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Factors influencing drug effects.

Influence of accompanying diseases on drugs effects.

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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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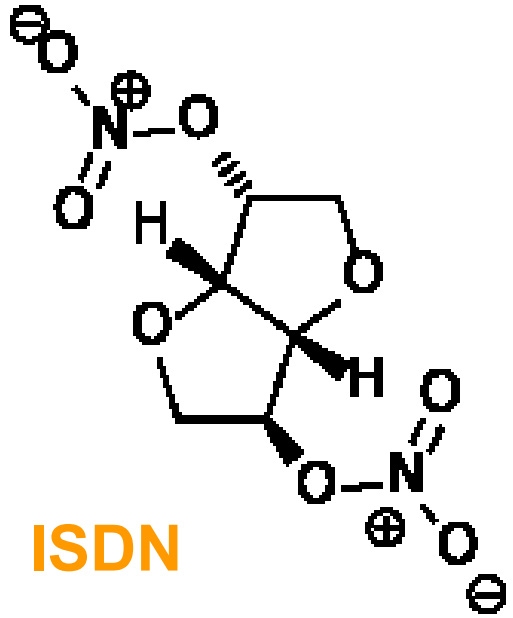
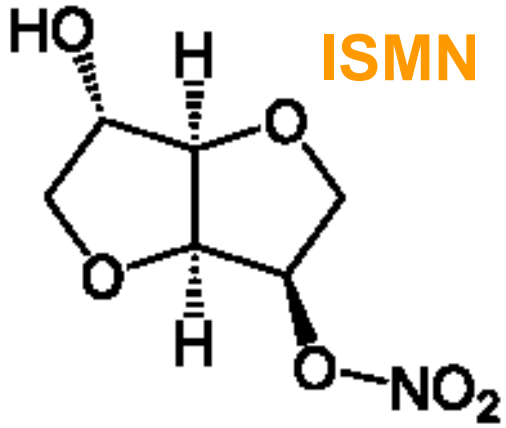
Relationship of chemical structure to PK



ISDN



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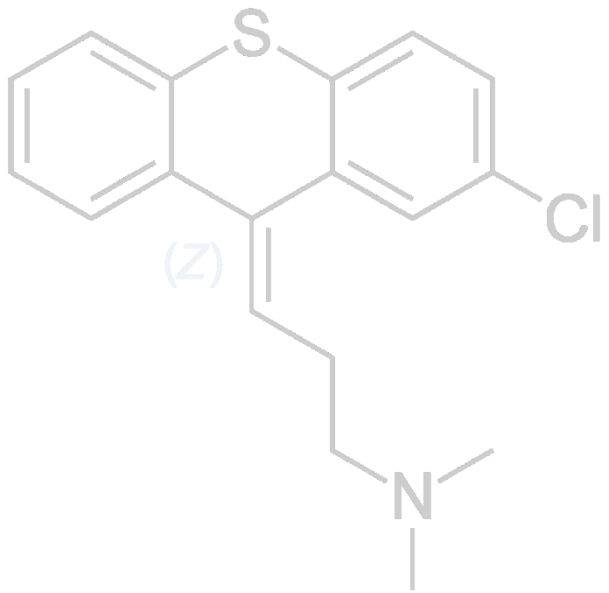
ISDN is more lipophilic than ISMN
ISDN may be administrated sublingually
ISMN is almost not subject to the hepatic FPE
Another example: atenolol x metoprolol

Stereoisomerism

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



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II. Drug dose - dosage

- In preclinical trials

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

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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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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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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 (histamine x cetirizine)
- physiological (histamine x salbutamol)
- chemical (heparin x protamin sulfate)
  (metals x 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

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

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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, aminoglykoside 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
- 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

- 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
- 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)

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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)

- 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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