DRUG INTERACTIONS
Is a phenomenon based on interplay of simultaneous application of several drugs, which results in change of drug action of some of them, what may have profitable or unprofitable clinical implications.

This is an influence of one drug on the final result of an action of another one, simultaneously applied drug.

Phases of drug interactions:

1) pharmaceutical
2) pharmacodynamic
3) pharmacokinetic

1) Pharmaceutical interactions – prescription discrepancies
or
drugs interactions in vitro

It occurs outside organism during:
- preparation of complex medicament in the pharmacy
- during administration of several drugs in one syringe or infusion

2) pharmacodynamic phase
Interactions are based on change of:
- time
- force
- action range

of one drug under the influence of pharmacological functioning of the other, simultaneously used drug.

Division of pharmacodynamic interactions:
- receptor interactions
- enzymatic interactions
- physiological/functional interactions

Receptor and enzymatic interactions occur when we administer drugs acting on the same enzyme or receptor

3) pharmacokinetic phase
These occur when one drug alters
- absorption
- binding with proteins in the blood plasma
- transporting through biological membranes
- distribution
- biotransformation
- excretion

of another, thus increasing or reducing the amount of drug available to produce its pharmacological effects

Interactions concerning absorption from gastrointestinal tract

Interactions during absorption can lead to:
- decreasing or increasing the amount of absorbed drug
- deceleration or acceleration of absorption

1) creating insoluble complexes e.g.:
   - tetracyclines + Ca++ ions
   - phenobarbital + methylxantines

2) adsorption of one drug by other drug of a big surface
   e.g. medicinal charcoal, aluminium hydroxide, resin, dietary fibre

3) changing of pH in intestinal contents
- drugs neutrallising gastric acid:
↓ decreasing absorption of acidic drugs e.g. NSAIDs
↑ increasing absorption of alkaline drugs e.g. morphine, aminophylline

- drugs decreasing pH of stomach contents:
↓ decreasing absorption of alkaline drugs
↑ increasing absorption of acidic drugs

Interactions concerning distribution
concern binding of drugs with plasma proteins or with tissue proteins
Drugs binding with proteins depending on pH of the environment:
- alkalization of blood increases the degree of binding with light alkaline drugs
- acidifying of blood increases the degree of binding with light acidic drugs

Absorption capacity of blood plasma proteins decreases during diseases with proteins deficiency and high fever.

After simultaneous administration of several drugs to the patient these ones which result in a higher concentration in blood or have higher affinity to proteins, supplant these drugs which have lower affinity to proteins and drugs present in the blood in lower concentration

Drugs with high affinity to proteins:
- NSAIDs
- sulphonamides
- chloramphenicol
- verapamil
- amiodaron
- chinidine

Drugs with low affinity to proteins:
- oral antidiabetic drugs
- anticoagulation drugs
- antiepileptic drugs
- hydrocortisone
- oral contraceptive drugs
- methotrexate
- digoxin

Interactions concerning metabolism
Interactions in this phase consist in:
- increasing of metabolism (induction)
- decreasing of metabolism (inhibition)

by affecting activity of hepatic cytochrome P450 system

Enzymatic induction
is caused by the drugs which, when used for a longer time, increase the activity of enzymes metabolising other drugs taken at the same time.
Such drugs are called: enzymatic inductors

As a result of enzymatic induction of the drug, its concentration and pharmacological activity is lowered

Enzymatic inductors:
- barbiturates
- phenytoin
- rifampicin

Enzymatic inhibition
is caused by the drugs which when used for a longer time decrease the activity of enzymes metabolising other drugs taken at the same time.
Such drugs called enzymatic inhibitors

As a result of the inhibition of cytochrome P450 group enzymes (CYP1A1, CYP1A2, CYP2A1, CYP2A2, CYP2E1) concentration and pharmacological activity of drugs increase

Enzymatic inhibitors :
- cimetidine
- ketoconazole
- erythromycine
- sulfonamides

Interactions concerning excretion

Diuretics by increasing glomerular tuft filtration and the amount of urine may increase excretion of most of drugs and their metabolits.
It is used in practice in treatment of poisonings

Using drugs or other substances changing pH of urine:

1) urine alkalization:

- ↑increase of acidic drugs excretion
- ↓ decrease of alkaline drugs excretion

e.g. NaHCO3 (sodium hydrocarbonate), acetazolamide, vegetarian diet

2) urine acidifying:

- ↑increase of alkaline drugs excretion
- ↓ decrease of acidic drugs excretion

e.g. acidum ascorbicum, meat diet

POSSIBLE CONSEQUENCES OF DRUG INTERACTIONS

Two of the most common consequences of drug interactions:

a) inhibited pharmacological activity and connected with it loss of therapeutic effect

- **-** pharmacodynamic antagonism
- inhibited absorption
- acceleration of biotransformation processes
- increased excretion

b) increased pharmacological activity and/or adverse effects and toxicity of drugs

- pharmacodynamic synergism
- drug displacement from its binding with plasma/tissue proteins
- deceleration of biotransformation processes
- decreased excretion