Factors that influence drug effects.

Effect of concomitant diseases and polypharmacy.

Adverse drug reactions.

Overview of factors

- **A. Factors related to drug:**
  - Physical and chemical properties
  - Drug form
  - Food administered together with a drug

- **B. Factors related to drug and to organism:**
  - Dose
  - Combination of drugs
  - Repeated administration

- **C. Factors related to organism:**
  - Age
  - Sex
  - Weight and body constitution
  - Circadian rhytms
  - Pathological state of organism
  - Genotype/fenotype
  - (Race group/ethnic group)

A. Factors related to drug

I. Physical and chemical properties

II. Drug form

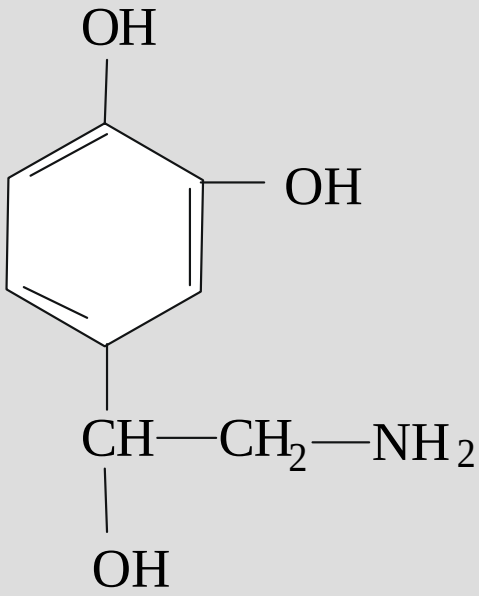
III. Food administered together with a drug

I. Physical and chemical properties of drug

Influence on the transport trough membranes

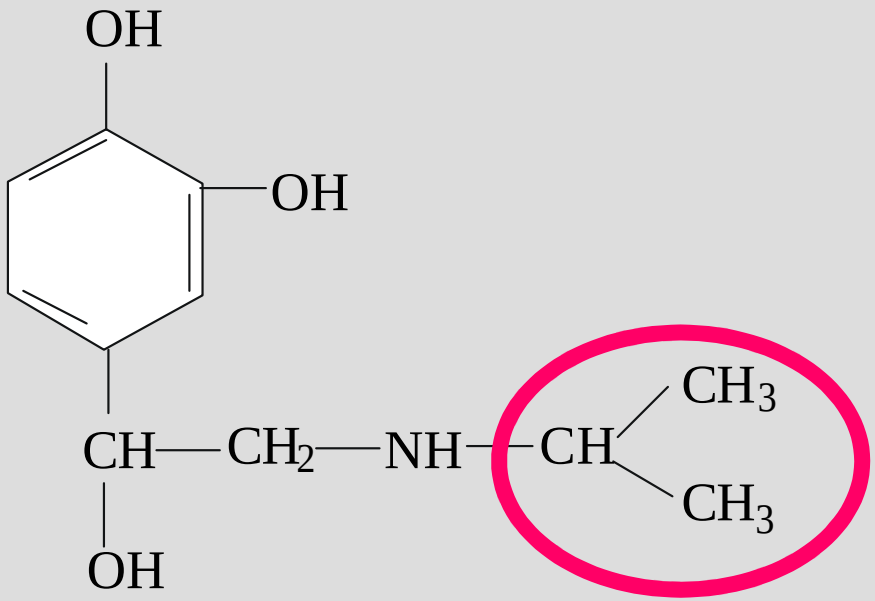
- Chemical configuration
- Size and shape of the molecule
- Solubility in water and fats
- Acidobasic properties

Relationship between chemical structure and character of the effect



noradrenalin

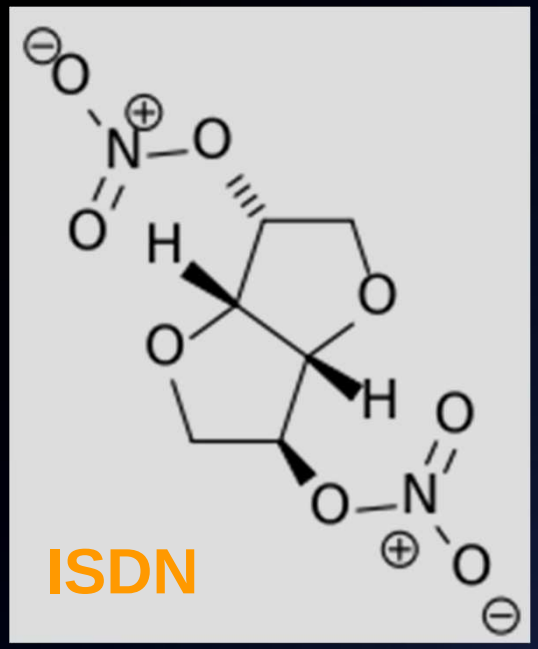
účinky převážně
α mimetické

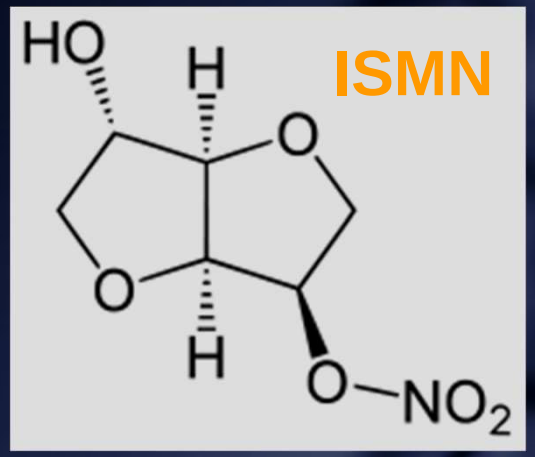


isopropylnoradrenalin

účinky převážně
β_1 α $\beta_2$mimetické

Relationship of chemical structure to PK

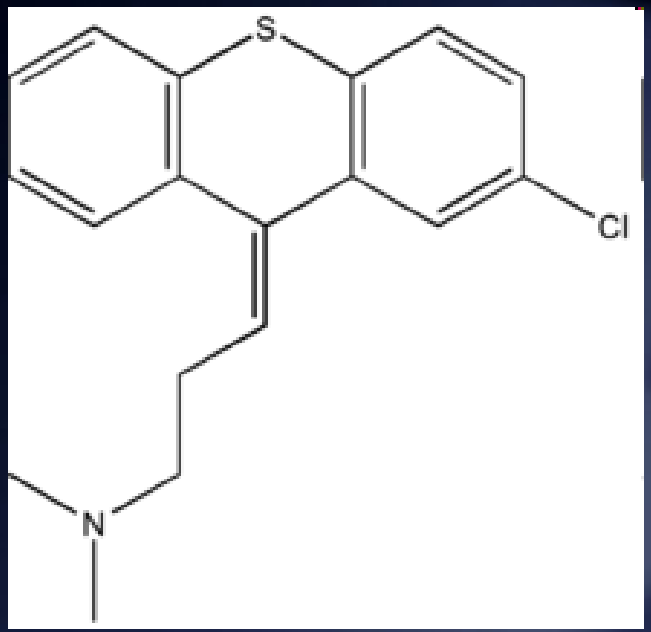




- ISDN is more lipophilic than ISMN
- ISDN may be administrated sublingually
- ISMN is almost not subject to the hepatic FPE
- Another example: atenolol x metoprolol

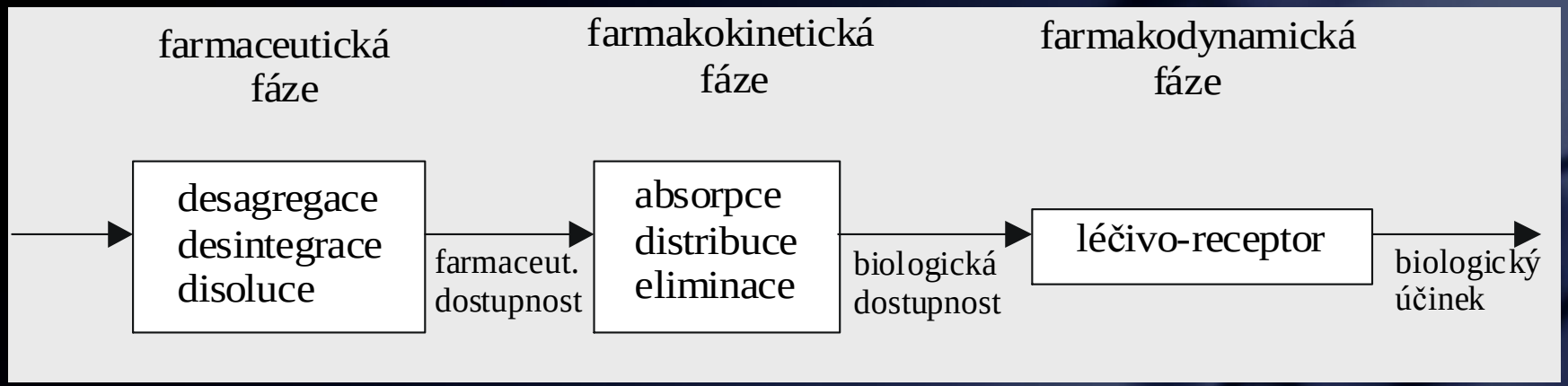
Stereoisomerism

- *Cis-trans* isomerism: only the *cis* form of chlorprotixen is efficient



II. Drug form

- definition: a substance or combination of substances presented as having therapeutic or preventive properties administered to set the medical diagnosis.

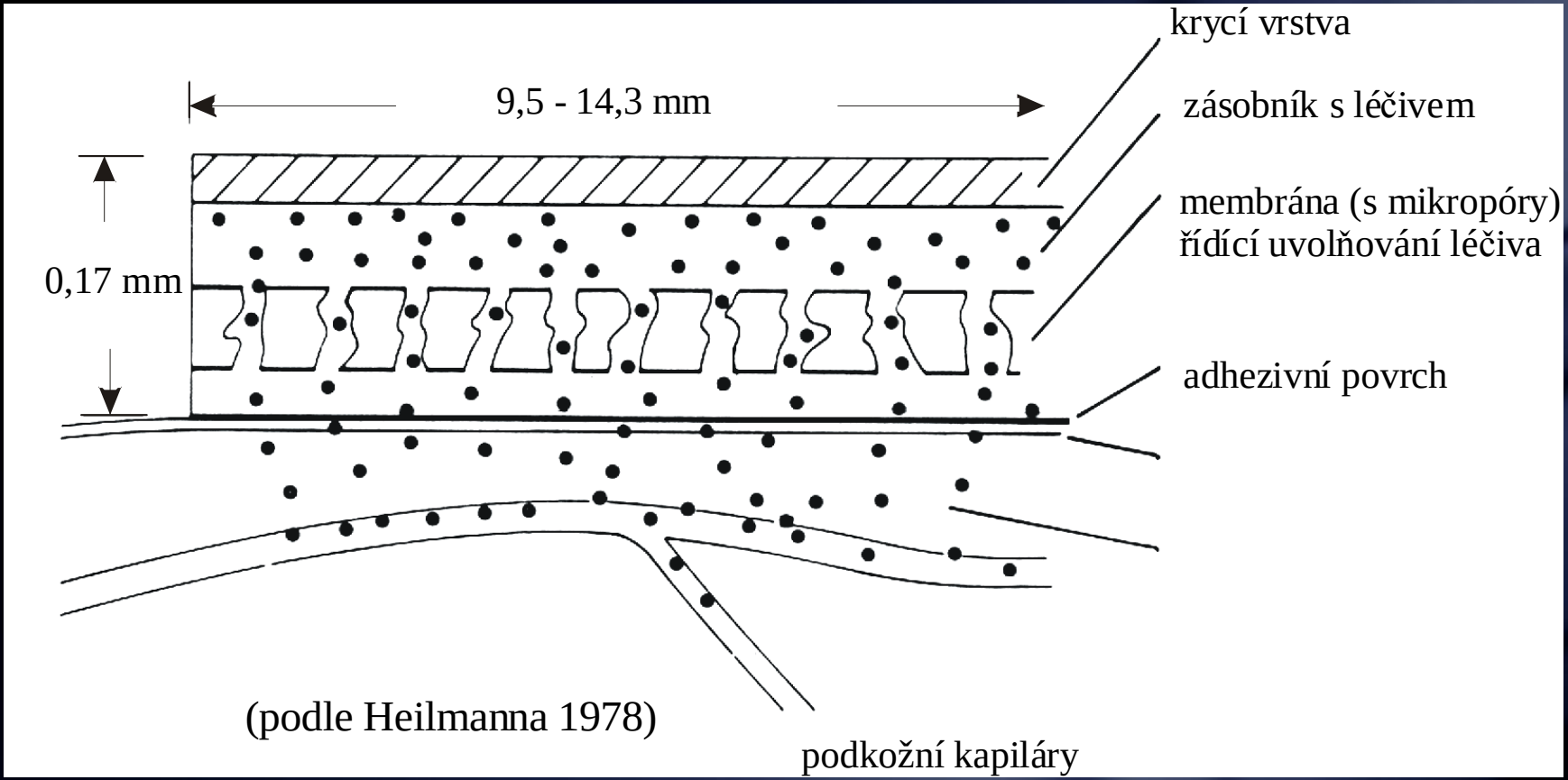

farmaceutická fáze
farmakokinetická fáze
farmakodynamická fáze
desagregace
desintegrace
disoluce
farmaceut. dostupnost
absorpce
distribuce
eliminace
biologická dostupnost
léčivo-receptor
biologický účinek

Drug form generations

- 1. generation – conventional DF
- 2. generation with controlled release
  - with prolongated release (SR,XR...)*
  - transdermal therapeutic system
  - gastrointestinal therapeutic system
- 3. generation with targeted drug delivery

*SR=sustained release, slow release
LA=long acting, SA=slow acting, XR=extended release
CR=continuous (controlled) release, retard atd.

Example of transdermal therapeutic system



- Liposomal vers. conventional drug (e.g. amfotericin B)
- Stealth liposomes = PEGylated (daunorubicin, doxorubicin)
- Nano-liposomes

III. Food intake

FD interactions

- non-selective inhibitors of monoaminooxidase increase the bioavailability of tyramine from food (fermented food is risky, e.g. some cheese, red wine, smoked meat, bananas). There is a menace of excessive wash out of catecholamines and hypertense crisis.

- food with high content of vitamin K (e.g. broccoli) can decrease the effect of warfarin (vitamin K antagonist)

FK interactions

- more often- influence at the level of absorption, but also in metabolism and excretion

Farmacokinetic interactions with food

Food can:

- slow down the absorption without the change of extension of bioavailability (inappropriate in analgetics, hypnotics…)
- decrease bioavailability
- inrease bioavailability

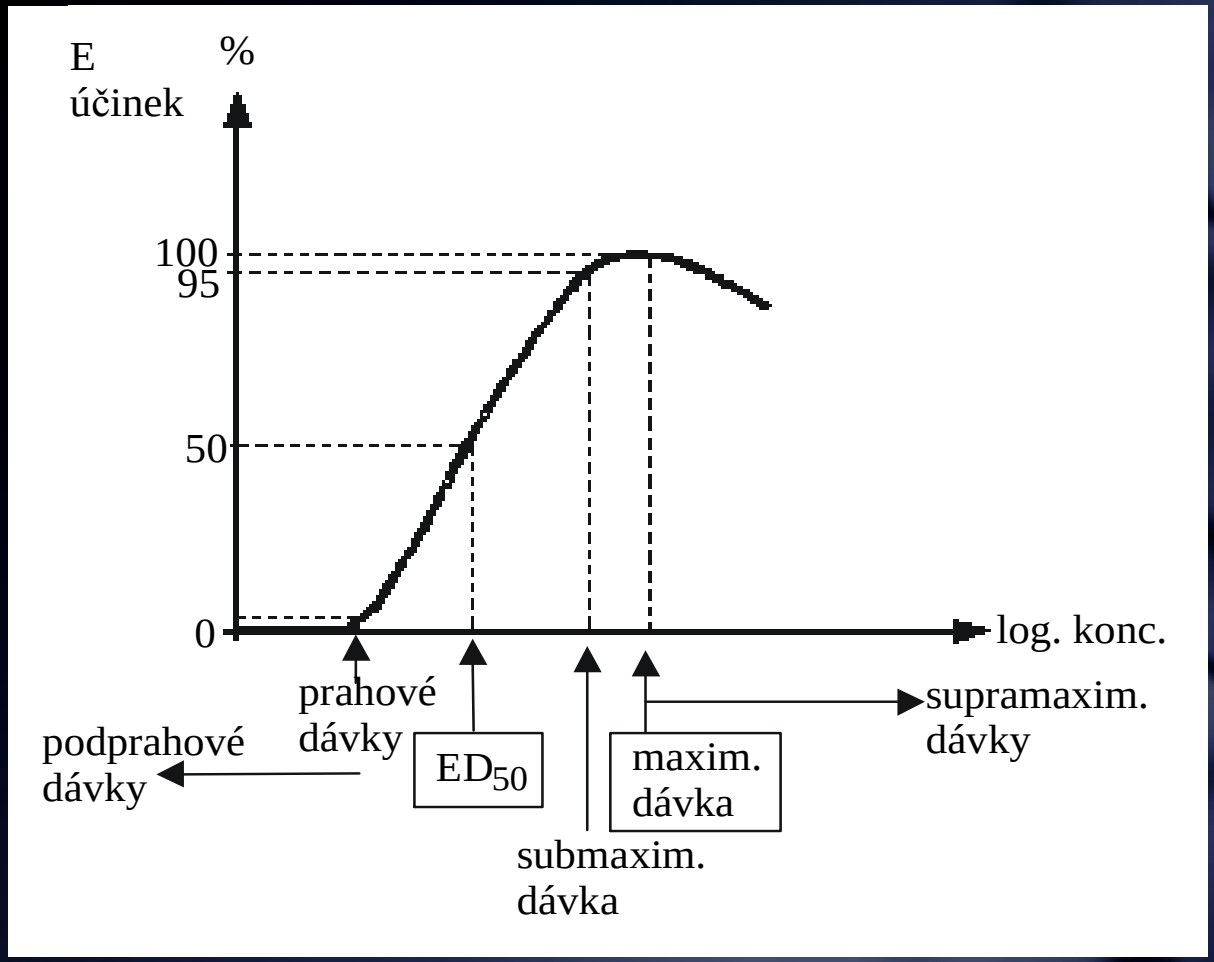
Division of factors

- **B. Factors related to drug and to organism:**
  - Dose
  - Combination of drugs
  - Repeated administration

Dose - dosis

- In preclinical trials
- In clinical trials phase I: MTD (maximal tolerated dose)

Quantitative test– dose-effect curve



Doses in pharmacotherapy

- Dosis therapeutica (therapeutic dose)
  - pro dosi (singula)
  - pro die
- Dosis maxima (maximal dose)
  - pro dosi (singula)
  - pro die
- Dosis curativa – therapeutic dose (cumulative)

Information about doses

- **SPC** = summarizing information about LP
  (Summary of Product Characteristics)

Available on:

  - **AISLP** -Automated informative system LP
  - SÚKL database (State authority for control of drugs)

- **Czech pharmacopoeia**

II. Combinations of drugs

The effect is 

S y n e r g i s m

- Sumation: both drugs have the same (similar) effect and, if we combine them, the final effect is a total of effects, which the drugs would have when administered in monotherapy

  one-sided : analgetics anodynes + narcotics

  two-sided : combination of cytostatics

- Potenciation

  one-sided : Ca^{2+} + digoxin

  two-sided : digoxin + thiazid diuretics

Combinations of drugs

The effect is 

A n t a g o n i s m

- pharmakological (ACH + atropin)
- physiological (ACH + adrenalin)
- chemical (heparin + protamin sulfate)

  (metals + dimerkaprol, EDTA)

C. Division of factors

- **Factors related to organism :**
  - Age
  - Sex
  - Weight and body constitution
  - Circadian rhytms
  - Pathological conditions of organism
  - Genotype/fenotype

Age

Administration of medicinal product (MP)

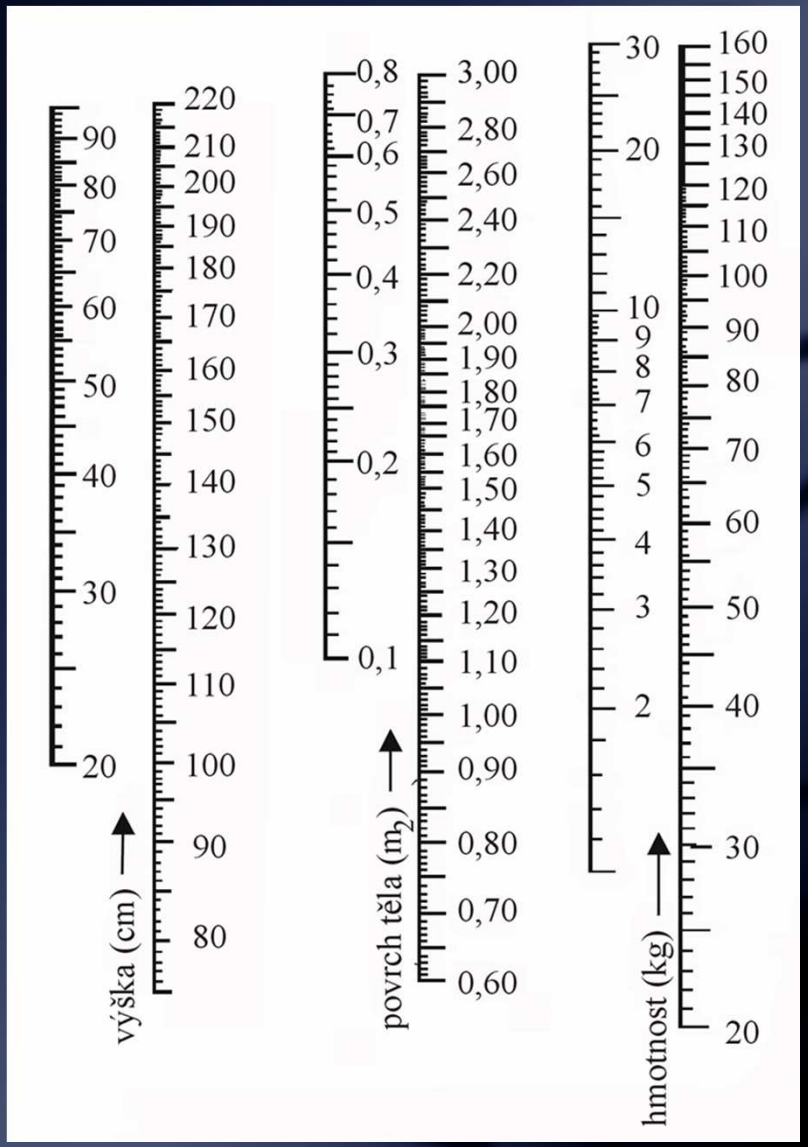
- to children
- to old people

Administration of MP to children

approximate dose for children

=

$$\frac{\text{body surface area } (m^2) \times \text{dose for adult}}{1,7}$$



Administration of MP to children

A child is not a miniature of an adult

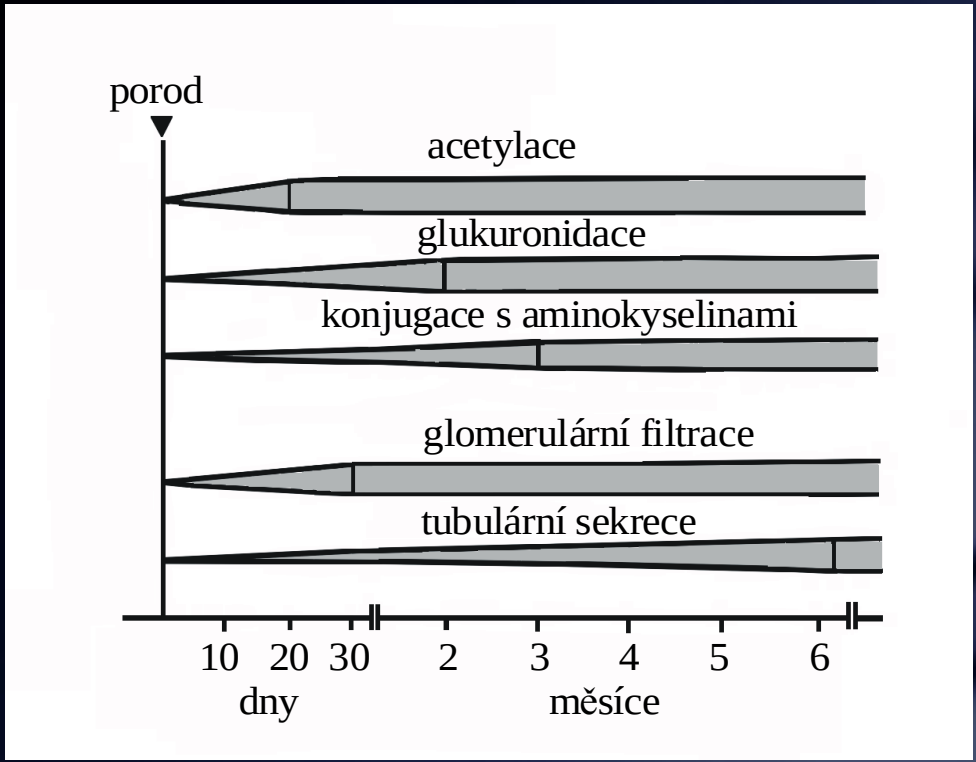
- particularities of FD
- particularities of FK

Particularities of PK of drugs in child

Particularly on newborns (especially premature):

- relatively bigger volume of extracelular liquor
- lower binding on plasmic proteins
- unfinished developement of hematoencephalic barrier
- immaturity of enzymatic systems
- Immaturity of renal functions

Postnatal developement changes of selected hepatic and renal functions



- In newborns - activity of majority of the hepatic enzymes is lower
- There is a big risk of cumulation of drugs and of toxicity if the dosage is not adapted.

Particularities of pharmacodynamics of drugs in child

Antihistaminics

- in adult- sedation (somnolency, fatigue)
- In child- even excitation (convulsions)

Administration of MP to old people

- 60 – 74 older person
- 75 – 89 elderly
- > 90 longevity

- physiological changes
- multimorbidity
- polypragmasia (administration of many drugs together, risk of drug interaction is increasing)
- higher incidence and severity of adverse effects

Changes of FK of drugs in old age

- absorption (passive diffusion of subacid substances thanks to hypoacidity, active transport is decreasing)
- binding on plasmic proteins
- elimination: decrease of blood flow through kidneys and GFR, flow through liver and activity of redox enzymes

=> **Prolongation of $t_{1/2}$**

(e.g. digoxin, aminoglycoside atb)

Changes of FD in old age

- Very variable
- Tissue hypoxia
- Dysfunction of regulatory mechanisms
- Change of sensibility of target structures
  = hyperergic reaction

Changes of FD in old age

Examples:

- ATB aminoglykosides:

  lower doses in case of lower GF (correction according to CL CR)
- Antihypertensives: orthostatic hypotension, psychical alternations (confusion)
- Anticoagulants: bleeding from GIT (decreased absorption of vitamin K and decreased synthesis of prothrombin)
- NSAID: in 25% hematemesis
- Anticholinergic substances: higher toxicity, depression, confusion

Sex

- Women are in general more sensitive to effects of some drugs, e.g. because of lower weight, but also of lower CL (olanzapin)

- Specific periods are:
  - menstruation
  - gravidity
  - lactation
  - menopause

Gravidity

- slowed stomach and intestinal motility
- increased volume of plasma, body water can be raised up to 8 litres more
- hypoalbuminemia, occupancy rate of plasmic proteins by hormones
- increased flow through kidneys and increase of GFR

Weight and body constitution

- In many cases drugs are dosed in consideration to the weight of the patient (it's recommended to use dosing per 1kg of body weight, respecting the patient's age)
  - Dosage mode: dose per time period
  - Dose: mg/kg, mg/kg/age, mg/m^2

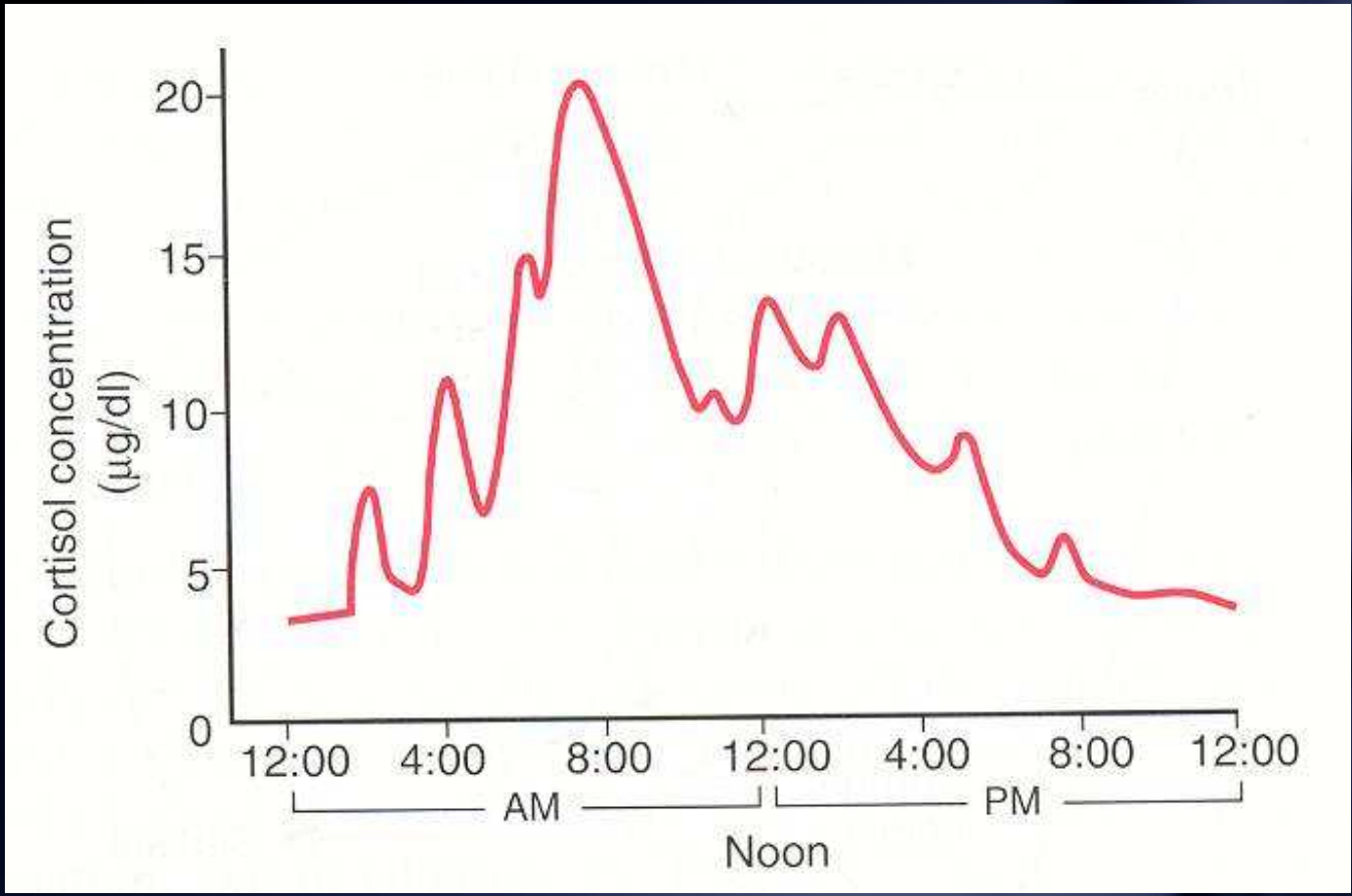
Infuence of weight and body constitution

- „muscular type“ needs higher doses of substances affecting neuromuscular junction or binding on muscles
- „obese type“needs higher doses of substances binding on fats

Circadian rhytms

- are the object of studies of *chronopharmacology* a *chronotherapy*
- Biorhytms of body functions in dependence on time of day or season
- base = diurnal rhytm of release of hormones and of activity of some enzymes
- Example: Incidence of asthmathic attacs is the highist in early morning time, when the tone of sympatikus is low and also the level of endogene glucocorticoids is low.

Circadian rhytm of secretion of cortizol



Pathological state of organism

- Influence of lesion/dysfunction of kidneys, liver and thyroid gland on pharmacokinetics
- Influence of pathological state on drug pharmacodynamics

Hypofunction of kidneys

- The most common reason for customisation of the dosage
- Customisations of dosage in accordance to the tables – GFR is a clue
- For the majority of drugs, the customisation of the dosage means prolongation of intervals (AMG, vankomycin)
- In drugs with very long $t_{1/2}$ we keep the same interval, but administer a lower dose (digoxin)

Influence of liver deseases

- No reliable quantitative criteria is available for measuring disturbed liver elimination capacity (analogy CL_{cr} in kidney dysfunctions) ⟶ empirical attitude

- Liver function tests (aminotransferases, albumine, blood coagulation factors) are not a good clue for the dosage of drugs

In persons with liver diseases

- Prefer drugs eliminated mostly by kidneys, if possible (or those whose kinetics is not disturbed by liver hypofunction) e.g. atenolol
- Prefer drugs acting directly – without activation of biotransformations in liver (lisinopril x enalapril)
- Think about the possibility of increased biol. availability when drugs with big first-pass effect are administered p.o (e.g. metoprolol)

In persons with liver diseases

- Think about the possibility of disturbed elimination of drugs which are eliminated mainly by liver (over 60 - 70%)
- Reduce the doses when a progressed liver disease is present: diazepam, paracetamol, fenobarbital, fenytoin, valproic acid, mesokain, morfin, teofylin, calcium channel blockers
- Administer carefully: antidiabetics, diuretics, anticoagulants, antihypertensive drugs (follow the achieved effect)
- Monitoring of levels is recommended in: antiepileptics, theofylin, cytostatics (low TI)

Other pathological states

- Heart failure (centralization of the circulation)
  - absorption after p.o. administration can be slowed down or decreased
  - biol. availability of the substances with strong FPE can be increased
  - absorption after i.m. administration can be slowed down
- GIT dysfunctions (malabsorption, stomach ulcers a nausea-provoking states, vomitting)
- Thyroid gland dysfunctions (by hyperfunction- the intensity of metabolism is commonly increased) e.g. hyperthyreosis can intensify the effect of warfarin
- Fever (↑GF, acceleration of elimination of gentamicine)
- Edema (↑ V_d gentamicine)
- Obesity

Genetic factors

- The answer on drugs varies among individuals qualitatively and quantitatively

interindividual variability – polymorfism

- Genetic factors influence FD and also FK

Genetic factors

- **Genetic polymorfism** = existence of several (at least two) alleles for a concrete gene, the least frequent one of which has the population frequency at least 1%

- **Pharmacogenetics**
  is a field which is focused on studies of genetically conditioned variability in answering of the organism to a drug

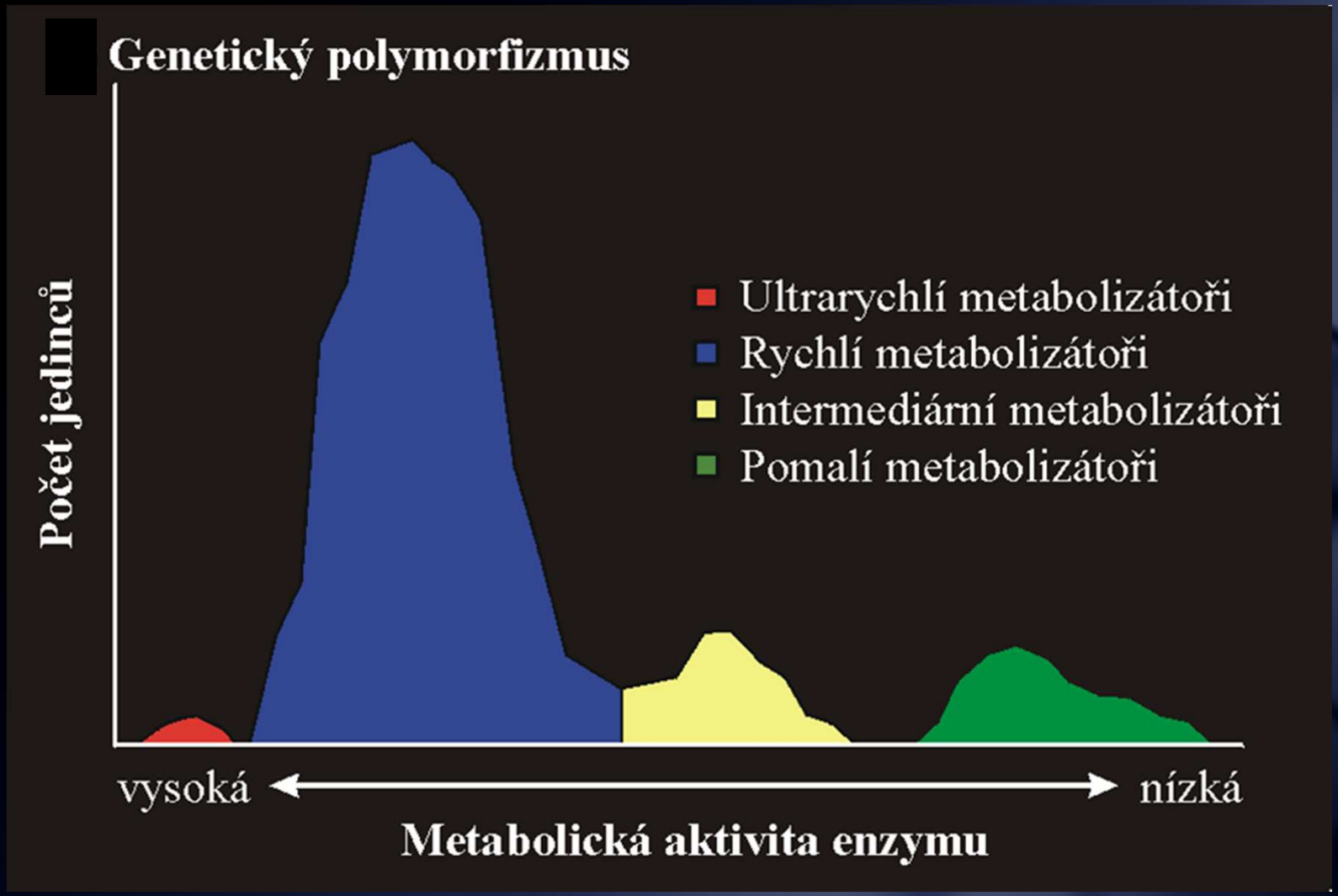
  (**Pharmacogenomics** investigates the relationship of drug effect at the level of the whole genome, resp. transcriptome)

Genetic factors- FK

- **Genetic polymorphism** of enzymes metabolizing drugs and transporters for drugs:

  In our population, there exist more different fenotypes (slow, middle, fast, eventually ultra-fast metobolisator)
  with a frequencey higher then 1%, which are caused by mutation of one gene (monogene dependence)

- Genetic tests of deviations in the metabolism and transport of drugs are not done commonly, although the findings about the big influence on pharmacokinetics exist and the methods for examining polymorphism are available and fast (but expensive).



Monogenní mutace x polygenně podmíněná

Examples of pharmacogenetic variability

- Polymorphism of N-acetyltransferase
  - inactivation of drugs in liver: slow X fast activators
  - isoniazid, prokainamid, hydralazin
  - peripheral neuropathy (prevention – pyridoxin)

- Polymorphism of thiopurin S-methyl-transferase
  - participates in the metabolism of azathioprine
  - there is available a commercially fabricated genetic test for setting the rate of activity, prevention of severe adverse effects

Examples of polymorphism in the genes for CYP P450

- CYP2D6 and antidepressants (especially the classical ones): remarkable pharmacokinetic dirrefences, hardly titrate dose for slower development of the effect, long term pharmacoterapy

- CYP2C9 and peroral antidiabetics – derivates of sulphonylurea (e.g. glimepirid, glipizid a tolbutamid) In heterozygotes CYP2C9*1/*3 the total clearance is 50% and in homozygotes CYP2C9*3/*3 20% compared to wt

- CYP2C9 and anticoagulants – (warfarin) In heterozygotes CYP2C9*1/*3 the total clearance is 70% and in homozygotes CYP2C9*3/*3 40% compared to wt

Factors affecting interindividual variability of pharmacokinetics

Clinical pharmacologists …… integrate and critically look on the findings of preclinical and clinical trials and in the course of judging the sources and signification of interindividual variability in pharmacokinetics …. use methods of pharmacogenetics and therapeutic monitoring of drugs.

Drug adverse effects

The term PHARMACOVIGILANCE

Monitoring of adverse effects of drugs in the common clinical practice/ work experience – active control of the drug safety

Drug adverse effects

- Adverse Event (may but needn’t to be in direct relationship with the administered drug)
- Adverse Drug Reaction (is in relationship with the administered drug)

- Expected / Unexpected
- Severe
- Regulatory Agency : announcement of severe unexpected adverse effects of drugs

Drug adverse effects

Adverse effects are adversed answers to the therapeutical doses

They go with the pharmacotherapeutical effects

Drug adverse effects

A – **augmented** – caused by the same mechanism as pharmacotherapeutical effects.

- B – **bizzare** – „pacient's reaction" –are caused by a genetic mechanism (idiosyncrasy) or by an imunological mechanism (allergies).
- C – **chronic** – are caused by a long term taking
- D – **delayed** – show after a longer period of latency
- E – **end-of-use** -syndrom caused by discontinuing a drug

A – augmented

caused by the same mechanism as the pharmacotherapeutical effects. Induced by unappropriate dosage or by change in pharmacokinetics as a result of pathological process.

- predictable
- directly dependent on the dose
- frequent, seldom fatal

- Insulin > hypoglycaemia
- Anticoagulants> bleeding
- beta-blockers > bronchi-constriction > astmatic attack

B - bizzare

Caused by a genetic mechanism (idiosyncrasy) or by an imunological mechanism (allergies).

- unpredictable
- do not depend on the dose
- less frequent (1:1 000 až 1:10 000)
- higher mortality

Idiosyncrasy – reaction on the first dose, without previous sensibilisation (suxamethonium in individuals with atypical cholinesterase), polymorfisms.

Allergic reaction - reaction after a previous sensibilisation.

C - chronic

- **caused by a long term taking**

- e.g. analgetics > nefropathy
- prednisolon > iatrogenic Cushing’s syndrome
- laxatives > dysfunction of GIT.

D - delayed

show after a longer period of latency (or in children of the treated patients)

-mutagenesis, teratogenesis and cancerogenesis

Common characteristics:

- change of the genetic information because of the effect on DNA
- sensibility of the dividing and growing tissue
- ireversibility of the induced changes

E – end of use

Appears after the administration of a drug is finished. Like a syndrom caused by discontinuing a drug (*rebound fenomen, withdrawal syndrome*).
up/down-receptors regulation

- Examples:
- Tachykardia after discontinuing **betablockers**.
- Adrenocortical insufficiency after discontinuing **glucocorticoids**.
- Attacs after discontinuing **antiepileptics**.

Drug interaction

Administration of two drugs together influences the effect of one or even both of them.

↑ probability of interactions:

- Highly efficient drugs
- Inductors or inhibitors of hepatic enzymes
- During administration of more medicaments in the same time
- Pacients with kidney or liver diseases
- Senioři

Drug interactions

- pharmacokinetic

  biotransformation, distribution, absorption, exkretion

- pharmacodynamic

  the effect of a drug is influenced

- synergic
- antagonistic