



## **Factors influencing drug effects.**

**Influence of accompanying diseases on  
drugs effects.**

## **Copyright notice**

The presentation is copyrighted work created by employees of Masaryk university.

Students are allowed to make copies for learning purposes only.

Any unauthorised reproduction or distribution of the presentation or individual slides against the law.

# 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 rhythms
- Pathological state of organism
- Genotype/phenotype
- (Race group/ethnic group)

## 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

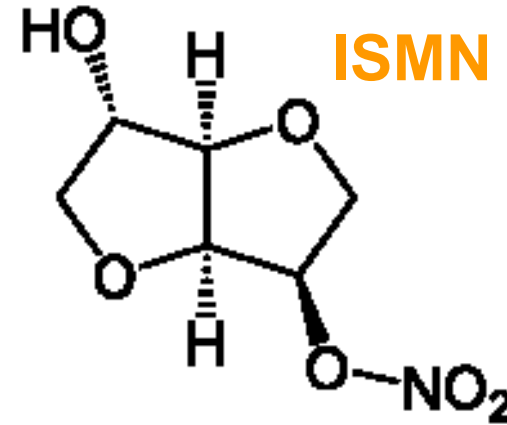
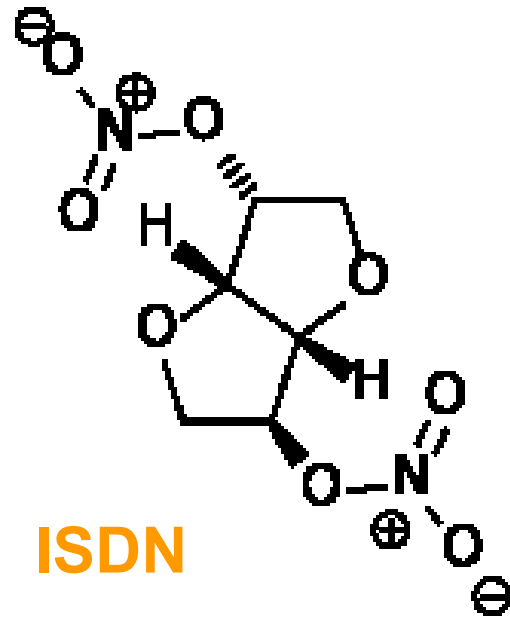
# I. Physical and chemical properties of drug



Influence on the transport through membranes

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

# Relationship of chemical structure to PK

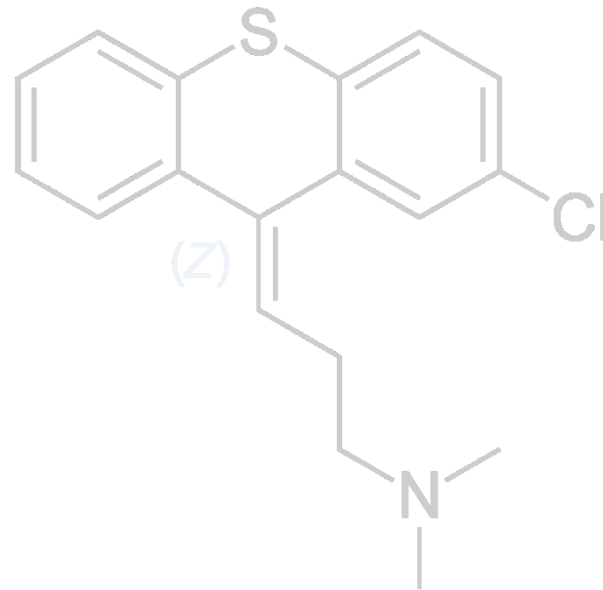


ISDN is more lipophilic than ISMN  
ISDN may be administered sublingually  
ISMN is almost not subject to the hepatic FPE  
Another example: atenolol x metoprolol

# Stereoisomerism



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



## II. Drug dose - dosage



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



# 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**

### III. Drug dosage form



□ definition:

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



### III. Drug dosage forms

- 1<sup>st</sup> generation – conventional DDF
- 2<sup>nd</sup> generation with controlled release
  - with prolonged release (SR, XR...)\*
  - transdermal therapeutic system (TTS)
  - gastrointestinal therapeutic system
- 3<sup>rd</sup> 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.

## 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

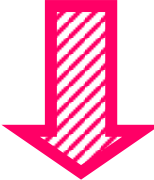
□ Potentiation

one-sided :  $\text{Ca}^{2+}$  + digoxin

two-sided : digoxin + thiazide diuretics



## IV. Combinations of drugs

The effect is 

### **A n t a g o n i s m**

- pharmacological (histamine x cetirizine)
- physiological (histamine x salbutamol)
- chemical (heparin x protamin sulfat)  
(metals x dimerkaprol, EDTA)



## 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



## V. Pharmacokinetic interactions with food

Food can:

- slow down drug absorption without changing its bioavailability  
(inappropriate in analgetics, hypnotics...)
- decrease bioavailability
- increase bioavailability

## B. Factors related to organism



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



# Age



## Administration of medicinal product (MP)

- to children
- to elderly people

# Administration of MP to children



approximate dose for children =  
body surface area (m<sup>2</sup>) x dose for adult/1,7 (m<sup>2</sup>)

# Administration of MP to children



A child is not a miniature of an adult

particularities of PD  
particularities of PK

# 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

# 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



## 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, aminoglykoside atb)

## Changes of PD in old age



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



## Changes of PD in old age

### Examples:

- ATB aminoglycosides: lower doses in case of lower GF
- 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



# Gender



- Women are in general more sensitive to effects of some drugs, e.g. because of lower weight, but also of lower CL
  
- Specific periods are:
  - menstruation
  - gravidity
  - lactation
  - menopause



## Pregnancy

- slowed stomach and intestinal motility
- increased volume of plasma, body water can be raised up to 8 litres
- hypoalbuminemia, occupancy rate of plasma proteins by hormones
- increased blood 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)

# Pathological state of organism



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



## 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)

## Influence of liver diseases



- No reliable quantitative criteria is available for measuring impaired liver elimination capacity (analogy  $CL_{cr}$  in kidney dysfunctions)
- Liver function tests (aminotransferases, albumin, 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 high first-pass effect are administered orally (e.g. metoprolol)

# Genetic factors



- The drug response varies among individuals qualitatively and quantitatively

interindividual variability – polymorphism

- Genetic factors influence PD and also PK





## 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)