Drug Interactions

By this term, we understand the interaction between two or more pharmaceuticals - administration of two different drugs will affect the action and effects of at least one of them.

The causes and consequences of interactions are very different, and therefore we can divide them in several ways:

1. *Division according to benefit for the patient*
   - Positive interactions
   - Negative interactions
2. *Division according to the mechanism of formation*
   - Functional synergism
   - Change in pharmacokinetics
   - Change in pharmacodynamics

Medications with frequent interactions

These include medicines that have any of the following properties:

- **High binding** to proteins (aspirin, sulfonamides,...) - these drugs easily displace others, in which the free fraction increases.
- **Stimulation of the metabolism of** other drugs by induction of microsomal enzymes (cytochrome P 450) (anticonvulsants, rifampicin , griseofulvin).
- Inhibition of the metabolism of other drugs.
- Influence of renal clearance (diuretics , probenecid , aminoglycoside antibiotics , substances affecting urinary pH).
- Medicines for which a small change in dose produces a relatively large change in effect (warfarin).
- Medicines with **a small therapeutic index** – medicines for which the therapeutic level is only slightly lower than the toxic level (anticoagulants , anticonvulsants , antihypertensives , digoxin , cytostatics and immunosuppressants)

Categorizing interactions by patient benefit

Positive interactions

These are interactions whose outcome is beneficial for the patient. The similar effect of different drugs is often used (synergism - the effect of the drugs adds up or supports each other). This makes it possible to use smaller doses of individual drugs while achieving the same effect and thereby reduce toxicity, or to achieve a greater effect. This principle is used, for example, in the combination of some antihypertensives, immunosuppressants, antitumor treatment, caffeine with analgesics, antibiotics, etc.

- A concrete example can be the combination of amoxicillin and clavulanic acid (= co-amoxicillin, in Amoksiklav or Augmentin) - clavulanic acid prevents the degradation of amoxicillin by bacterial beta-lactamase and thus enhances its effect.

Positive interactions can also include some cases of antagonism (the effect of drugs is mutually reduced) - use, for example, in antidotes.

Negative interactions

These are interactions whose consequences are undesirable for the patient. Unfortunately, most drug interactions belong to this group. They can occur at all levels of pharmacokinetics (absorption, distribution, metabolism, elimination) and pharmacodynamics. Examples of negative interactions can be found below in the chapter Division of interactions according to the mechanism of occurrence.

Division of interactions according to the mechanism of formation

Functional synergism

Administered drugs cause a similar effect, their effects thus add up (although it does not always have to be an exact sum) and can be too strong. E.g.:

- Excessive inhibition of conduction in the heart during the combination of β-sympatholytics and antiarrhythmics from another group.
- A more significant decrease in blood pressure with the administration of nitrates , while reflex tachycardia is simultaneously treated with β-sympatholytics .

Change in pharmacokinetics

Change in resorption

The drug changes the rate of absorption of another drug in the digestive tract and thus changes the level of the drug in the body. E.g.:

- When digoxin and adsorbing antacids are administered simultaneously, digoxin partially binds to the adsorbing surface of the antacid and cannot be resorbed in the intestine.
- The simultaneous administration of divalent cations and tetracyclines leads to the formation of complexes and a decrease in the intestinal absorption of tetracyclines. These are, for example, iron or calcium cations, and dairy products should therefore be avoided when using tetracyclines.
- Reduced reabsorption of the estrogen of hormonal contraception (oral) in the intestine during simultaneous use, especially of broad-spectrum antibiotics (changing the intestinal microflora), can lead to unwanted pregnancy, as the effect of hormonal contraception will be reduced .

Acceleration of decomposition in the liver after enzyme induction

- The administration of phenobarbital after only a few days induces the proliferation of the endoplasmic reticulum in the liver and the formation of enzymes that metabolize phenobarbital and a number of other substances, so that their effectiveness is shortened and weakened.
- Rifampicin is also a strong enzyme inducer – an anti-tuberculosis agent. It can also cause the estrogens from hormonal birth control (oral) to break down so quickly that they won't prevent pregnancy.

Slowed metabolism by inhibition of decomposing enzymes

- The H2-antihistamine cimetidine inhibits the enzymes of the cytochrome P450 system, so when cimetidine is administered, the plasma level of a number of different substances that should be destroyed by cytochrome P450 can be increased and prolonged.
- Inhibition of warfarin metabolism during simultaneous use of clarithromycin , amiodarone or cimetidine (see above) can thus lead to severe bleeding.
- The antidepressant tranylcypromine inhibits monoamine oxidase and thereby the metabolism of adrenaline. Therefore, e.g. after the administration of a local anesthetic with the addition of adrenaline, acute adrenaline intoxication may occur during treatment with tranylcypromine.

Competitive mutual displacement

Competitive mutual displacement from binding to proteins in plasma, extracellular fluid and in cellular structures. Displacement from binding to the protein increases the free (effective) fraction of the drug, which can lead to a dangerous increase in its concentration. This type of interaction is significant for drugs that are more than 90% bound to plasma proteins.

- The concentration of free molecules of the anticoagulant phenprocoumon in the plasma increases with simultaneous administration of sulfonamides , resulting in increased bleeding. In the same way, sulfonamides can enhance the effectiveness of oral antidiabetic drugs that bind strongly to plasma proteins, e.g. glibenclamide .
- Furthermore, binding interactions can occur, for example, in epilepsy between phenytoin and nonsteroidal anti-inflammatory drugs (NSAIDs), or between an oral antidiabetic drug (tolbutamide) and an NSAID .

Competitive displacement from renal excretory mechanisms

Medicines with high urinary excretion can easily be affected by changes in renal function, leading, for example, to reduced elimination of medicines by the kidneys. Thus, interactions arise with drugs that affect renal function (diuretics , aminoglycosides , probenecid , ACE inhibitors).

- Concomitant administration of phenylbutazone or sulfonamides reduces the active secretion of sulfonylurea-type oral antidiabetic drugs in the proximal tubule. The result is a relative overdose of the antidiabetic drug.

Increased reactivity or sensitivity of organs

- Halothane sensitizes the heart to catecholamines by an unknown mechanism. The simultaneous administration of a normal dose of adrenaline can cause severe arrhythmias and even ventricular fibrillation under halothane anesthesia.

Drug interaction statistics

- Interactions are said to account for around 7% of adverse drug reactions, with about a third of patients who die from a drug dying from a drug interaction.
- The risk of an adverse reaction due to a drug interaction increases rapidly with the number of drugs administered – up to 5 simultaneously administered drugs it is around 4%, over 16 drugs already 40% or more.

Links

Related Articles

- Cytochrom P450
- Relationship between dose, plasma level and effect

References

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