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Factors influencing drug effects.

Overview of factors

A. Factors related to drug:

Physical and chemical properties
Dose
Drug form
Combination of drugs
Food administered together with a drug
Repeated administration

B. Factors related to organism:

Age
Gender
Weight and body constitution
Circadian rhytms
Pathological state of organism
Genotype/fenotype
(Race group/ethnic group)

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A. Factors related to drug

I. Physical and chemical properties

II. Drug dose

III. Drug dosage form

IV. Drug combination with other drugs

V. Food administered together with a drug

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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

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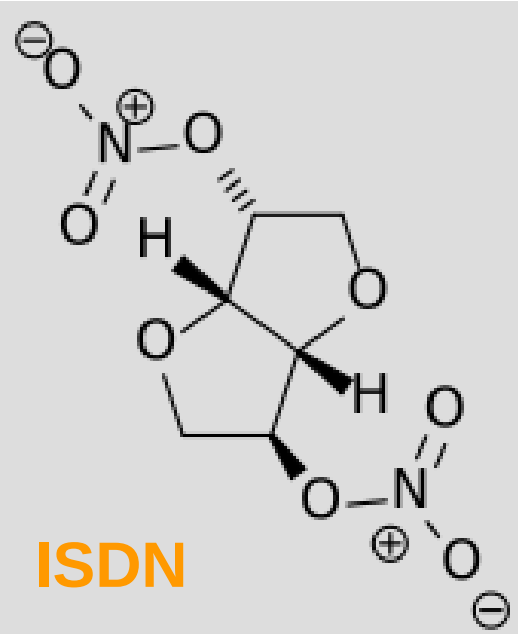
Relationship of chemical structure to PK



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

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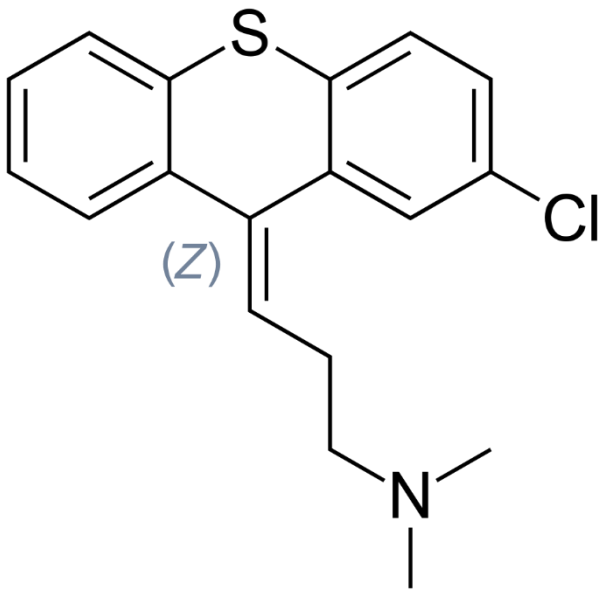
Stereoisomerism

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



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Drug information sources

- **SPC** = summarizing information about MP

  (Summary of Product Characteristics)

  part of the marketing authorisation of a

  medicinal product

  - **AISLP** - electronic drug information database for MP
  - SÚKL MP database (State authority for control of drugs)

- **Czech pharmacopoeia**

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II. Drug dose - dosis

- In preclinical trials

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

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III. Drug dosage form

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

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III. Drug dosage forms

1st generation – conventional DDF

2nd generation with controlled release

with prolongated release (SR,XR...)*
transdermal therapeutic system (TTS)
gastrointestinal therapeutic system

3rd 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.

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Liposomal vers. conventional drug (e.g. amphotericin B)

Stealth liposomes = PEGylated (daunorubicin, doxorubicin)

Nano-liposomes

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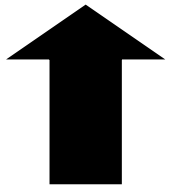
IV. Combinations of drugs

The effect is 

S y n e r g i s m

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

one-sided : analgetics anodynes + narcotics

two-sided : combination of cytostatics

Potentiation

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

two-sided : digoxin + thiazide diuretics

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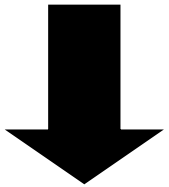
IV. Combinations of drugs

The effect is 

A n t a g o n i s m

pharmacological (ACH + atropin)

physiological (ACH + adrenalin)

chemical (heparin + protamin sulfate)

(metals + dimerkaprol, EDTA)

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V. Food intake

PD 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) -> risk of excessive wash out of catecholamines and hypertensive crisis

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

PK interactions

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

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V. Pharmacokinetic interactions with food

Food can:

slow down drug absorption without changing its

bioavailability

(inappropriate in analgetics, hypnotics…)

decrease bioavailability

increase bioavailability

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B. Factors related to organism

Age
Gender
Weight and body constitution
Circadian rhythms
Pathological conditions of organism
Genotype/phenotype

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Age

Administration of medicinal product (MP)

to children

to elderly people

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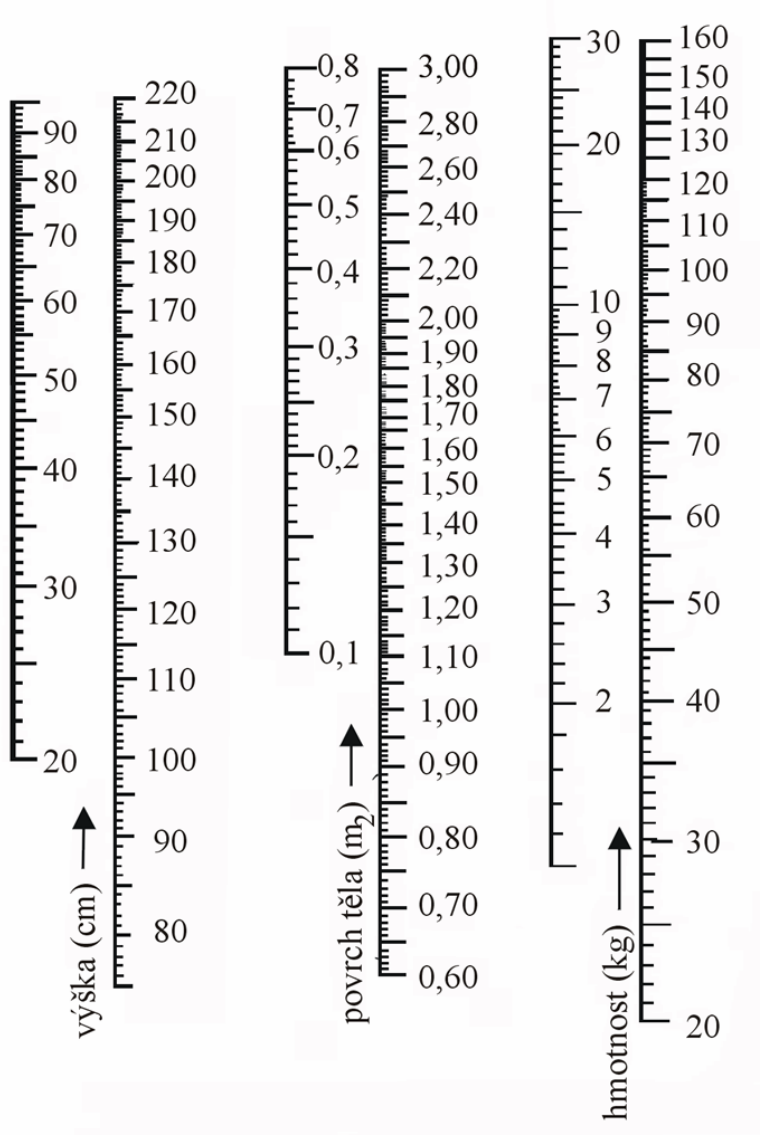
Administration of MP to children

approximate dose for children

=

body surface area (m^2) x dose for adult

1,7 (m^2)



Administration of MP to children

A child is not a miniature of an adult

particularities of PD

particularities of PK

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Particularities of PK of drugs in child

Particularly on newborns (especially premature):

relatively bigger volume of extracellular liquor

lower binding on plasma proteins

unfinished development of hematoencephalic barrier

immaturity of enzymatic systems

Immaturity of renal functions

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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 interactions is increasing)

higher incidence and severity of adverse effects

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Changes of PK of drugs in old age

absorption (passive diffusion of subacid substances thanks to hypoacidity, active transport is decreasing)

binding on plasma 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)

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Changes of PD in old age

Very variable

Tissue hypoxia

Dysfunction of regulatory mechanisms

Change of sensibility of target structures

= hyperergic reaction

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Changes of PD in old age

Examples:

ATB aminoglycosides:
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 drugs: higher toxicity, depression, confusion

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Gender

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

Specific periods are:

- menstruation
- gravidity
- lactation
- menopause

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Pregnancy

slowed stomach and intestinal motility

increased volume of plasma, body water can be raised up to 8 litres more

hypoalbuminemia, occupancy rate of plasma proteins by hormones

increased blood flow through kidneys and increase of GFR

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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

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Pathological state of organism

Influence of lesion/renal dysfunction, liver and thyroid gland on pharmacokinetics

Influence of pathological state on pharmacodynamics

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Hypofunction of kidneys

The most common reason for a drug dose adjustment

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, vancomycin)

In drugs with very long $t_{1/2}$ we keep the same interval, but administer a lower dose (digoxin)

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Influence of liver diseases

No reliable quantitative criteria is available for measuring impaired liver elimination capacity (analogy CL_{cr} in kidney dysfunctions)

→ <u>empirical attitude</u>

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

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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 high first-pass effect are administered orally
(e.g. metoprolol)

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Genetic factors

The drug response varies among individuals qualitatively and quantitatively

interindividual variability – polymorphism

Genetic factors influence PD and also PK

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Genetic factors

Genetic polymorphism = 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

focused on studies of genetically conditioned variability in response of the organism to a drug

(**Pharmacogenomics** investigates the relationship of drug effect at the level of the whole genome)

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Adverse effects

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Adverse effects

AE frequency - SPC

very common (with occurrence frequency ≥10 %)

common (1 %- 10 %)

uncommon (0.1 % - 1 %)

rare (0.01 %- 0.1 %)

very rare (< 0,01 %)

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Type A – 95%
dose dependent
pharmaceutical, pharmacokinetic

Type B – 5%
dose non-dependent
immunological reactions, pseudoallergic reactions,
pharmacogenetic variations

Type C
during longer application

Type D
delayed reactions

Type E
after withdrawal

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Adverse effects – type A

pharmaceutical reasons:

unsatisfactory clean preparations – admixtures of pyrogens, bacteria, etc.

expired preparations

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Adverse effects – type A

pharmacokinetic variant

liver diseases (hepatitis, cirrhosis) - lower production of blood albumines during cirrhosis

kidney disease (accumulation of medical substances eliminated by glomerular filtration or tubular secretion)

heart diseases (decreased blood flow in liver and kidneys, impaired absorption from GIT absorption from GIT due to lower blood flow and gut mucous membrane oedema)

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Adverse effects – type A

thyroid gland disorders - changed metabolization during hyperthyreosis or hypothyreosis

interactions of medical substances

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Adverse effects – type B

immunological
- hypersensitivity (allergies)

pseudoallergic reactions
- clinical symptoms are like in hypersensitivity, but there are no immunological markers

reaction to the same drug will not necessary develop after the next administration

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Adverse effects – type C (after longer administration)

tolerance

dependence

specific for various substances

corticosteroids – adrenal cortex atrophy

phenacetin – kidney inflammation

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Adverse effects – type D (delayed)

carcinogenic

hormonal interventions during pregnancy

genetic toxicity

cyklophosphamide → ca of gall-bladder

immunosuppression

immunosuppressive substances → ca of liver, biliary tract

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Adverse effects – type D (delayed)

interfere with reproduction

- decrease in fertility
- teratogenic effects
- cumulation in breast milk

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Adverse effects – type E

„rebound“ phenomenon -
deterioration of the original difficulties after stopping of administration

anxiolytic drugs → anxiety
antihypertensive drugs → hypertension

withdrawal syndrome in addictive substances

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