PHYSIOLOGICAL AND PATHOLOGICAL FACTORS INFLUENCING DRUG EFFECTS

Factors influencing drug effects

- factors related to the drug
- factors related to the drug and organism
- factors related to the organism

- hyperergic reaction
- hypoergic reaction
- normoergic reaction

Factors influencing drug effects

1. Factors related to the drug

- A Physico-chemical properties
- B Drug dosage form and way of administration
- C Effect of meal, nutrients

A Physical and chemical properties of the drug

- lipid and water solubility
- onset of action, distribution
- the size and shape of the molecule
- chemical configuration
- acid-base properties

The relationship of chemical structures and the nature of the effect

Examples:

atenolol x metoprolol /hydrophilic vs. lipophilic / longer vs. shorter half-life

Cis-trans isomers: only the cis form of chlorprothixene is effective

ISDN more lipophilic than the ISMN:

- ISDN can be given sublingually
- ISMN almost does not undergo hepatic FPE

B Drug dosage form

- the ultimate form of processing of active substances and excipients
- the composition and the shape = predestiny for the intended use
- influences pharmaceutical availability

B Drug dosage form

- Pharmaceutical stage
- Pharmacokinetic stage
- Pharmacodynamic stage
- desagregation,
- desintegration
- dissolution
- ADME

DRUG DOSAGE FORM GENERATIONS

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

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

3. generation „Drug targeting“

- targeted therapy - selective action on specific cellular or subcellular targets

- some liposomal LF
- most of biological drugs (monoclonal antibodies)
- antibody drug conjugate - e.g brentuximab –vedotine

- delivers an antineoplastic agent that results in apoptotic cell
- death selectively in CD30-expressing tumour cells
- - antisense therapies
- - gene therapy

C Concomitant food + drug intake

Pharmacodynamic interactions

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

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

C Concomitant food + drug intake

Pharmacokinetic interactions

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

- food can:
- slow down the absorption without the change of
- extension of bioavailability
- (inappropriate in analgesics, hypnotics…)
- decrease bioavailability
- increase bioavailability

2. Factors related to the drug and organism

A Dose (dose-response curve)
B Drug Combinations
C Repeated administration
D Delayed effects

3. Factors related to the organism

- age
- sex (males/females)
- body weight, physiognomy
- circadian rhythms
- pathological condition of the body
- genotype / phenotype

Pharmacogenetics focuses on the study of genetically conditioned variability in the response to a drug; examines the relationship of drug effect on the level of the whole genome, respectively transcriptome (e.g. GENETIC POLYMORPHISM OF BIOTRANSFORMATION ENZYMES)

EFFECT OF OTHER PATHOLOGIES/ DISEASES ON THE EFFECT OF DRUGS

- heart failure (centralization of circulation) - possible slowdown and reduced absorption after oral administration
  - possible increase of bioavailability of substances with extensive first pass effect
- absorption slow down after IM
- gastrointestinal disorders (malabsorption , gastric ulcers and
- conditions inducing nausea , vomiting)
- thyroid disorders (hyperfunction - generally increased intensity of metabolism), hyperfunction - potentiated effect of warfarine
- fever (^ ventilation and GF, increased elimination of gentamicine)
- edemas (^ Vd gentamicine)
- obesity

EFFECT OF DISEASES ON THE EFFECT OF DRUGS - OTHER PATHOLOGIES

- impact of liver disease: there is no reliable quantitative measure of impaired liver elimination capability for drugs (creatinine clearance analogy with kidney disorders); therefore - empirical approach
- liver function tests (ALT, AST, albumin, clotting factors) are not a good guide for the drug dosage schedule - nonspecific
  - reduce the dosage in advanced liver diseases:
    diazepam, paracetamol, phenobarbital, phenytoin, valproic acid
    mesocaine, morphine, theophylline, calcium channel blockers
  - carefully: antidiabetics, diuretics,anticoagulants,
    antihypertensives
- therapeutic drug monitoring (TDM)- appropriate for antiepileptics, theophylline, cytostatics (low TI), AMG antibiotics, antipsychotics

ADVERSE DRUG EFFECTS

Classification according to frequency

- Very frequent .1/10 patients
- frequent .1/100 patients
- Less frequent 1/100 - 1/1 000 patients
- Rare 1/1 000 - 1/10 000 patients
- Very rare . 1 / 10 000 patients

Classification according to the intensity of ADRs:

- mild - no action needed
- moderate - results in change of dosing or treatment
- severe - potential harm, necessity of drug withdrawal

ADVERSE DRUG EFFECTS

LEGISLATION - Pharmaceutical act (378/2007 SB.)

- SADR – serious adverse reaction
- UADR – unexpected adverse drug reaction
- USAR – unexpected serious adverse reaction
- SUSAR - suspected unexpected serious adverse reaction

PHARMACOVIGILANCE

- monitoring of adverse drug reactions in routine clinical practice - the active drug safety

ADVERSE DRUG EFFECTS

A – augmented – (95 %) caused by the same mechanism as pharmacotherapeutical effects, •predictable
•directly dependent on the dose •frequent, seldom fatal, insuline > hypoglycaemia, anticoagulants> bleeding

B – bizzare – (5 %) - 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

C – chronic – are caused by a long term drug administration
•e.g. analgetics > nefropathy, •prednisolon > iatrogenic Cushing's syndrome

D – delayed – show after a longer period of latency (mutagenesis, terat.)
•become apparent after a longer period of latency (or in children of the treated patients)

E – end-of-use - syndrom caused by discontinuation of a drug
• tachycardia after discontinuing betablockers