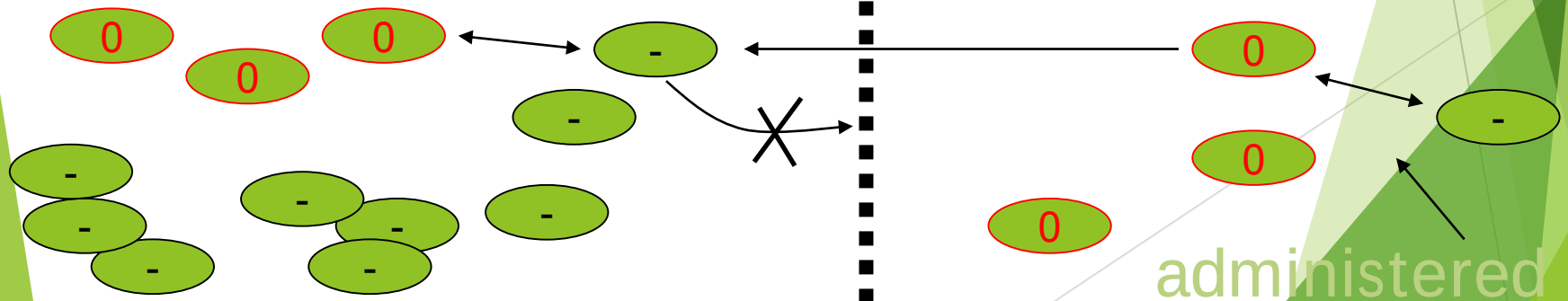


The concentration of the easily-movable non-ionized fraction must be in equilibrium on the two sides of the wall of the stomach. Thus, basic drug molecules accumulate in the lumen of the stomach. (Even after being administered directly into the blood vessels.)

Acidic drug molecule

vascular lumen pH7.4
e.g. 25% of the acidic drug is non-ionized

lumen of stomach pH1-2
e.g. 75% of the acidic drug is non-ionized

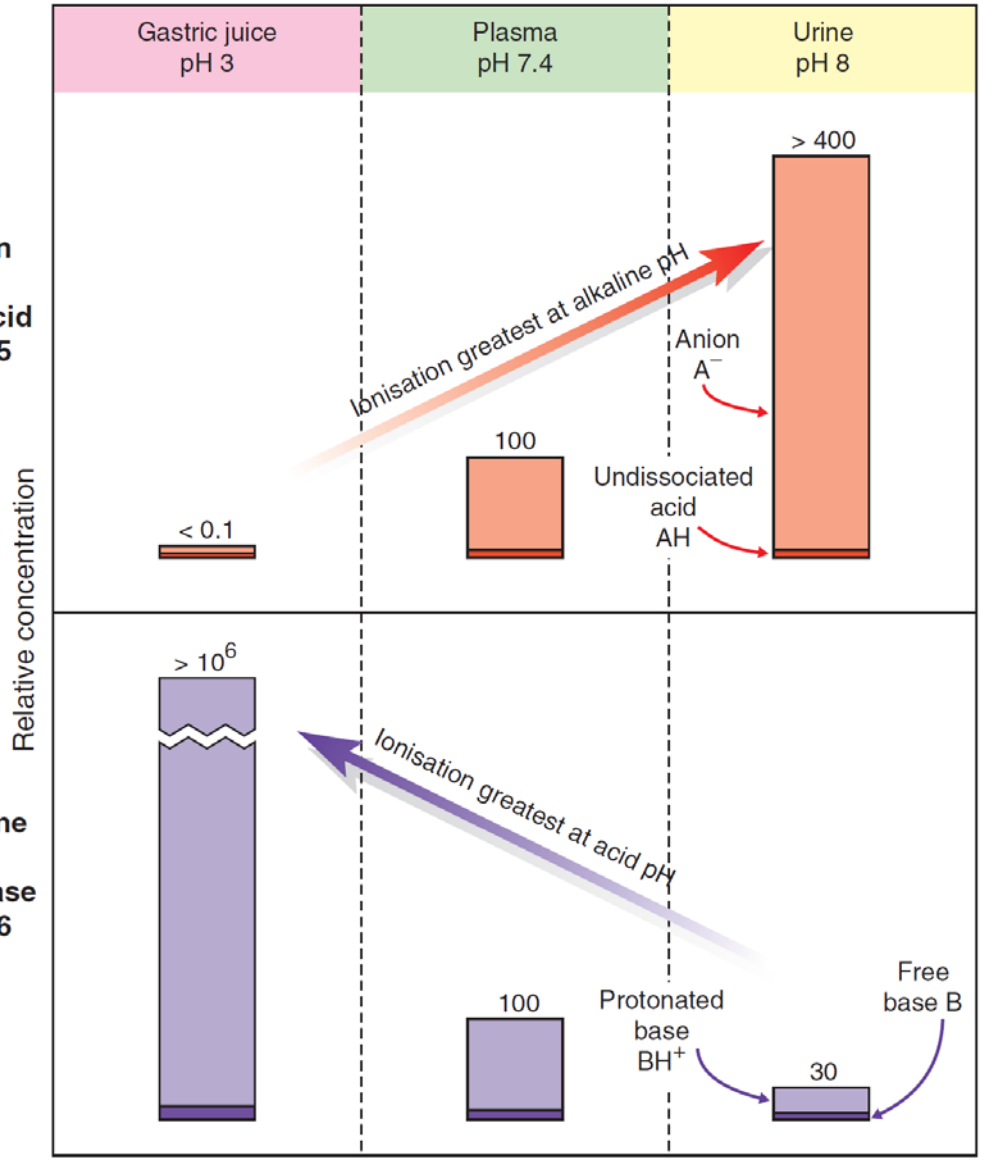


administered p.o.

Administered orally, acidic drug molecules quickly pass through the wall of the stomach, and they would accumulate in the blood, but they are carried away by the blood stream. That's the reason why acidic drugs can easily be absorbed from stomach.

Examples of „ion trapping”

•pH low
•Aspirin is undissociated
•It is absorbed quickly by the stomach mucosa



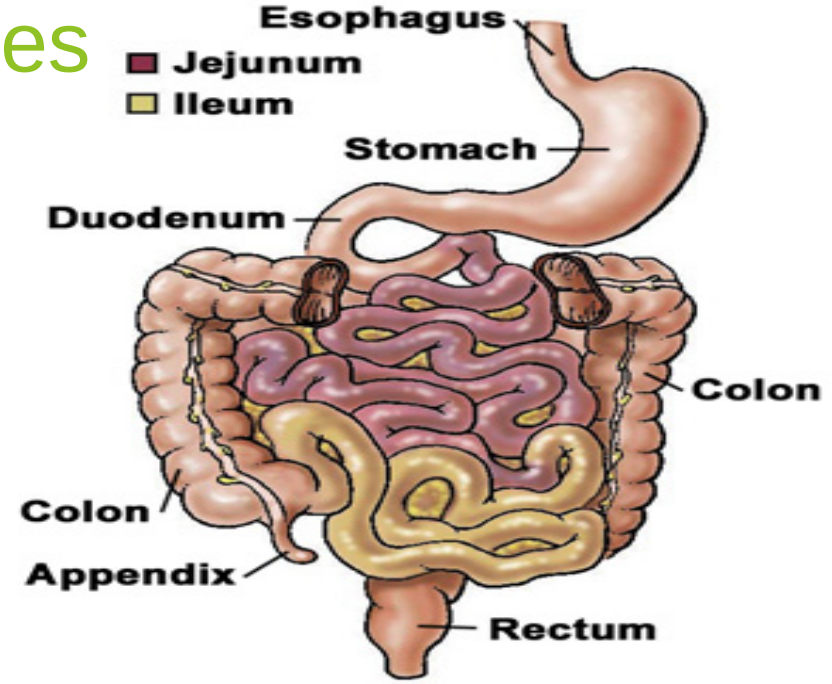
•pH low
•Pethidin is protonated
•It is trapped in the stomach

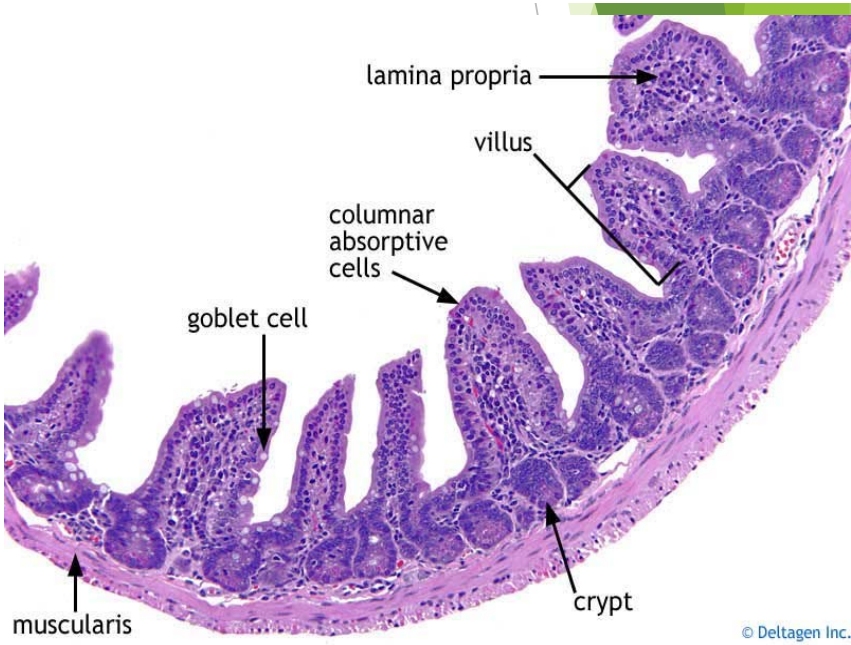
•Inside stomach mucosa cells: pH higher
•Aspirin dissociates in the cytoplasma
•Cannot „go back” into the lumen
•Causes more damage
•(+ PGI inhibition)
•ulcer

Such large gradients are not achieved in reality ➔ equilibrium is rarely reached: the gastric juice and the urine are in motion

Oral administration - Intestines

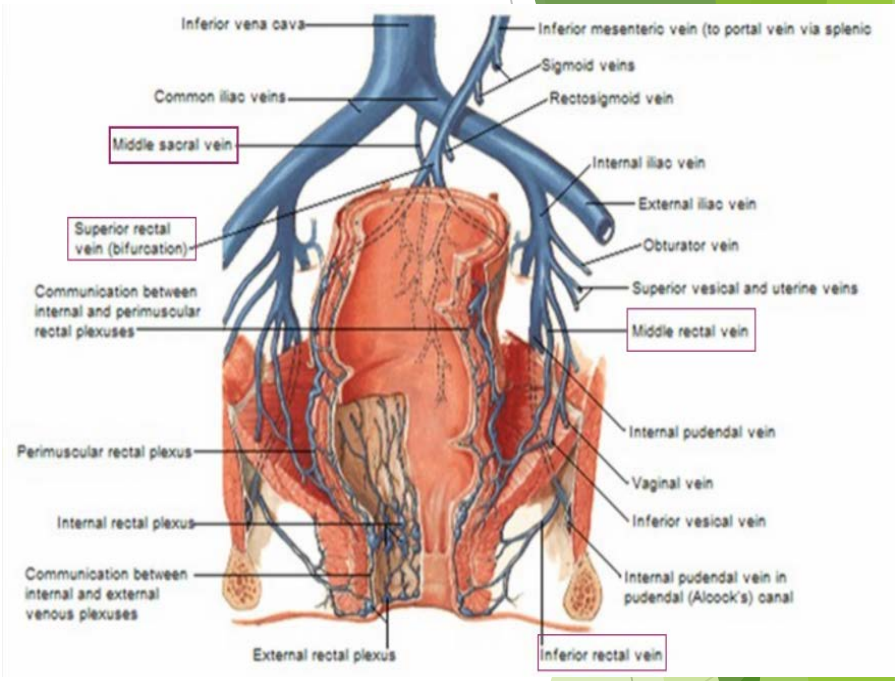
- Small intestines: duodenum, jejunum, ileum. Single columnar epithelium;
- Large surface: villi (plural of villus)
- Well supplied with blood and lymph vessels.
- pH= 5-6
- Dominantly passive diffusion occurs.
- In large intestines usually drug-absorption does not take place (mainly just water).
- Absorption from GI tract is affected by:
  - lipid-water distributional ratio,
  - blood flow,
  - emptying of stomach,
  - drug effect on GI tract,
  - diseases,
  - food,
  - administration form etc.





Rectal administration

- Rectal administration is used to produce:
  - local effect (e.g. anti-inflammatory drugs, or antihaemmorrhoidals)
  - systemic effects (e.g. antipyretics, antiepileptics).
- Veins of the rectum
  - Lower and middle part: drained into iliac vein, then vena cava
  - Upper part: drained into portal circulation ➔ liver
- Rectal drug administration is faster than the oral administration, because 2/3 of the dose avoids first pass metabolism by the liver
  - smaller amount is metabolized, and also smaller dose is enough to exert the same drug-effect
- It can be useful in patients who are vomiting or are unable to take medication by mouth
  - Infants, small children
  - Epileptic seizure

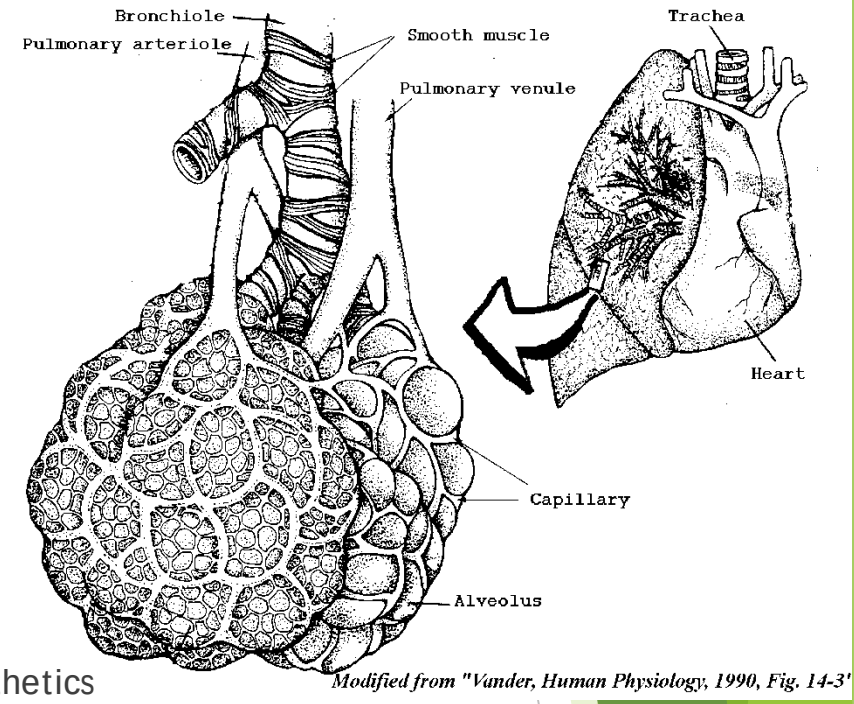


Factors affecting gastrointestinal absorption

- Gastrointestinal motility (see laxatives!)
- Splanchnic blood flow
- Formulation of drug
- Particle size of drug molecule
- Physico-chemical features of drug molecule
- Gastrointestinal content

Etc.

Lungs - Administration by inhalation



Modified from "Vander, Human Physiology, 1990, Fig. 14-3"

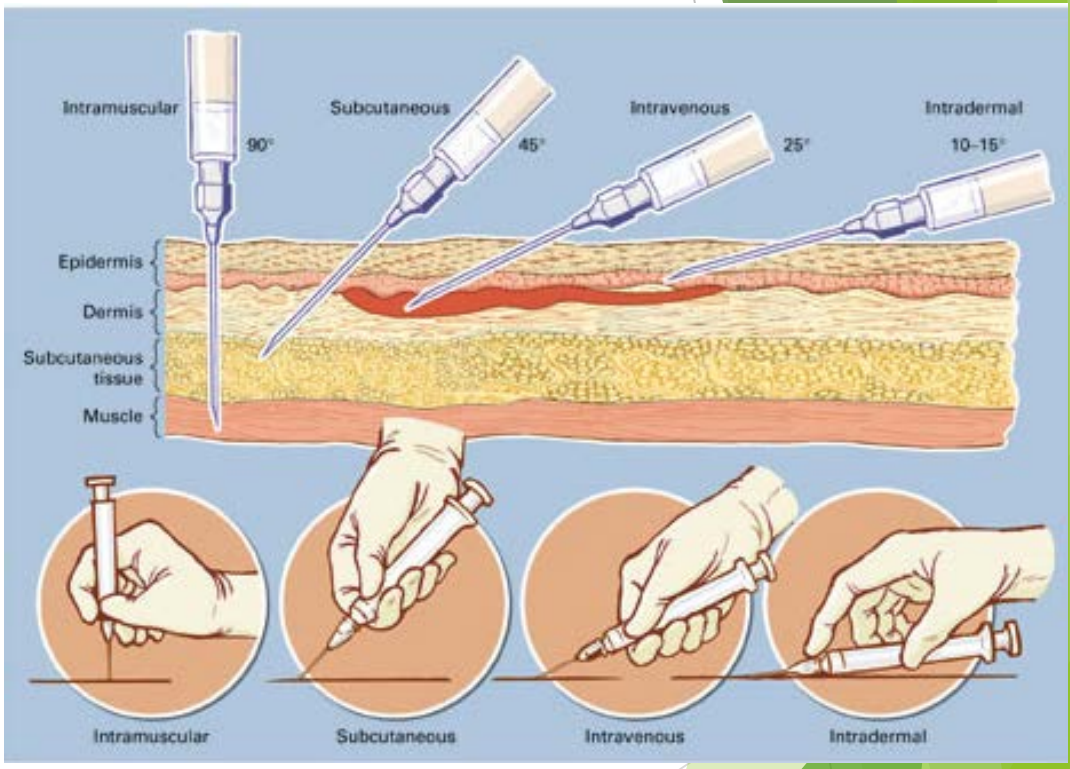
- Very large, 50-100 m^2 alveolar surface.
- Thin membrane (0.2 µm).
- 100% of the cardiac output volume go through the lungs.

Rapid absorption

- Inhalational route is used for:
  - systemic application e.g. volatile and gaseous anaesthetics
  - Local application e.g. aerosols of non/steroid anti-inflammatory drugs; bronchodialtors
- the lung serves as the route of both **administration and elimination**.
- Passive and facilitated diffusion is crucial, but phagocytosis of solid particles is also important
- Factors influencing systemic absorption through lungs:
  - Partial pressure of drug in breathed mixture
  - Alveolar ventillation (= respiratory minute volume)
  - Crossing of drug from the alveoli of lungs into the blood (= Condition of cellmembranes in the alveoli of the lungs)
  - Lipid-water distributional ratio
  - blood-air distributional ratio

Absorption of parenteral administrated drugs - injections

- Most often im., sc. } Absorption is faster than oral
- Things that have effect on absorption:
  - Blood supply,
  - densitiy of connective tissue,
  - vasocontractive treatment
  - pH,
  - concentration,
  - volumen,
  - solvent,
  - lipid-water distributional ratio etc.



- By intravenous administration there is no absorption!!
- Other exotic injection locations: intraperitoneal, intrathecal, epidural, intravitreal, retrobulbar, intraosseous, intra-articular, etc.

Skin - percutaneous, dermal absorption

- Moderate surface.
- Well supplied with blood and lymph vessels.
- Keratinized stratified squamosus epithelium inhibits the absorption.
- Mainly molecules of lipophylic character get through, but along the perspiratory and sebaceous glands watersoluble molecules may get inside as well.
- Factors influencing skin absorption
  - Concentration
  - Duration of contact
  - Solubility of medication
  - Physical condition of the skin
  - Part of the body exposed including the amount of hair on the skin.
- Dermal administration route:
  - Local application (e.g. dermatological ointments)
  - Systemic application (transdermal therapeutic systems, TTS; see on a later seminar).

Other routes of administration

- Nasal mucous membrane.
- Urethra.
- Vagina.
- Eye.
- Ear.
- Implants.

Bioavailability. AUC

Bioavailability

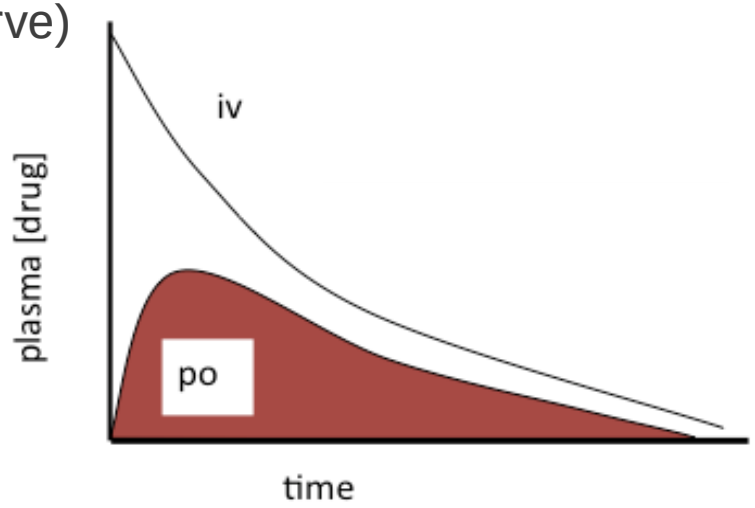
- During absorption a drug may be metabolized (see first-pass effect on next seminar)
- The term *bioavailability* is*:*
  - the fraction (F) of an administered dose that reaches the systemic circulation as intact drug
- *F is measured:*
  - *by determining the* c_p versus time curves in a group of subjects…
  - 1. …following oral administration and
  - 2. …(on a separate occasion) following intravenous administration

    (because the fraction absorbed following an intravenous dose is 100% by definition)
  - 3. calculation:

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

$AUC_{0-\infty}$

- The **area under the curve** (AUC) is the ”integral” (= indeed the area under the curve) in a plot of plasma-concentration of a drug against time.
- The AUC (from zero to infinity) represents the *total drug exposure over time*.
- Or it represents the total amount of drug that reaches the blood circulation

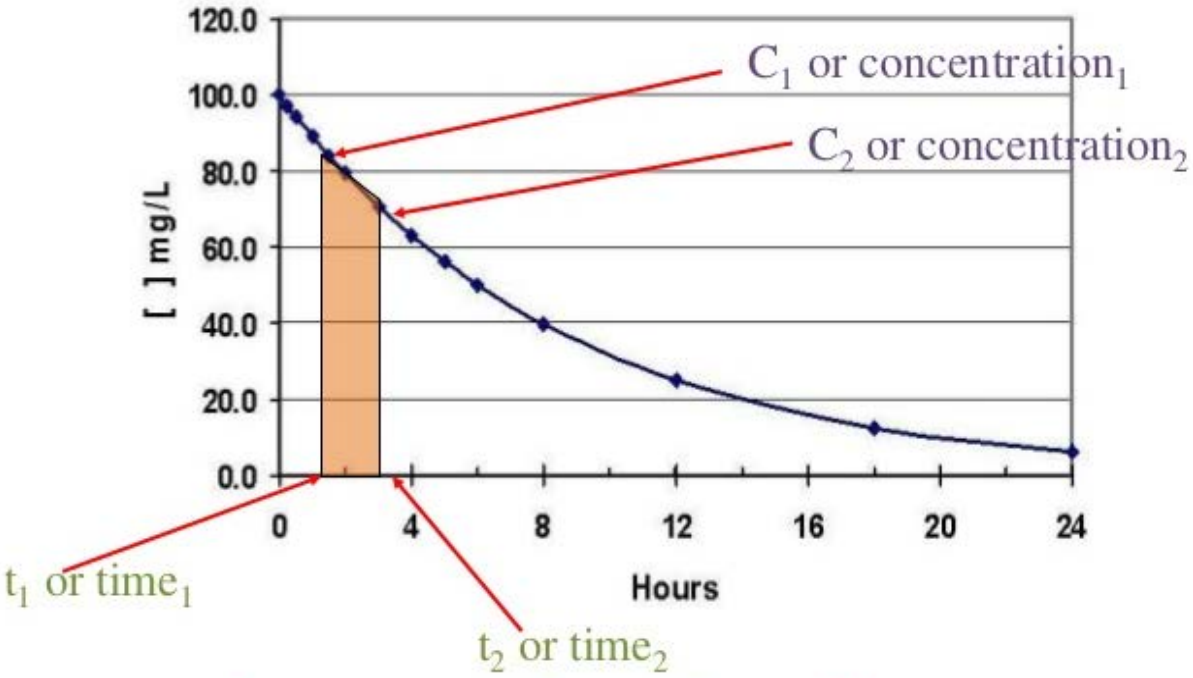


- In practice AUC is used for:
  - Measuring absolute bioavailability of different forms of a medicine (same drug, e.g. per os versus i.v.)
  - Or measuring the relative bioavailability (comparing two different medicines)

How to calculate AUC

- the area is computed starting at the time the drug is administered and ending when the concentration in plasma is negligible.
- In practice, the drug concentration is measured at certain discrete points in time and the trapezoidal rule is used to estimate AUC.

Trapezoidal Rule:



$$Area = ((C_1 + C_2)/2)(t_2 - t_1)$$

Between two concentrations the curve is almost a straight line ➔ if we know the 4 edge points, we can calculate the area of the trapeze

Bioequivalence - Generic drugs

- So, AUC is useful to compare 2 different medicines containing the same active substance.
- It used for evaluating the bioequivalence of an original and a generic drug.

- **What is a generic drug?**
- If „someone" „invents" a new drug molecule
- research costs approx. 600-1200 MILLION DOLLARS!!
- If everything went fine, the drug is effective and harmless, it can be marketed
- For original drugs, in most countries**, patents** give 20 years of protection = only the owner can produce and sell the drug („copyright")
  - So that the invested money pays off

Bioequivalence - Generic drugs

- After this 20 years, every pharmaceutical company is allowed to produce the same active substance, and make a new medicine from it,
- they only have to confirm that their formula is BIOEQUIVALENT with the original.
- This procedure costs much less, so the company can sell the new drug in a low price but make much money ☺

According to this, the definition of generic drugs is the following:

- A **generic drug** is "a drug product that is comparable to an original brand drug product in dosage form, strength, quality and performance"

<u>How to confirm this bioequivalence? – use the AUC!</u>

- Take 20-20 patients, 20 will take the original tablet, 20 take the generic.
- Measure the c_p/t curves of the active substance ➔ calculate AUC
- Compare the average AUC of the generic drug with the AUC of the original – if it is in the range from 80-125%, **the 2 medicines are BIOEQUIVALENT**
- From this time you can sell your generic drug, you don't have to prove that ist's effective and that it's not toxic, because they have proven it years before (for the original substance).

Some more about AUC

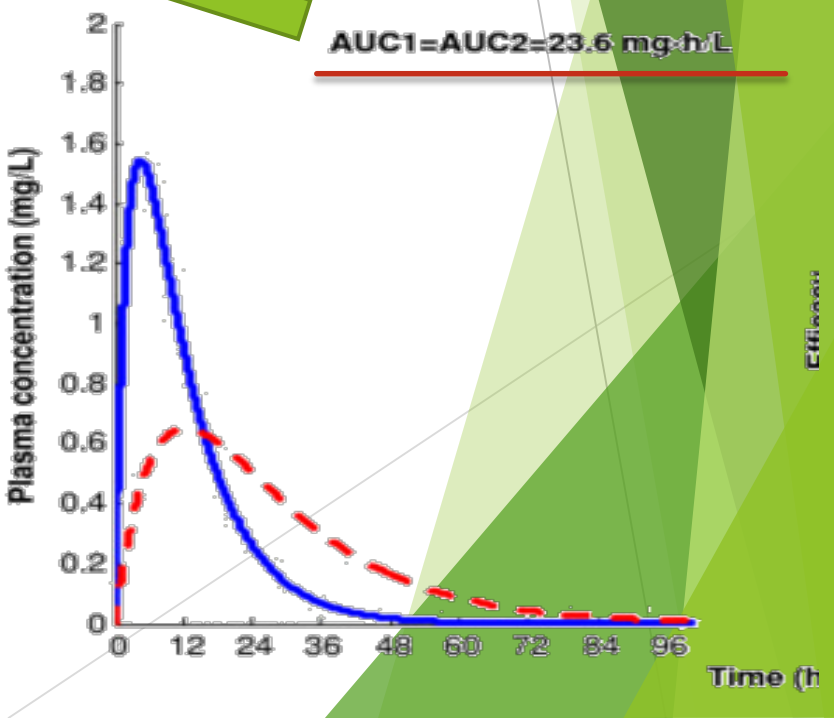
- the AUC is directly proportional to the total amount of drug administered
- but irrespective of the rate of absorption.

AUC provides no information about the rate of absorption or elimination kinetics!

e.g.

- Drug licensing authorities require not only AUC for bioequivalence

- $AUC_{(0-\infty)}$, c_{max}, t_{max} must lie between 80% and 125% of the original product
  - c_{max} is the maximal concentration
  - t_{max} is the time between dosing and c_{max}



Prescriptions for the exam

2. Prescribe Digoxin injections

Rp./

Injectionum Digoxin

ampullas originales No.: tres (III)

D.S.: Suo nomine, into the hands of the doctor.