Masaryk University

Faculty of Medicine

Selected chapters from general pharmacology for students of general medicine and dentistry at MF MU

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CONTENT

1. Introduction to Pharmacodynamics

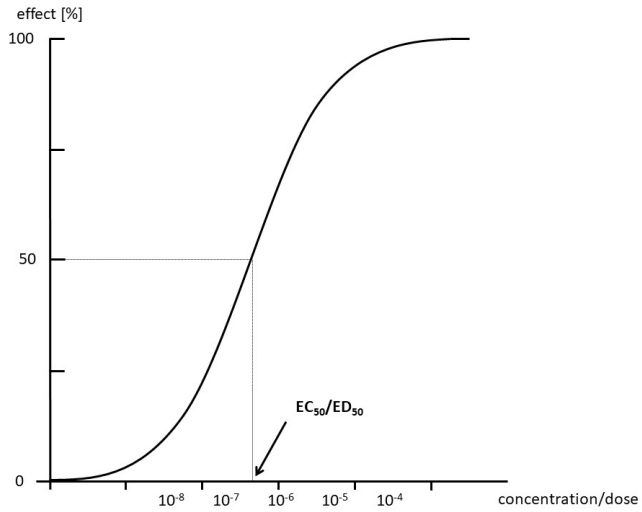
Pharmacodynamics is a sub-branch of general pharmacology, which studies the mechanisms of effects of drugs. It investigates how a drug affects an organism on different levels and focuses not only on the therapeutic effects but the toxic effects too. Essentially, pharmacodynamics describes “what the substance does to the body” (in comparison, pharmacokinetics looks at “what the body does with the substance”).

The mechanism of a drug’s effect can be divided into *specific* and *non-specific*. The basis of non-specific mechanisms of action are the physical and chemical properties of the substance. Drugs with this mechanism affect all parts of the body into which they were administered in the same way. With specific mechanisms of action, the drug interacts with a particular structure in the body; frequently a receptor, enzyme, carrier or ion channel (for example, components cell signalling).

To induce the effect of a drug, not only the pharmacological activity of the molecule but also its concentration at the location of its action is important. This depends not just on the amount of drug administered but also on its pharmacokinetics (see Chapter 2. Introduction to Pharmacokinetics). Based on these factors the effect of the drug can range from ineffective to therapeutic to toxic and at the extreme, lethal. Sometimes even a change of concentration of the substance can lead to a change in the character of the effect. For example, salicylic acid applied to the skin can have effects ranging from keratoplastic (concentrations of around 1-5%) to keratolytic (conc. 10%), but at higher concentrations induces necrosis.

To express the relationship between dose and effect, a graph known as the dose-response curve is used (see Fig. 1).

Figure 1. *Relationship between dose and effect. The curve of dependence of the dose of administered substance and its effect has (with semilogarithmic representation) a typical sigmoid shape. (The X axis shows concentration in logarithmic scale and the Y axis shows the effect on a linear scale).* EC_{50} *and* ED_{50} *depict the dose (concentration) required to reach 50 % of the maximum possible effect*.



1.1 Non-specific mechanisms of action

The effects induced by substances with a non-specific mechanism of action are not limited to specific tissues or organs containing the corresponding target structure (e.g. receptors). This is in contrast with substances with specific mechanisms of action, which are. The effect of these substances is therefore non-selective, which can lead to (especially with systemic administration) a host of undesirable effects and because of this they are used primarily for local application.

Examples of non-specific mechanisms of action and their therapeutic uses:

Substances acting on the basis of their osmotic properties

These substances do not pass through the cell membrane, which nevertheless allows the passage of water. Water moves along the concentration gradient from areas of low concentration to areas of high concentration until the osmotic pressures are balanced (Fick's diffusion law). Saline laxatives such as magnesium sulfate (for the emptying of the bowel before endoscopy) and osmotic diuretics such as mannitol

(for the decrease of intracranial pressure and oedema of the brain) both work in this manner.

Substances which affect pH

Antacids: basic substances which balance protons, e.g. magnesium hydroxide, aluminium hydroxide, sodium bicarbonate and calcium carbonate (for excessive acidification of the stomach and mild forms of oesophageal reflux disease)

Substances which change the pH of urine-acidifying substances such as ammonium chloride (for treatment of mmphetamine intoxication). Alkalizing substances such as sodium bicarbonate (for treatment of intoxication by barbituates, salicylates or tricyclic antidepressants).

Substances used to treat systemic disruption of acid-base balance - for example sodium bicarbonate for metabolic acidosis; sodium citrate or potassium citrate for metabolic alkalosis.

Substances acting via oxidation-reduction properties

Oxidating agents: hydrogen peroxide (3% solution for disinfection); reducing agents: methylene blue (for treatment of methemoglobinemia). Note: methylene blue has, apart from its oxidoreductive properties, a range of specific effects e.g. inhibition of NO synthase and inhibition of guanylate cyclase.

Substances with a large adsorption area

Intestinal adsorbents such as Carbo adsorbens (activated charcoal) or diosmectite (for treatment of diarrhoea) are able to bind other substances and toxins to themselves.

Surfactants and detergents

Surfactants, or surface active agents such as carbethopendecinium bromide and other quarternary ammonium salts are used primarily as antiseptics. By decreasing the surface charge they disrupt the protective barrier of the microorganism’s membrane, disturbing the internal environment leading to its death.

Some antibiotics (e.g. polymyxins - basic peptides) act as cationic detergents and disrupt phospholipids in bacterial membranes.

Chelating Agents

These substances form complexes (chelates) with metals, preventing their bonding. An example of these agents is EDTA (for the treatment of heavy metal poisoning) or deferoxamine (for the treatment of iron overdose).

Mechanical covering of surfaces

One member of this group is sucralfate. This substance acts locally and forms a protective layer of proteins of the necrotic tissue in an ulcerated area. The layer formed protects the wound from the action of pepsin, stomach secretions and bile salts (for the treatment of stomach and duodenal ulcers), but also prevents the absorption of a range of different medications.

Ionizing radiation

For the therapy of some tumours or inflammatory diseases, it is possible to use radionuclides (e.g. $^{13}1$I or ^{90}Y). Ionizing radiation also aids in diagnostic purposes (^{18}F, ^{11}C).

Alkylating agents

Alkylating cytostatics (e.g. cisplatin, oxaliplatin, busulfan, thiotepa) are abundantly used in the therapy of some tumour diseases. In essence, the action of these substances is facilitated by their highly reactive alkylation properties, which change the structure of DNA and cause a cytotoxic effect on rapidly-dividing tumour cells. The fact that they behave non-specifically means that they will also affect physiologically rapidly-dividing cells, manifesting as a host of typical undesirable effects (anaemia, neutropenia, thrombocytopenia).

1.2 Specific Mechanisms of Action

Specific mechanisms of action are further divided according to the target structure which they influence into

- receptor mechanisms
- non-receptor mechanisms

The word “receptor” in this instance is understood to mean a specific cell structure, usually a protein, which participates in the transfer of the signal from outside of the cell into the cell.

1.2.1 Receptor mechanisms of action and receptor theory

Receptors can be localised on the cell membrane (transmembrane) and in the cytoplasm or nucleus of the cell (intracellular). Substances, which are able to bind to receptors can be referred to as ligands. In most cases, ligands bind to a location which endogenous (i.e. the body’s own) substances also bind to under physiological conditions - known as orthosteric binding. In some situations, the ligand can bind to other locations apart from those for normal ligation. In this case, we speak of allosteric binding. This type of interaction is known as allosteric modulation, an example of which is the binding of benzodiazepine to $GABA_A$ receptors.

Certain substances exist which can bind orthosterically and allosterically. For example, the antiemetic palonosetron acts via the serotonin $5\text{-}HT_3$ receptor. Binding to a non-substrate location on the receptor (allosteric binding) increases the ease of binding of a second molecule of palonosetron to the binding site of serotonin (orthosteric binding). In this case we speak of an allosteric antagonist (see next pages) with positive cooperation.

1.2.1.1 Types of receptors

Receptors are divided by their means of signal transfer into 4 basic types:

I. Ligand-gated ion channels (ionotropic receptors). Receptors of this type facilitate in the nervous system the fastest form of synaptic transmission (in the order of milliseconds). An example of these channels are nicotinic N_M receptors of the neuromuscular junction (for acetylcholine).

After the binding of the ligand, the ion channel is opened through which a stream of ions flow from the extracellular environment to the intracellular environment. It is a non-specific ion channel, across which Na^+ and K^+ ions are able to pass. After the opening of the channel, the flow of Na^+ ions into the cell is somewhat higher than the K^+ ion flow out of the cell. This is a result of the fact that the internal surface of the membrane is, during a polarized state, negatively charged and this supports the entry of particles with a positive charge into the cell. The influx of Na^+ ions causes depolarization of the neuromuscular junction and this causes an action potential in its surroundings which further propagates.

II. G-protein coupled receptors (metabotropic receptors). This group includes a large number of receptors which are well-influenced pharmacologically. The response occurs in a matter of seconds. This group contains for example muscarinic receptors, adrenergic receptors, serotonergic receptors, dopaminergic receptors, opioid receptors, cannabinoid receptors, histamine receptors, prostaglandin receptors and a whole host of others. The receptor protein is formed from a peptide chain, which is in the shape of an α-helix and crosses the phospholipid membrane 7 times. Transmission of the signal is facilitated by a protein, which binds guanylnucleotide (from this point on, G-protein). This protein is found on the internal side of the cell membrane and has 3 subunits: α, β, γ. On the α-subunit, guanosine diphosphate (GDP) is bound during the resting state.

Upon binding of a ligand with the same character as the agonist (see following pages) to the binding site of the receptor, the protein receptor undergoes a conformational change which enables contact with the G-protein subunits. Subsequently the α-subunit releases GDP and binds guanosine triphosphate (GTP). The α-subunit with bound GTP splits from the remaining two subunits and induces a functional change of the effector protein located in the cell membrane. The α-subunit has GTPase activity; it removes one phosphate group from GTP, creating GDP. Following this, the α-subunit dissociates from the effector protein and once again binds to the subunits β and γ, by which it returns the system to the original resting state.

Cell signalling facilitated by G-proteins makes use of intracellular signalling molecules called “second messengers”. According to the type of second messenger molecule, we are able to divide metabotropic receptors into subgroups, among which the most important are:

• Gs: a system based on the activation of the enzyme adenylyl cyclase, which forms the second messenger cAMP from ATP (e.g. beta-adrenergic receptors, histamine H_2 receptors)

• Gq/1l: a system based on the activation of phospholipase C which breaks the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP2) into second messengers inositol triphosphate (IP3) and diacylglycerol (DAG) (e.g. α_1 adrenergic receptors and histamine H_1 receptors)

• Gi/o: a system which includes the inhibition of adenylyl cyclase resulting in the decrease of cAMP levels in the cell (e.g. muscarinic M_2 receptors or opioid μ receptors).

Receptors with tyrosine kinase activity (receptors with enzymatic activity).

Note: In the last few years these receptors have become the target of a range of antitumor drugs which work by the suppression of activation of proliferation in many haematological malignancies. These drugs include imatinib, sunitinic, dabrafenic, trametinib, dasatinib, vemurafenib, ponatinib and many more.

Endogenous ligands of these receptors are in most cases hormones, cytokines and growth factors of protein nature. An example of these receptors is the insulin receptor or the receptor for vascular endothelial growth factor VEGF. The speed of signal transmission is in the order of minutes.

The insulin receptor is composed of two α and two β subunits, which are connected by a disulphide bond. A-subunits are located extracellularly and carry a binding site for insulin. The phosphorylation of tyrosine on the intracellular part of the receptor causes activation of the intracellular signalling cascade. Upon the binding of insulin, a conformational change in the intracellular β-subunit is induced which initiates tyrosine

kinase activity. Tyrosine kinase transfers phosphate groups onto tyrosine in some proteins, which change their functional state. Subsequently, the enzyme catalyses the phosphorylation of the β-subunits and this increases the enzyme activity. In this way, insulin stimulates the transport proteins in the membrane of the cell (e.g. transport proteins for glucose).

Receptors which regulate the transcription of DNA (cytoplasmic and nuclear receptors). These receptors, in contrast with the aforementioned types, are found intracellularly. They bind to substances which have the ability to cross the cell membrane (e.g. steroids or thyroid hormones). The biological response to the stimulation of these receptors manifests with a latency of hours to days.

After binding of the ligand to the receptor a complex forms, which acts as a transcription factor and can stimulate or inhibit the expression of genes, depending on the corresponding gene. Changes in the expression of genes result in changes of mRNA (transcription) for the synthesis of proteins by ribosomes (translation). For the manifestation of an effect, two complexes of ligand and receptor (dimers) must form.

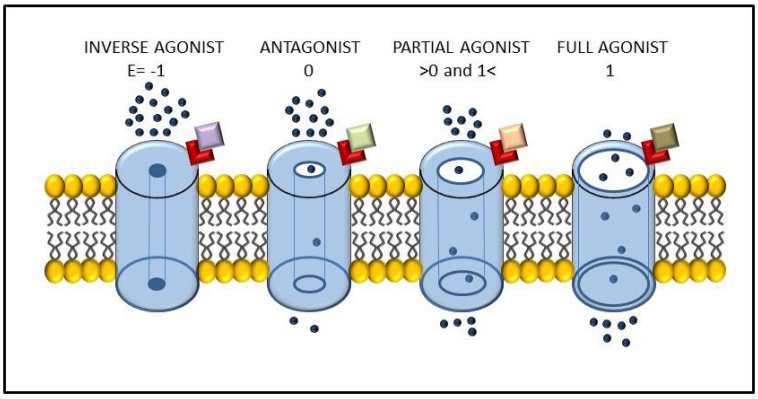
Receptors on the presynaptic terminal can be, from the point of view of sensitivity to mediators of various origins, classified as heteroreceptors and autoreceptors. Heteroreceptors regulate the synthesis and/or release of mediators of other ligands than their own. They are receptors which correspond to synapses in the nervous tissue, neuromodulators or neurohormones released from neighbouring neurons or cells. An example of such receptors are GABAergic inhibitory receptors or $5HT_{2A}$ or $5HT_{2C}$ receptors, which suppress the release of dopamine and noradrenaline in specific regions of the CNS. In contrast to heteroreceptors are autoreceptors, which are sensitive only to neurotransmitters or hormones released by cells attached to their cell membrane. Autoreceptors serve to transmit the signal as part of a feedback mechanism (usually negative). For example, the presynaptic neuron releases into the synaptic cleft noradrenaline. Noradrenaline acts on the postsynaptic adrenergic receptors, and also the α_2 autoreceptors localized presynaptically. Activation of these autoreceptors causes, by negative feedback mechanisms, the inhibition of further noradrenaline release. In a different example, the release of acetylcholine from presynaptic terminals of the parasympathetic system. Acetylcholine binds to the presynaptic muscarinic M_2 receptors and inhibits, by negative feedback, its further release. $5HT_{1A}$ presynaptic receptors behave similarly.

1.2.1.2 Most important ligand types

For the sake of repetition: ligands are characterized as substances which bind to receptors. Every ligand has two basic properties - affinity and intrinsic activity (efficacy - E). Affinity defines the ability of the substance to bind to a receptor. Intrinsic activity describes the ability of the ligand to activate the receptor - i.e. induce the transmission of a signal.

According to the differences in intrinsic activity we are able to define the following types of ligands (Fig. 2 and 4):

Figure 2. *Ligands separated by their intrinsic activity (E). This example shows a ligand-gated ion channel.*



Agonists (full agonist): have the maximal possible intrinsic activity and following their binding to a receptor, induce the maximal possible transmission of a signal. Intrinsic activity is of order 1 (100%). We can categorize most endogenous ligands as full agonists. Examples of drugs in this group include fentanyl (full agonist of opioid μ receptors) and adrenaline or noradrenaline (full agonists of β_2-adrenergic receptors).

Partial agonists (dualists:) bind to receptors but do not cause the maximal transmission of the signal. Intrinsic activity of these ligands lies in the range of 0-1 (0%-100%). When not in the presence of full agonists, dualists act as agonists - i.e. activate the receptor. In the presence of full agonists however, they behave as

antagonists. This is because they do not allow the full agonist to exert its (100%) intrinsic activity. An example of this type of ligand is the partial agonist of nicotinic receptors (subunits $\alpha_4\beta_2$) vareniklin, which is used to help quit smoking. The effect of partial agonists is schematically depicted by curve B in Figure 3.

Antagonists: have an intrinsic activity of 0 (0%). When they bind to a receptor, they prevent the binding of endogenous ligands, and therefore the transmission of a signal. An example of an antagonist is the parasympatholytic atropine which blocks M receptors, or the drug naloxone which blocks the effects of morphine on opioid receptors.

Inverse agonists: Specific parts of a signal may be transmitted by a receptor, even though an agonist is not bound to it (for example, a partially opened ion channel through which a small number of ions are able to pass through). In such a case, we speak of the resting activity of a receptor, which does not change after the binding of an antagonist. Ligands do however exist which have a negative intrinsic activity. They are known as inverse agonists and their binding to a receptor leads to decrease of resting activity (i.e. the receptor goes from a resting state to an inactive state). In recent times a large number of drugs which were known as antagonists have been found to actually be inverse agonists (e.g. H_1 and H_2 antihistamines).

Figure 3. *The difference in affinities of substances. Curves A and C depict the effects of full agonists with different affinities to the same receptor, while curve B shows the effect of a partial agonist on the same receptor. Differences in the affinity of these substances can be determined by comparison of the concentrations which are able to produce half the maximal effect (EC_{50}). The lower EC_{50} is, the higher the affinity of the substance to the given receptor. This means that the affinity of these substances can be described in this order: C<B<A.*

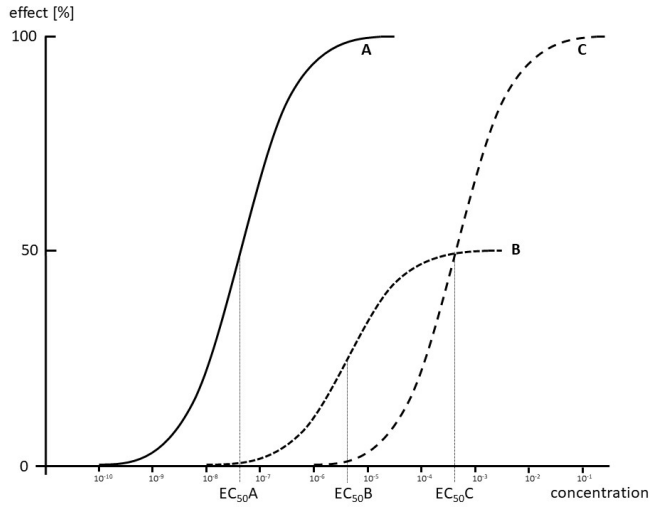
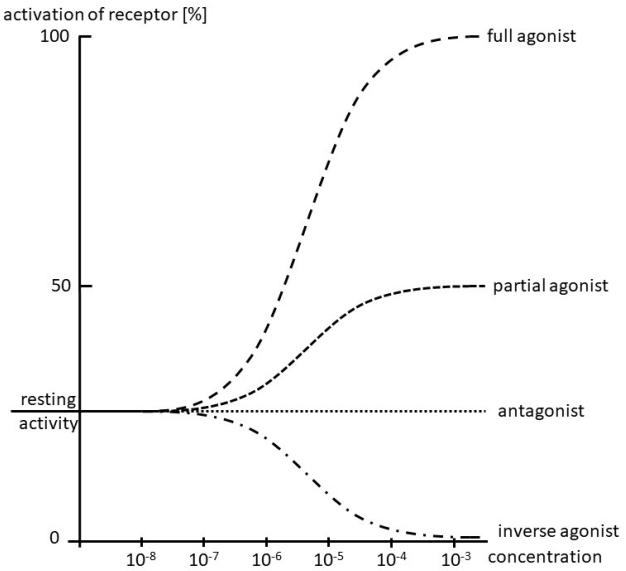


Figure 4. *Comparison of ligands according to their abilities to activate a receptor and induce a cell response. Full agonists in a sufficient concentration induce the maximal possible response of the organism, which is not able to be increased by further increases in concentration (the receptor is activated 100%). Partial agonists at certain concentration are able to reach their maximum effect, this maximum is however less than the maximum of full agonists. Antagonists induce zero effect, respectively preventing agonists from inducing their effect (the receptor stays in a resting activity state). Inverse agonists suppress even this resting (physiological) activity.*



1.2.1.3 Interactions of receptor ligands

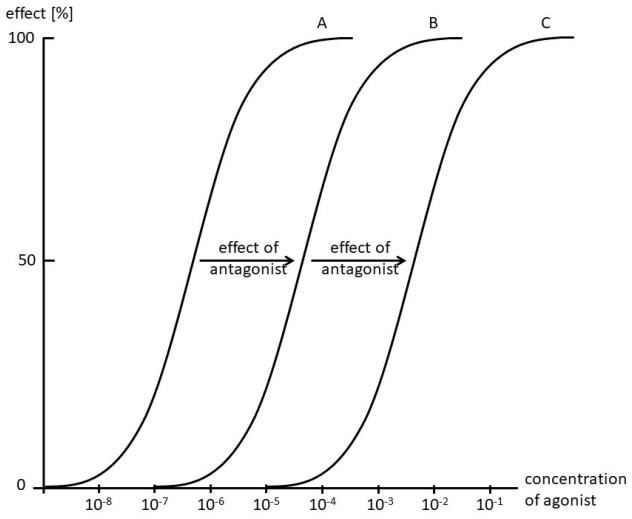
If, nearby to the receptor, ligands are present which differ in their intrinsic activity, this will affect the transmission of the signal to the receptor. In the body there are practically always natural (endogenous) full agonists in the vicinity of the receptor. Administered drugs may also have agonist behaviour and in such cases their effect and the effect of the endogenous agonists is combined - known as additive effect.

In cases where the administered drug behaves as a partial agonist or antagonist, an antagonistic reaction will result. The reason for this is that the intrinsic activity of these ligands is, in comparison with the full agonist, lower and therefore the stimulation of the receptor will also be lower than if only the full agonist was to bind to the receptors in question (e.g. endogenous ligands).

Speaking generally about the possible effects of drugs (medicaments) and not just with a view to the receptor mechanism of the effect, we could define their combined effect as synergy and antagonism. Synergy can be further subdivided into summation and potentiation. In an example of summation, if the effect of drug A is for example 50 % and the effect of drug B is also 50 % then their combined administration would result in effect C of 100 % (C = A + B). In the example of potentiation where drug A would have an effect of 20 % and drug B would have an effect of 40 %, the resulting effect C when they are administered together would be 100 % (C > A + B). Antagonism in this example would mean a reverse effect (the effect is weakened or suppressed).

The character of antagonistic interactions is dependent on many factors in the case of receptor mechanisms of action of two substances. If both ligands bind to the same binding site on the receptor, it is known as competitive antagonism (see Fig. 5). Substances compete for this binding site and are able to mutually displace each other. The resulting effect is then given by the affinity and the concentration of the ligands in proximity to the receptor. This can be described by the following relationship, in which the higher the affinity to the receptor and the higher the concentration of the substance in the vicinity of the receptor, the higher the likelihood that the ligand will occupy the receptor binding site. This means that if we increase the concentration of the agonist we can decrease or even eliminate the effect of the antagonist, because the antagonist will be displaced from the receptor (or vice versa).

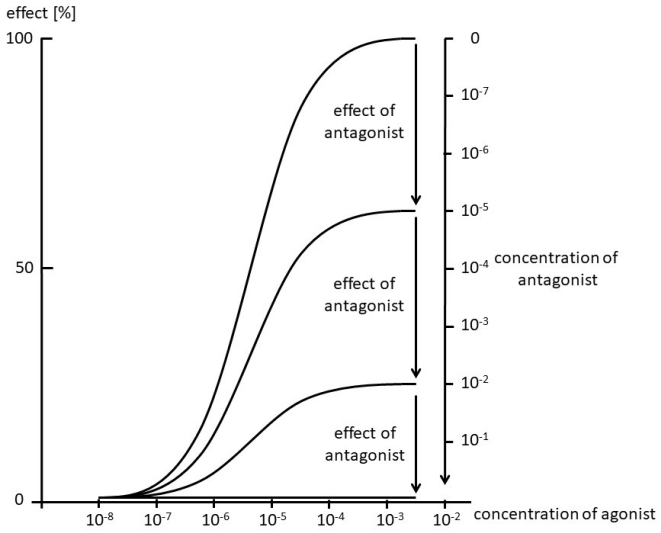
***Figure 5**. Competitive antagonism. This figure shows the interaction between full agonists and competitive antagonists. Curve A describes the effect of the full agonist without the presence of the antagonist. Curve B and C then show the interactions between agonist and competitive antagonist where the competitive antagonist is at a lower (B) or higher (C) concentration. With increasing concentration of competitive antagonist, increase in concentration of agonist is also required to produce the same effect (curve moves to the right).*



If the antagonist binds to the receptor allosterically (at a different location than that of the normal ligand) or irreversibly, this would be known as non-competitive antagonism. It is not possible to displace such a substance from the place of its binding and even increased concentration of agonist will not result in stimulation of the receptor (Fig. 6).

In the case of two ligands, one of which is a partial agonist, the result would depend on the character of the other ligand. In the interaction of a partial agonist and a full agonist, the partial agonist in this instance would behave as an antagonist. If the second ligand is however an antagonist, then the partial agonist will behave as an agonist. This is the reason why partial antagonists are also called “dualists”.

Figure 6. *Non-competitive antagonism. This figure depicts the interaction between full agonists and non-competitive antagonists. With increasing concentration of antagonist, the effect of the agonist decreases regardless of concentration (downward shift of the curve of the agonist).*



Competitive and non-competitive antagonism represent so called pharmacological *types* of antagonism. Apart from the type of antagonism at the level of the receptor, in pharmacology we can also describe more general forms such as chemical antagonism, pharmacokinetic antagonism and physiological antagonism. An example of chemical antagonism can be a situation where a solution contains two substances, one of which weakens the effect of the other (chelator dimercaprol binds to heavy metals and decreases their toxicity, infliximab has an anti-inflammatory effect due to its abilities to inhibit inflammatory cytokine TNF). In pharmacokinetic antagonism, the "antagonist" decreases the concentration of active substance in the location of its action (e.g. decreasing the anticoagulative effect of warfarin by the administration of phenytoin, which speeds up its metabolism in the liver). In physiological antagonism, two differing ligands work simultaneously on differing target structures, and their converse effects manifest in the organ (e.g. histamine causes bronchoconstriction in the lungs via H_1 receptors, while salbutamol causes bronchodilation via adrenergic β_2 receptors in the lungs. Histamine acts on the H_2 receptors of the parietal cells in the mucosa of the stomach and stimulates the secretion of acid, whilst omeprazol blocks this effect by inhibition of the proton pumps).

1.2.1.4 Regulation of the number of receptors and changes in their sensitivity over time

The number of receptors and their sensitivity to ligands is not constant, but changes over time depending on the current state of the effector cells, which serve as one of the mechanisms for maintaining homeostasis. The organism is able to react to activation or inhibition of receptors in two ways with differing time courses. The acute effect is comprised of desensitisation of receptors and the long-term effect of

agonistic or antagonistic stimulation is a change in the number of receptors. If an excessive stimulation of receptors occurs it attempts to protect the effector cells by decreasing the number of receptors or their sensitivity to ligands (and vice versa).

Regulation of the number of receptors

If receptors are excessively stimulated a decrease in their number results, known as **down-regulation**. The process of decreasing the number of receptors is facilitated by their internalization into the cell, where they are not accessible to their ligands or by the decrease in their genetic expression and therefore de novo production; these processes are also able to combine. In clinical practice this manifests after long-term administration of medications which behave as agonists. An example of this is sanorinism, which occurs after the administration of decongestive substances from the α_1 sympathomimetic group, or alternatively chronic administration of opioid analgesics. The clinical expression of down-regulation is a decrease in the effects of the administered medications.

The opposite situation is an increase in the number of receptors presented on membranes which occurs after the administration of antagonists, known as **up-regulation**. In up-regulation the cell reacts to insufficient stimulation by physiological ligands by increasing the number of receptors. Similarly to down-regulation this may also run the risk of changing the efficacy of the medication. A different problem can occur with the sudden cessation of intake of a drug. In this case there is now an abnormally increased number of receptors to which the physiological ligands of the body may bind producing an excessive response by cells or tissues to these endogenous stimuli. This is known as **rebound phenomenon**. A typical example of rebound phenomenon is tachycardia and hypertension after a sudden withdrawal of β_1 receptor antagonists (beta-blockers) without internal sympathomimetic activity.

Desensitization of receptors

If, after administering the same dose of a drug, we do not induce the same level of response from receptors as with the previous dose, we classify this as desensitization of receptors. Mechanisms of desensitization are different in dependence on its type. With long-term administration of agonists, resulting chronic stimulation leads to dissociation of the G-proteins from metabotropic receptors, which

causes an inability of the activated receptor to transmit the signal. Similarly to down-regulation, this mechanism occurs during the development of tolerance to the effects of opioid analgesics. This phenomenon has also been described in nicotinic or (glutamatergic) NMDA receptors. If desensitization occurs within minutes to hours after the administration of the substance, this is known as **tachyphylaxis**. In this situation the cause may be the depletion of the substrates of the signalling cascade which, under physiological conditions, is not stimulated continuous way. For example, after the administration of amphetamine an increased release of catecholamines from the presynaptic terminals takes place which is so quick and intensive that it outpaces the neuron's ability to synthesize new catecholamines and create new vesicles. In this way the stores of neurotransmitters are depleted. If we therefore administer amphetamines a short time after the previous dose, no psychostimulatory effect will usually occur. The most common cause of development of desensitization in clinical practice is the long-term and regular administration of agonists of a given receptor (e.g. β_2 sympathomimetics in therapy of asthma or α_1 sympathomimetics in decongestant nasal drops). It is possible to overcome this (if the state of the patient allows it) by administration of the drug in an interrupted manner, e.g. administration of β_2 mimetics only during an asthma attack. Note: Some authors class desensitization and tachyphylaxis as synonyms, however desensitization occurs after a long-term administration of the ligands, whereas tachyphylaxis occurs quickly and after each individual administration, within several hours.

1.2.2 Non-receptor mechanisms of action

I. Influencing of ion channels

Ion channels are gates in the cell membrane which selectively allow the passage of individual ions, and in which it is possible to induce opening and closing by a whole host of mechanisms. Two important types are *ligand-gated ion channels* and *voltage-gated ion channels*. Ligand-gated ion channels are opened only by the binding of one or more molecules of an agonist, and are more correctly classified as receptors (see above) for the reason that for their activation the binding of an agonist is required. Voltage-gated ion channels are controlled by changes in the transmembrane potential.

The functions of both can generally be affected by medications via several mechanisms:

• Binding onto the protein structure of the channel, either to the binding site of the physiological ligand (orthosteric) or to a different (allosteric) site, or in a simpler case (e.g. the mechanism of local anesthetics on voltage-gated sodium channels) the molecule physically blocks the channel and prevents the passage of ions.

• Altering the level of expression of the ion channel on the surface of the cell. For example, the antiepileptic gabapentin decreases the embedding of neuronal calcium channels into the plasma membrane.

• Activating the opening of the ion channel - levosimendan (apart from its binding to troponin causing increased sensitivity to calcium) opens ATP-sensitive K^+ channels in blood vessels (vasodilatory effect).
Other examples include calcium channel blockers (nifedipin, isradipin - treatment of hypertension) or potassium channel blockers (fampridine - treatment of multiple sclerosis, flupirtin - treatment of pain, oral antidiabetics - treatment of type 2 diabetes).

II. Control of enzymes

Many medications act via the control of enzymes. Often, the medication is a substrate analogue, which behaves as a competitive inhibitor of the enzyme (e.g. antihypertensive kaptopril, affecting angiotensin converting enzyme); but in other cases, the binding is irreversible and non-competitive (e.g. acetylsalicylic acid which blocks cyclooxygenase 1). Medications can also behave as false substrates, where the molecule of substance undergoes a chemical transformation and forms an abnormal product, which disrupts the normal metabolic pathway. An example of this effect is the cytostatic fluorouracil, which replaces uracil as an intermediate product in the synthesis of purine, therefore inhibiting thymidylate synthetase by which it blocks the synthesis of DNA and prevents cell division.

It is also necessary to mention that some medicaments use enzymatic degradation as a means of changing themselves from an inactive form (prodrug) to an active form

(e.g. enalapril is transformed via esterases to enalaprilat, which is an inhibitor of angiotensin converting enzyme).

The result of this transformation by enzymatic activity can also affect the toxicity of the medication (changing molecules of medication into a reactive metabolite). Paracetamol, respectively its metabolite NAPQI (N-acetyl p-benzoquinoneimine) causes in this way damage to the liver in this way. If this affects the effect of the drug it is classed as an unwanted side-effect with great clinical significance.

Further examples of therapeutic uses of enzyme inhibition: reversible inhibition of acetylcholinesterase (pyridostigmine - treatment of myasthenia gravis), reversible inhibition of phosphodiesterase (methylxanthine - treatment of asthma, sildenafil PDE V - treatment of erectile dysfunction, amrinone, milrinone iPDEIII - cardiotonicity), reversible inhibition of monoaminoxidase A (moclobemide - antidepressant), irreversible inhibition of monoamine oxidase B (selegiline – antiparkinson drug), irreversible inhibition of aldehyde dehydrogenase (disulfiram - treatment of alcohol addiction).

III. Control of transport systems

Transport of ions and small organic molecules across cell membranes is generally facilitated either via channels (see above) or with the help of transport proteins, because transported molecules are often too polar (i.e. insufficiently liposoluble) to be able to cross the lipid membrane independently. There are many such transporters known, but examples with special pharmacological importance are, for instance, the transporters for the transport of ions and many organic molecules across the kidney tubules, intestinal epithelium and the blood brain barrier, transport of Na^+ and Ca^+ out of the cell, uptake of transmitter precursors (such as choline) or transmitters of such molecules (such as amines and amino acids) at nerve endings and transport molecules of medications and their metabolites across membranes and epithelial barriers.

In many cases the energy required for the transport of substances against their electrochemical gradient is obtained by the hydrolysis of ATP. Such transport proteins have a separate binding site for ATP known as the ABC (ATP-binding

cassette) proteins. Important examples include sodium pumps (Na^+/K^+ ATPase) and transporters of multiple drug resistance (MDR), which pump out cytostatic drugs from tumour and microbial cells, which causes resistance to these medications.
Na^+/K^+ ATPase is the target structure for digoxin (treatment for heart failure). It is located in the cell membrane of cardiomyocytes and its blockade has positive inotropic effects.

If the transport of the molecule connected to the transport of the ion (often Na^+) occurs in the same direction we designate this as a symport, and if the transport occurs in the opposite direction then we call this an antiport.

Transport proteins contain a recognition site, which marks them as specific for a transported agent/molecule, and these recognition sites can also be the target for medications whose effect is to block this transport system.

As an example, the control of a transport mechanism can be achieved by fluoxetine - antidepressant of the SSRI class (Selective serotonin reuptake inhibitors), which blocks serotonin transporters and in doing so prevents the reuptake of serotonin to the cell from which it was released. Tricyclic antidepressants behave similarly, although nonspecific for more transporter systems (5-HT, NA, DA).

Another example of inhibition of transport systems, in this case of lipids, is lomitapide, inhibitor of microsomal transfer proteins (MTP, of intracellular proteins, transporter of lipids between membranes in the lumen of the endoplasmic reticulum) or ezetimibe, which is the inhibitor of intestinal transporter Niemann-Pick C1-Like 1, which transports sterols.

IV. Other mechanisms

• Inhibition of the formation of tubulin chains of colchicine prevents the formation and repair of the cytoskeleton, which prevents cell division.

• Alkylating or intercalating cytostatics affect DNA transcription.

• Control of the immune response, specifically of certain pathways (filgrastim, erythropoietin, IFN, glatiramer acetate - RS).

• α-dornase cleaves extracellular DNA (used in patients with cystic fibrosis).

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2. Basics of pharmacokinetics

Pharmacokinetics is part of general pharmacology which describes the fate of a drug in an organism from its administration to its excretion. It describes four basic pharmacokinetic processes that the drug undergoes from its administration to the patient – absorption, distribution, metabolism, and excretion – both qualitatively, and quantitatively. Knowledge of the pharmacokinetics of an individual drug is as essential for the clinical practice as its mechanism of action. Based on the pharmacokinetic parameters of the drug, we can set a patient's dosing regimen properly. If we know what is happening to the drug after its administration, we can predict how the effect of the substance changes due to comorbidities or concomitant drugs, and by adjusting the dosing regimen, we can prevent complications such as ineffectiveness or risk of toxicity.

2.2 General patterns of drug movement in the body

How the drug overcomes the biomembranes that form natural barriers between parts of the body is essential for all pharmacokinetic processes. To a large extent, it is possible to estimate the pharmacokinetic properties of a substance on the grounds of generally applicable principles of the movement of molecules in the body. These principles are dependent mainly on the following factors:

2.2.1. Physico-chemical properties of the drug

The fate of the drug in the body is mostly dependent on its physico-chemical properties, particularly the size and shape of the molecule, the partition coefficient between the aqueous (polar) and lipid (non-polar) phases, and the acid-base properties.

2.2.1.1 Molecular size and shape

Generally, smaller molecules pass through the biomembranes easier. Most of the therapeutically used drugs have a molecular weight 100−1000 Da. Clinically used drugs with the lowest molecular weight include, for example, lithium (7 Da). In contrast, high molecular weight drugs, such as monoclonal antibodies (up to 150 000 Da), penetrate the biomembranes slowly or not at all. The influence of molecular

weight must be considered by choosing a proper route of administration or formulation of an advanced dosage form (see Chapter 3 - Routes of drug administration and drug dosage forms).

2.2.1.2 Partition coefficient of the drug between the aqueous and lipid phases

The partition coefficient value indicates the ratio at which the drug is distributed between the lipid membrane bilayer and the aqueous phase. Drugs that are more soluble in fats diffuse better through biomembranes. The partition ratio is determined experimentally in the octanol−water system.

2.2.1.3 Acid-base properties of the drug

Most drugs are electrolytes, i.e., they dissociate in the aqueous environment of the organism, and act as weak acids or weak bases depending on the pH of the environment and the dissociation constant of the molecule (pKa). The **Henderson-Hasselbach equation** expresses the relationship between pH, pKa and the ratio of dissociated and undissociated fractions:

$$\mathrm{AH} \overset{\mathrm{ka}}{\leftrightarrow} \mathrm{A^-} + \mathrm{H^+} \qquad \mathrm{pka} = \mathrm{pH} + \log\left(\frac{[\mathrm{AH}]}{[\mathrm{A^-}]}\right)$$

$$\mathrm{B} + \mathrm{H^+} \overset{\mathrm{ka}}{\leftrightarrow} \mathrm{BH^+} \qquad \mathrm{pka} = \mathrm{pH} + \log\left(\frac{[\mathrm{BH^+}]}{[\mathrm{B}]}\right)$$

The dissociated (charged) form of the molecule is hydrophilic and does not cross non-polar membranes. In contrast, the non-dissociated (non-charged) form is more lipid-soluble, and therefore can readily permeate through a phospholipid bilayer. From the equations mentioned above, it is possible to infer that in the acidic environment drugs acting as weak acids penetrate the biomembranes easier and in the basic environment, substances of basic character penetrate easier.

Example: Ibuprofen is a weak acid (pKa = 4.9), and its dissociation is suppressed in the acidic environment of the stomach. As most of its molecules in the stomach are non-dissociated (not charged), the absorption of ibuprofen by passive diffusion begins there. On the contrary, phenytoin is a weak base (pKa = 8.3). In the stomach, a larger percentage of the drug is dissociated and charged. Thus, phenytoin

molecules cannot pass through the stomach wall by simple diffusion. The situation changes after the drug passes into a more alkaline environment of the intestine. A higher percentage of drug molecules are not dissociated there and can be absorbed.

2.2.2 Drug permeation through biological membranes

2.2.2.1 Simple diffusion

Simple diffusion is quantitatively the most important transport mechanism for drugs. It is a non-saturable process for which Fick's laws apply. The rate of transfer is directly proportional to the concentration difference of the drug on both sides of the membrane (the higher the concentration difference, the faster the diffusion). Other factors that affect diffusion rates are the thickness of the membrane and the surface through which the molecule diffuses. The drug must be lipophilic (to some extent) to cross the phospholipid barrier. Simple diffusion of substances with a larger molecule or charge is quite difficult.

2.2.2.2 Membrane pores

The passage through membrane pores is determined by the size of a drug molecule and its water-solubility. Molecules larger than the pore diameter cannot penetrate, as well as water-insoluble drugs (pores are filled with the aqueous environment). Drugs pass through the pores in two ways. Firstly, by simple diffusion of the substance through the pore downstream the concentration gradient. Secondly, by filtration, which means the solute passes through the pore with the solvent based on differences in hydrostatic and osmotic pressure on both sides of the membrane. Filtration is not a typical process in pharmacology. Example of this transport is the excretion of a drug by renal glomeruli. Under physiological conditions, the limit for permeation through glomerular filtration is a molecular weight up to 60−70 kDa.

2.2.2.3 Carrier-based transport

Facilitated diffusion

In contrast to simple diffusion, a membrane protein which mediates substance transfer is involved in facilitated diffusion. A common feature with simple diffusion is no energy consumption and the alignment with the direction of the concentration gradient. Organic cation transporters (OCTs) belonging to the solute carrier family

(SLC transporters) are an example. They are involved in drug transport in the renal tubules, hepatocytes, and blood-brain barrier, and their substrates include, for example, some antiviral drugs (lamivudine, acyclovir), cytostatics (paclitaxel, oxaliplatin), and antidiabetics (metformin). Since the carrier protein has a specific capacity, this transfer method is, in contrast to simple diffusion, saturable and its capacity is determined by the concentration of carrier molecules in the membrane. After reaching a maximum, the speed of transport can no longer be increased. Furthermore, substrate specificity and the possibility of competition or inhibition (e.g., omeprazole inhibits OCT) are typical for this transport.

Active transport

This mode of transport usually takes place against a concentration gradient, and therefore, it requires the supply of energy in the form of ATP. The carrier membrane protein, substrate specificity, saturation, and the possibility of its inhibition are features shared with the facilitated diffusion. Examples of active transport from human physiology are tubular glucose reabsorption or a sodium pump.

There are several important drug carrier proteins. Two major groups are ABC proteins (ATP-binding cassette protein) and SLC transporters. Of the ABC group, **P-glycoprotein** (permeability glycoprotein) is the most important. It is a transmembrane pump that is coded by the MDR1 gene (multidrug resistance). It can be found in many tissues and organs where it physiologically performs a barrier and excretion function. From the pharmacological point of view, its ability to interfere with the pharmacokinetics of some drugs and to significantly influence their effects is particularly important. In enterocytes, P-glycoprotein can reduce the bioavailability of drugs. In proximal renal tubule cells or hepatic canaliculi, it can increase drug elimination. P-glycoprotein can also be found in tumours, and its overexpression is the cause of resistance to cytostatics. Many drugs inhibit P-glycoprotein, which can lead to clinically severe drug interactions. An example is an increase in digoxin plasma concentrations when combined with clarithromycin. Digoxin is a substrate of P-glycoprotein and clarithromycin is its inhibitor. This drug interaction results in increased digoxin bioavailability and reduced excretion.

Beside OCTs, which utilise facilitated diffusion, the SLC protein family also includes organic anion transporters (OAT), which use ATP for transport. OATs are part of the

secretory system in the kidneys and play an essential role in the excretion of drugs with weak acid properties. Competition for these proteins may slow the excretion. An example of this effect is the concomitant administration of penicillins or some of the antiviral drugs and probenecid, OAT inhibitor, which prolongs the half-life of these antimicrobial agents. Other examples of carrier proteins are MATE - 1 and MATE - 2K transporters (multidrug and toxin extrusion protein) responsible for the secretion of organic cations and zwitterions into bile and urine. These transporters are also an example of the so-called secondary active transport, where the transfer through the membrane uses the energy of the primary membrane gradient of other ions.

2.2.2.4 Vesicular transport

From the pharmacological point of view, there are two most important types of vesicular transport:

1. **Fluid endocytosis** – drug-containing fluid is taken up by a cell;
2. **Receptor-mediated endocytosis** – active endocytosis mediated by the megalin (LRP2 protein) system is an example. Megalin is a receptor present on the apical membrane of epithelial cells of renal tubules or in the placental and small intestine epithelium. It mediates the entry of many endogenous and exogenous proteins, larger peptides, and some drugs into cells. For instance, nephrotoxicity of aminoglycosides is caused by the reabsorption and accumulation of these antibiotics in the proximal tubular cells by megalin. Generally, large molecules such as monoclonal antibodies are transported by vesicular transport, as well.

2.2.3 Drug binding

Drugs in the body are present not only in a free form but to some extent also as bound. The nature of the binding may be either depot, where the bound substance does not produce any effect on the structure, or it may be a pharmacodynamically active binding, where the substance induces a change in the state of the target structure, and consequently a pharmacological effect. The level of drug binding is determined *in vitro* and knowledge of this parameter is very important because it affects the pharmacokinetics (depot binding) and pharmacodynamics (active binding) of the drug. Drug binding can be characterised by the ratio of the bound and free fraction, the strength of the binding, and the number of binding sites. The affinity of

depot binding sites for substances is generally lower than that of active sites. On the other hand, depot binding sites are present in a higher number, and thus can bind a large amount of the drug.

We distinguish the following types of binding:

2.2.3.1. Plasma protein binding

According to the affinity for specific ligands, we distinguish specific and non-specific plasma proteins. Specific include, e. g., binding proteins for thyroxine, cortisol, and sex hormones, with high affinity for these substances. Three types of proteins are non-specific and essential for drug binding: **albumin**, **glycoproteins**, and **globulins**.

Albumin is the most abundant plasma protein of 68 000 Da. It has an exceptional binding capacity and binds a wide range of different drugs. It can bind weak acids (e. g., warfarin, non-steroidal anti-inflammatory drugs, sulphonamides, penicillins), lipophilic drugs (e. g., cyclosporin A, acitretin), basic drugs (benzodiazepines), neutral drugs, as well as anions.

The most important of the glycoproteins is the **α_1-acid glycoprotein** (orosomucoid) with a molecular weight of 41 100 Da. Although it has a much lower concentration in plasma than albumin, it is an important binding protein for some drugs. It is also an acute-phase protein that increases in some pathological conditions. It is mainly associated with binding of weak bases and cations (e. g., verapamil, dipyridamole, vincristine, imatinib, beta-blockers, digoxin).

Globulins are a wide group of proteins with molecular weight about 150 000 Da. Lipoproteins that bind lipophilic drugs (e. g., nystatin, amphotericin B, glucocorticoids) also belong to this group.

Plasma protein binding is rapid and reversible. If the free drug concentration in the plasma decreases due to metabolism or excretion, the appropriate proportion of the substance is released from the plasma protein binding, and equilibrium is restored. When two different drugs have an affinity for the same binding site, competition occurs, and one drug may force out the other. This pharmacokinetic interaction increases the plasma free fraction of the drug that has been forced out. The drug is then available for further distribution in the body or binding to receptors. This

interaction can lead to an increase of pharmacological effect or even trigger intoxication.

2.2.3.2. Binding to blood cells

Binding of the drug to blood cells is not as crucial as plasma protein binding. Examples of drugs that bind to blood cells are methotrexate (erythrocytes) or heparin (platelets). Binding of heparin together with cytokine PF4 (platelet factor 4) to platelets can lead to antibody production. Antibodies against the complex of heparin and PF4 induce peripheral platelet thrombus formation (heparin-induced thrombocytopenia type II).

2.2.3.3 Binding in tissues

This type of binding is drug-specific. An example is the binding of tetracyclines to hydroxyapatite in teeth and bones. Intensive binding of a drug in tissues results in a decrease of drug plasma level, although the substance is not yet eliminated.

2.2.4 Tissue perfusion

One of the factors determining how quickly a drug is distributed to a given tissue or organ is the rate of blood flow. Drugs reach the tissues with abundant blood supply (brain, kidney, liver, heart) faster and in higher concentrations. On the other hand, the drug is eliminated more rapidly from these tissues. In the case of poorly perfused tissues, the situation is inverse. The drug reaches them more slowly, and the elimination is slow (e. g., adipose tissue). In some cases, especially with lipophilic drugs (e. g., general anaesthetics), drug accumulation can occur.

2.3 Pharmacokinetic processes and parameters

We distinguish four basic pharmacokinetic processes: **absorption**, **distribution**, **metabolism**, and **excretion**. The processes of absorption and distribution together are called the phase of **drug invasion** into the organism. The processes of metabolism and excretion are called the phase of **drug elimination**.

The individual processes are described by pharmacokinetic parameters which divide into **primary** and **secondary**. The primary parameters change when changes in the

physiological variables (blood flow, plasma protein content, glomerular filtration) occur. They include:

clearance (Cl)

distribution volume (Vd)

Secondary parameters depend on the primary parameters and include:

maximum plasma concentration (c_{max})

time at which c_{max} (t_{max}) is reached

biological elimination half-life ($t_{1/2}$),

area under the curve (AUC)

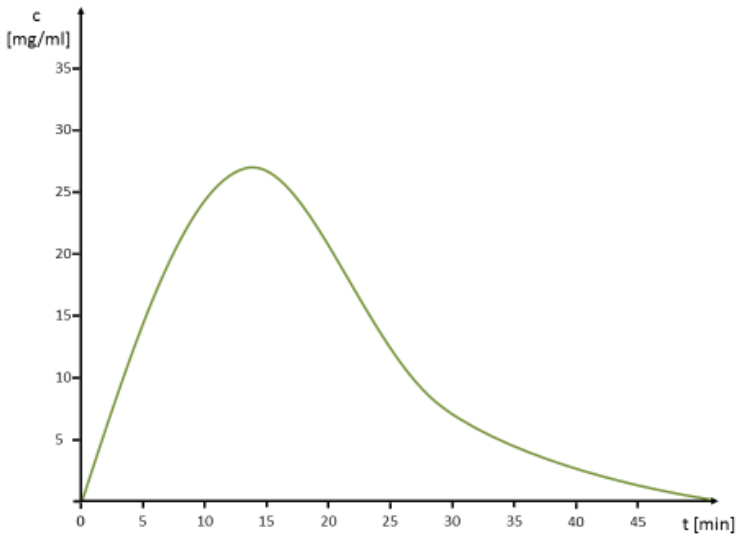
drug bioavailability (F)

absorption constant (k_a)

elimination constant (k_e)

Diagram of plasma concentrations (y-axis) versus time (x-axis) is usually used to represent pharmacokinetic events and parameters (Fig. 7).

Figure 7. *Diagram of plasma concentrations of a drug versus time after extravascular drug administration*



2.3.1 Drug invasion

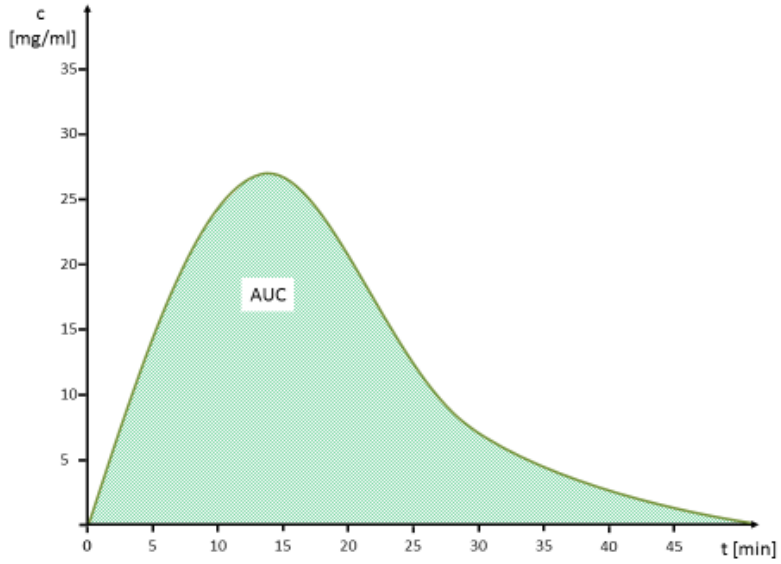
2.3.1.1 Drug absorption

Absorption is required to achieve a systemic effect of the drug. It does not apply only in case of the intravascular route of administration, as the entire dose of a drug is administered directly to the systemic circulation. Conversely, for drugs with a local effect absorption is undesirable because it reduces the concentration of the drug at the site of administration, and thus its efficacy and duration of action. Besides, systemic absorption of drugs with local effect possess a risk of systemic adverse effects.

It is important to know at what rate absorption is occurring and how much of the administered drug is absorbed at all. Pharmacokinetic parameters **t_{max}** and **c_{max}** describe the rate of absorption. The t_{max} value expresses the time required to reach the maximum plasma concentration (c_{max}) of the drug after a single administration. The lower the t_{max} value, the faster the absorption is. In the case of i.v. administration, the t_{max} value is 0 because the maximum plasma concentration is reached at the time of administration.

The extent of absorption is described by a parameter called **drug bioavailability** (F). Bioavailability is the ratio between the amount of drug that enters the systemic circulation (and is available to induce a systemic effect) and the total dose administered. It reaches 0 to 100% (or 0-1). After the intravascular administration, F is always 100%. For other types of administration, F depends on several different factors and reaches 0-100%, as was already mentioned. Bioavailability of a drug is frequently expressed by the **area under the curve of its plasma concentration** (AUC) (Fig. 8).

Figure 8. *AUC – Area under the curve of plasma drug concentration*



We distinguish absolute and relative drug bioavailability. **Absolute bioavailability** meets the general definition of bioavailability and indicates the actual amount of drug available in the body to induce an effect. For intravascular administration, it always equals 100%. For other routes of administration, it is calculated as the ratio of AUC after extravascular administration to AUC after intravascular administration. In addition to the route of administration, it also depends on the dosage form.

$$\mathbf{F} = \frac{\mathbf{AUC_{p.o.,i.m.,s.c....}}}{\mathbf{AUC_{i.v.}}}$$

Relative bioavailability is used to compare two extravascular routes of administration or two different dosage forms administered by the same way. Unlike absolute bioavailability, it does not inform us about the real amount of a substance that reaches the systemic circulation. Relative bioavailability describes the difference in bioavailability (in %) between the compared routes of administration or dosage forms. This parameter is essential especially in the **bioequivalence studies** used in the marketing authorisation process of generic drugs. Unlike the original medicinal product, generic drugs are tested only for so-called bioequivalence. Bioequivalence means that after administration of the same dose of the same drug by two different medicinal products, the course of plasma concentrations is similar (it may not be identical). The compared parameters (c_{max}, t_{max}, AUC) of the generic medicinal

product must not be outside the range of 80-125% of the values of the original product[1].

$$\mathbf{F} = \frac{\mathbf{AUC_{po}}}{\mathbf{AUC_{po}}}$$

or

$$\mathbf{F} = \frac{\mathbf{AUC_{po}}}{\mathbf{AUC_{i.m.}}}$$

Presystemic drug elimination

Factors that reduce the bioavailability of a drug can be covered by the term "presystemic drug elimination". There are many reasons why not all the amount of drug reaches systemic circulation.

The most common route of administration is oral use, and many influences are reducing the bioavailability of orally administered drugs. The drug can interact with co-administered food to form non-absorbable complexes (e.g. tetracyclines + polyvalent cations). It can be a substrate of efflux pumps present in enterocytes (**P-glycoprotein**), which actively excrete the drug back into the intestinal lumen. Due to GIT motility, the drug can then enter parts of the GIT unsuitable for its absorption (outside its absorption window). Part of the drug can also be metabolised in enterocytes, which are especially rich in enzymes of the cytochrome P450 family.

The so-called **"first-pass effect"** is also very significant. All substances absorbed from the intestine first enter the portal circulation, which brings the blood to the liver. After that, the blood goes to other tissues and organs where drugs usually act. In the liver, which is the primary metabolic organ, the biotransformation of a drug to inactive metabolites can occur before the drug enters the target organ. Cytochrome P450 enzymes are involved in this process. This first-pass effect significantly reduces drug bioavailability. It influences drugs administered orally and partly also rectally.

[1] The range of 80-125% does not apply to all products. For substances with a low therapeutic index, the acceptance interval is 90-111.11%, and bioequivalence studies are also more stringent for substances with non-linear pharmacokinetics (see below).

Examples of factors that can affect drug absorption:

- age (changes in liver enzyme activities, GIT motility)
- weight (adipocyte layer strength for transdermal or subcutaneous drug administration)
- pathophysiological condition (GIT atony, liver disease, circulatory disorders)
- perfusion at the site of administration (i.m. administration to subcooled vs heated muscle, ischemic tissue)
- area of absorption (GIT resection)
- concomitant administration of drugs (prokinetics, antibiotics)
- drug solubility
- concentration gradient

2.3.1.2 Drug distribution

After the absorption of a drug, the substance penetrates from the blood into various body tissues and organs. Distribution is a dynamic process in which a balance is continuously established between the amount of drug in the blood and other tissues. We are usually interested in the rate of the equilibrium establishment and the ratio of the concentration in the blood to the concentration in the monitored tissue.

The parameter describing the distribution phase is the **volume of distribution (Vd)**. Mathematically, the volume of distribution is the ratio of the total amount of drug in the body to its concentration in blood or plasma. The amount of drug in the body is calculated as the dose administered multiplied by the bioavailability. Combing these two equations we get:

$$\mathbf{Vd} = \frac{\mathbf{amount\ of\ drug\ in\ the\ body}}{\mathbf{c}} = \frac{\mathbf{D.F}}{\mathbf{c}} \quad [\mathbf{l}]$$

where c is the plasma concentration of the drug reached after absorption with no metabolism, D is the dose of drug administered, and F is the bioavailability.

The unit of volume of distribution is either a litre [L] or if we relate the volume to body weight, a litre per kilogram [L/kg].

The volume of distribution is a hypothetical volume in which the drug is dispersed to reach the same concentration as is its plasma concentration. Vd can reach low values for substances that are practically non-distributed and remain mainly in the blood (5 - 7L). However, it can also be very high (hundreds to thousands L), mostly for lipophilic substances that accumulate in adipose tissue or skeletal muscle and whose plasma concentration is very low compared to the dose administered.

The value of Vd informs us not only about the extent of drug distribution, but it can also be interesting from a practical point of view:

1. Based on the knowledge of the volume of distribution, we can calculate the **loading dose** according to the relation:

$$\mathbf{D = Vd.\, c_T}$$

where D is a loading dose, and c_T is the target plasma concentration.

2. Based on the knowledge of the volume of distribution, we can estimate the amount of drug in the body according to the relationship:

$$\mathbf{M = Vd.\, c}$$

where M is the amount of drug in the body, and c is the measured concentration of drug in the blood.

3. We can assess the **success of hemodialysis or hemoperfusion** for drug elimination in the case of intoxication caused by a substance known to us. Hemodialysis or hemoperfusion will be effective for substances with low Vd, and conversely, substances with high Vd cannot be effectively removed from the body by these techniques.

Factors influencing the distribution of drugs include, for example:

- physico-chemical properties of a drug
- comorbidities (cardiovascular disease – decreased perfusion and impaired distribution; liver disease – hypoalbuminemia; nephropathy, limb amputation, ascites etc.)
- binding of the drug to plasma proteins (it may be crucial for the efficacy of the drug, as the protein-bound drug is not able to exert an effect or cross biological barriers)

- age - the proportion of body fluid decreases, and the proportion of body fat increases with age, serum albumin decreases and α_1-glycoprotein increases with age[2]

2.3.2 Drug elimination

The term "elimination" includes all processes removing the active form of the drug from the body. The drug can be eliminated by metabolism (biotransformation) to the inactive metabolite, excretion in an unchanged form, or a combination of both.

According to the dependence of the elimination rate on the plasma concentration, we distinguish **zero-order and first-order elimination**. Most drugs are eliminated by first-order kinetics, meaning their rate of elimination and the drug plasma concentration is in direct proportion. The higher the plasma level is, the faster the drug is eliminated. The course of plasma concentrations as a function of time then has the shape of an exponential curve (Fig. 9A). In a semi-logarithmic representation, the curve gets linear shape, and thus the term "linear kinetics" (Fig. 10).

For elimination kinetics according to the zero order, the elimination rate is constant mostly due to a **saturable enzymatic or transport elimination system**. The same amount of drug is eliminated per unit time (Fig. 9B). The elimination pathway becomes saturated at a specific plasma concentration of the drug, and the organism cannot respond to further increases in plasma levels by faster elimination. Such drugs have a higher risk of intoxication and adverse effects. Ethanol or phenytoin are examples of substances eliminated by zero-order kinetics. Theoretically, zero-order elimination kinetics can be achieved for almost all drugs. However, we would have to use extremely high doses above the standard therapeutic range.

[2] Small children have a higher proportion of total body fluid, so hydrophilic drugs have to penetrate relatively larger extracellular space. Therefore, it is necessary to increase the relative dose administered to children in some cases.

Figure 9. *Drug elimination rate according to first (A) and zero order kinetics (B)*

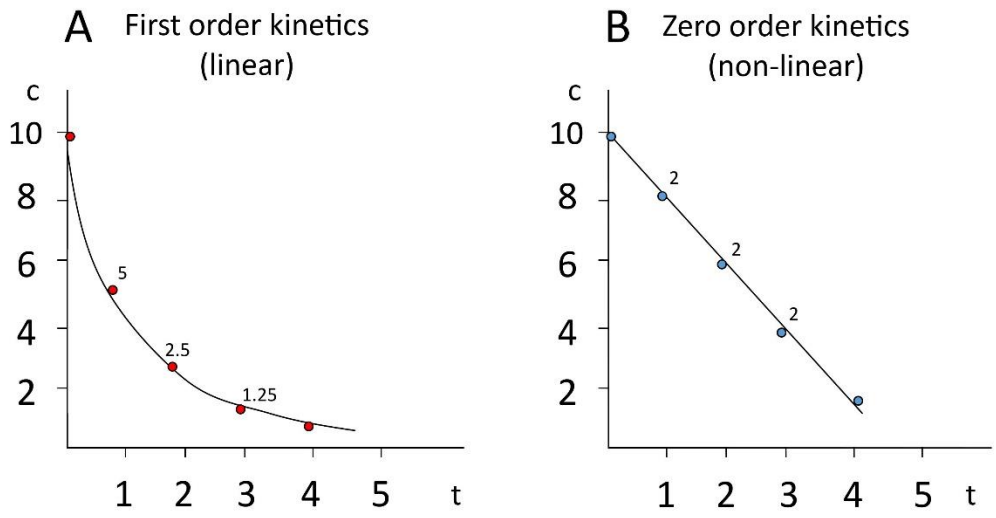
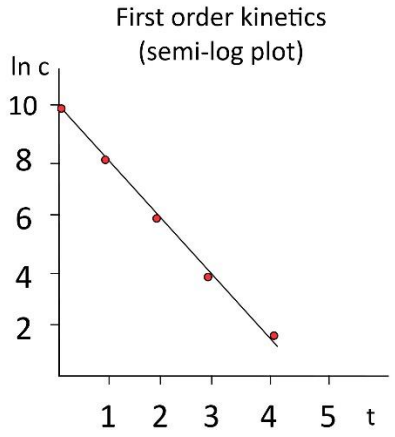


Figure 10. *Drug elimination rate according to first-order kinetics in semi-logarithmic representation*



The fundamental parameter describing elimination is **clearance (Cl)**. It is defined as the ability of the body to get rid of the drug. Specifically, it gives the volume of plasma that is completely purified from the drug per unit time, and the unit of Cl is the unit volume per unit time [L/min].

$$\mathbf{Cl} = \frac{\mathbf{elimination\ rate}}{\mathbf{c}}$$

The total clearance of the organism consists of individual organ clearances according to the ways by which the drug is eliminated from the organism:

$$\mathbf{Cl_{TOT} = Cl_{REN} + Cl_{HEP} + Cl_{PUL} \ ...}$$

The **elimination constant (k_e)** characterises the rate of elimination:

$$\mathbf{k_e = \frac{\ln c1 - \ln c2}{t2 - t1}}$$

From the practical point of view, biological half-life ($t_{1/2}$) is a more comprehensible constant. It also characterises the rate of elimination, and k_e is used for its calculation. $t_{1/2}$ is the time required for the plasma concentration of a drug to fall to half its value.

$$\mathbf{t_{1/2} = \frac{\ln 2}{k_e} = \frac{0,7}{k_e}}$$

2.3.2.1 Metabolism

Metabolism of most drugs is performed enzymatically. Based on the nature of the metabolites produced, metabolic reactions can be divided into **bioactivation** and **biodegradation**. Bioactivation reactions are essential for **prodrugs**. These are pharmacologically ineffective or less effective molecules that are converted in the organism to the active form. Prodrugs can be used to increase oral bioavailability (e.g. penamecillin). Biodegradation is a more common type of metabolism, and it leads to the production of less active or inactive metabolites.

Biodegradation processes usually have **two phases**. Their primary goal is to reduce the biological activity of substances and subsequently increase their hydrophilicity, improve their solubility in body fluids, and thus facilitate their elimination from the body. The **first phase** involves the oxidoreductase system of **cytochrome P450** (CYP), but also other enzymes (deaminases, hydrolases, reductases, etc.). Change in the structure of the drug is usually associated with a decrease in biological activity because the interaction of the drug with the target structure is dependent on the characteristic structure of the drug molecule. If the drug is sufficiently polar, it can be

excreted by the excretory organs. If not, it enters the **second phase** of metabolism, in which enzymes catalyse conjugation reactions. The resulting conjugates have a higher molecular weight and are more hydrophilic than the maternal drug. Examples of conjugation reaction are conjugation with glutathione, glycine, methionine, sulfuric acid, glucuronic acid, acetic acid, bile acids etc.

Drugs may undergo one or both of these phases. Some hydrophilic drugs are not metabolised at all are excreted in an unchanged form (e.g. aminoglycosides, gabapentin, penicillins). The most important biotransformation organs are liver and kidneys. Less important are lungs and intestines (intestinal enzymes).

Interindividual differences in the metabolic activity of biotransformation enzymes and drug interactions at the CYP level are essential for clinical practice. Metabolic activity is influenced by several exogenous and endogenous factors. Some medicines, as well as some food components, can affect the activity of CYP enzymes. CYP inducers increase its activity (rifampicin, carbamazepine, St. John's wort), leading to faster elimination of drugs and the need to increase their doses or shorten dosing intervals. In contrast, CYP inhibitors (fluoxetine, clarithromycin, grapefruit constituents) reduce enzyme activity and increase the risk of intoxication with standard doses of drugs. For example, tobacco smoking (exogenous factor) induces CYP1A2 activity, while genetic polymorphisms (endogenous factor) can influence plasma levels of CYP2D6, CYP2C9 and CYP2C19 substrates. Based on the observed change in the metabolic activity of a particular enzyme, we divide individuals into four categories (this does not apply to all biotransformation enzymes):

- **poor metabolisers** – low or no metabolic activity of the enzyme
- **intermediate metabolisers** – enzyme activity is between slow and fast metabolisers, with no change observed clinically
- **extensive metabolisers** – most of the population, normal enzyme function
- **ultra-rapid metabolisers** – duplication or multiplication of the gene for a given enzyme, metabolic activity is higher than in extensive metabolisers

Examples of other factors influencing drug metabolism:

- age – newborns do not have fully mature enzymes (CYP, UDP-glucuronosyltransferase), while elderly have reduced enzyme activity due to impaired blood flow to biotransformation organs

- gender – sex hormones affect biotransformation enzymes; adult men metabolise drugs faster than adult women by some CYP enzymes
- diseases of biotransformation organs – liver or kidney diseases can slow biotransformation processes and prolong the elimination half-life
- nutritional status of the organism, diet

2.3.2.2 Excretion

The journey through the body ends with excretion of the drug by a suitable excretory organ. The main excretory organs are kidneys, bile/stool and lungs, but other pathways exist, such as sweat, saliva, tears, breast milk, etc. From a quantitative point of view, these excretion pathways remove a negligible amount of drug.

Hydrophilic drugs are usually excreted by the kidneys, in which three mechanisms are involved: glomerular filtration, tubular secretion, and reabsorption. Only free substances not bound to plasma proteins with a molecule smaller than the size of albumin can enter the primary urine by filtration. Other drugs enter urine by the mechanism of tubular secretion using specific transporters. Competition of two substances for the same transporter can slow the elimination and prolong the biological half-life (e.g. penicillins + probenecid). The increase of drug reabsorption in the renal tubules can have the same effect.

Alkalinisation ($NaHCO_3$) or **acidification of urine** (NH_4Cl) affects reabsorption or increase solubility and reduce the risk of urinary tract precipitates of poorly soluble substances. Increasing the pH of the urine leads to ionisation of weak acid molecules present in the urine, which limits their reabsorption and thus increases their excretion. Weak bases, on the other hand, will be excreted less, because at higher pH they will have a non-ionized form and will more easily transfer from the filtrate back to the blood. The reverse situation occurs for acidified urine.

Bile plays a vital role in digestion and fat absorption. Substances excreted in bile can undergo **enterohepatic circulation**, as bile acids do. This prolongs their biological half-life. In some cases, substances are excreted to the bile in the form of conjugates and can only be reabsorbed after cleavage of the conjugates by the colonic microbiota. Colonic microbiota can significantly affect the pharmacokinetics of drugs. For example, the use of broad-spectrum antibiotics can disrupt the enterohepatic circulation of drugs and thus accelerate their excretion.

In breastfeeding women, drugs and other xenobiotics can be excreted to breast milk. Because the milk is slightly more acidic than plasma, weak bases (e.g. nicotine, caffeine, and theophylline) reach higher concentrations in milk than in maternal plasma.

2.4 Plasma concentrations of a drug over time

2.4.1 Single dose of a drug

Plasma concentrations of a drug differ significantly after extra- and intravascular administration of a single dose (Fig. 11 and 12). After intravascular administration, the absorption phase does not apply, and only the elimination part of the curve is present. In other words, c_{max} is reached immediately after administration, and drug levels continue to decrease after that. After extravascular administration, plasma concentrations are increasing (i.e. the drug is absorbed) until t_{max} and c_{max} are reached, and then the elimination phase similar to intravascular administration follows. Such a description of the course of plasma drug concentrations is only theoretical and very simplified compared to the real situation. Actually, the drug is eliminated from the body as soon as it appears in the plasma, while the elimination rate is very low due to the first-order kinetics (i.e. due to the low plasma concentration). On the other hand, high concentration of drug at the site of administration sets a significant concentration gradient for the movement of the drug into the blood, and the rate of absorption is therefore very high. With the decreasing concentration of the substance at the site of administration and increasing concentration of the substance in the plasma, the absorption and elimination rates start to balance, and right at t_{max}, both are equal. Subsequently, elimination predominates, and although the drug is still being absorbed into the body, the amount of drug absorbed decreases over time. The curve shape of the plasma levels at elimination phase after intravascular administration is not the very same as after the extravascular administration. After reaching c_{max} at time t_{max}, the curve of extravascular administration is deformed due to the ongoing absorption. This period is sometimes called the post-absorption phase.

Figure 11. *Time course of plasma drug concentrations after single intravascular (red) and extravascular (green) administration*

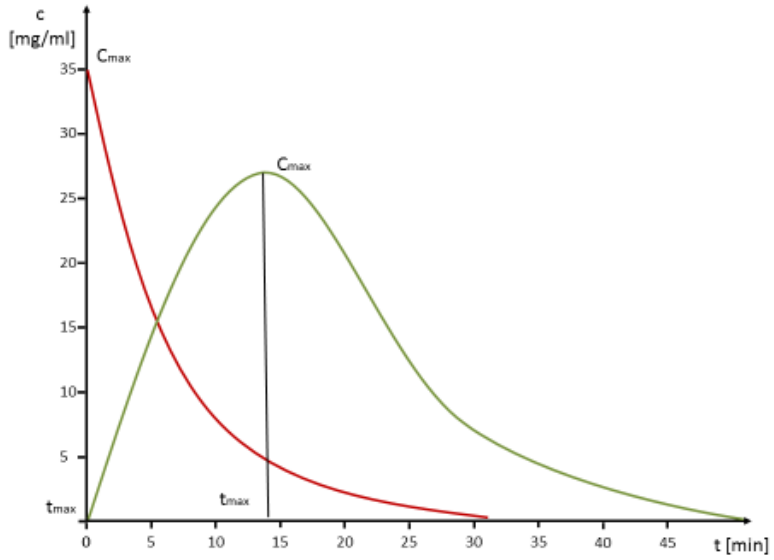
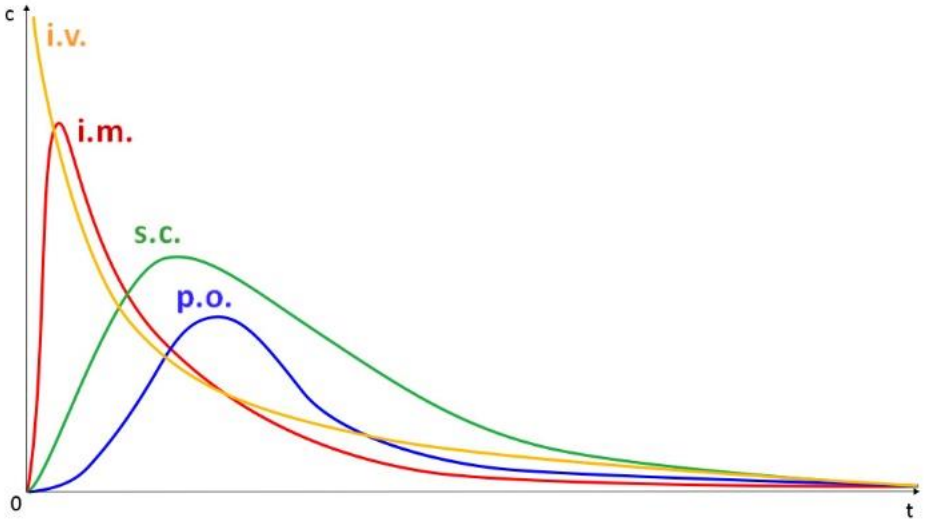


Figure 12. *Schematic representation of the time course of plasma drug concentrations after a single administration by various routes of administration*



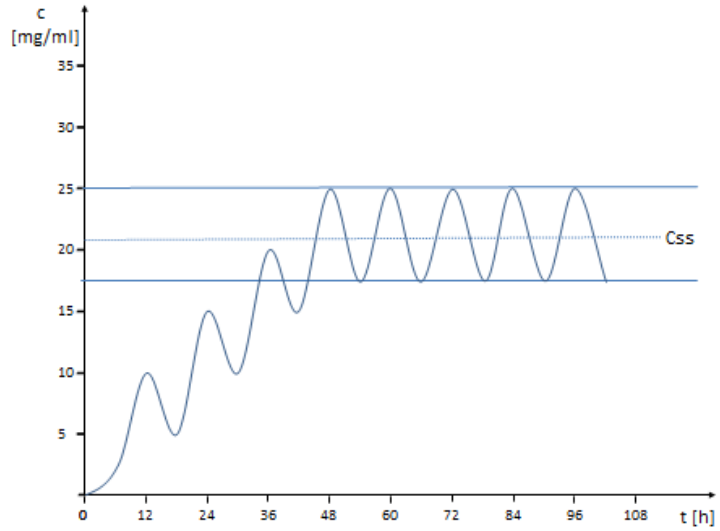
2.4.2 Repeated administration of the drug

Repeated administration of a drug means that the next dose of a drug is administered to the patient before the previous dose is completely eliminated from the patient's body. Assuming that the drug is administered at the same dosing intervals, a gradual increase in the mean plasma concentrations of the drug occurs within the dosing intervals. This phenomenon is called drug accumulation. However, the increase in mean plasma drug concentrations gradually slows down due to the same phenomenon described for single drug administration, i.e. with increasing plasma concentration, the elimination rate increases. After a specific time, equal to approx. 4-5 $t_{1/2}$, so-called **steady state** is reached. It is a state where the average plasma concentrations no longer change during the individual dosing intervals, as well as the minimum and maximum plasma concentrations. The mean plasma concentration during a single dosing interval is referred to as the steady-state concentration (Css) (Fig. 13) and depends mainly on the body's ability to eliminate the drug (Cl) and also on the dose or bioavailable portion of the dose (D x F) and dosing interval (τ). The following relation applies:

$$\mathbf{Css} = \frac{\mathbf{D}.\mathbf{F}}{\boldsymbol{\tau}.\mathbf{Cl}}$$

Dose and dosing interval determine the rate of fluctuation of plasma drug concentrations. With the lower dose and shorter dosing interval, the minima and maxima of plasma concentrations are closer to Css, and the fluctuation is lower. Dose size and frequency of drug administration are practical tools for changing plasma concentrations of drugs. Together with TDM, changing the dose or dosing interval is a useful tool for individualising therapy with drugs of a narrow therapeutic range.

Figure 13. *Time course of plasma drug concentrations after repeated extravascular administration*



2.4.3 Continuous drug delivery

When the drug is delivered at a constant rate, plasma concentrations increase, similarly to repeated administration, until the rate of delivery equals the elimination rate. At this point, the so-called **steady state** is reached, and the plasma concentration (C_{SS}) does not change any further. The time required to reach C_{SS} is again dependent on the elimination rate and is approx. 4-5 times $t_{1/2}$. The specific value of C_{SS} is also dependent on the elimination rate, so the same drug administered at the same rate to different patients leads to different C_{SS}. The following relationship applies:

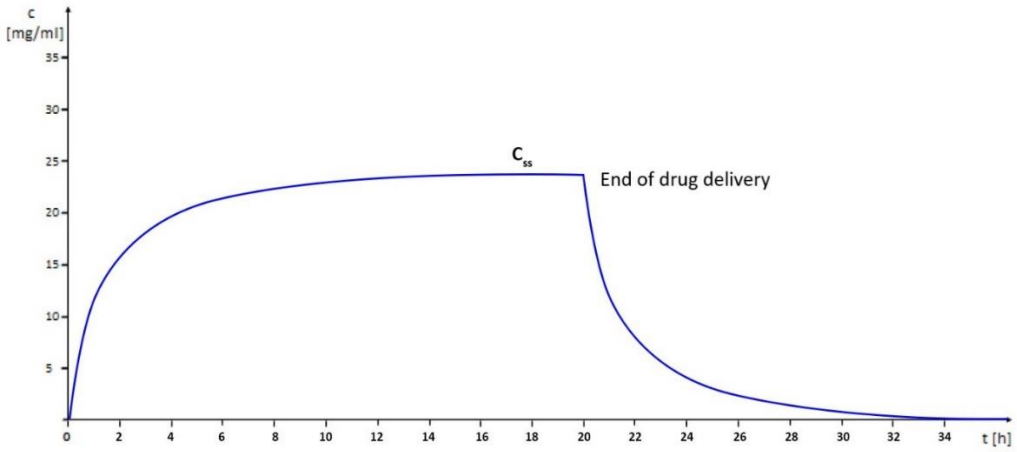
$$\textbf{drug delivery rate } \left[\frac{\textbf{mg}}{\textbf{min}}\right] = \textbf{Cl} \,.\, \textbf{Css}$$

If the patient has problems with drug elimination (hepatic or renal impairment), the drug delivery rate should be reduced to achieve the same C_{SS} as in the patient with intact elimination mechanisms. The crucial advantage of continuous drug delivery is the zero fluctuation of plasma concentrations. There is no risk that part of the dosing interval includes plasma concentrations outside the therapeutic range. Therefore, continuous drug delivery is the most preferred for drugs with a narrow therapeutic range. On the other hand, not all drugs have non-invasive methods of continuous

drug delivery in the form of patches. The administration of substances in the form of infusions or implants has several disadvantages, especially in terms of patient comfort and economic costs.

At the end of the continuous drug delivery, the shape of the curve corresponds to a single intravascular dose, and the substance is completely eliminated after approx. 4-5 biological half-lives (Fig. 14).

Figure 14. *Course of plasma drug concentrations after continuous drug delivery and after withdrawal*



2.5 Compartment models

Abstract compartment models are used to simplify the movement of the drug in the body (Figures 15 and 16). A compartment is a part of the body (e.g., plasma, tissue, organ, or organ system) of a specific volume or composition that exhibits the same properties. The drug is homogeneously dispersed in such compartment. For modelling using compartmental models, the human organism is simplified to various interconnected compartments. The rate constants define the movement of the drug between these compartments. As the number of compartments increases, so does the number of possible interconnections. Thus, the mathematical complexity of such system increases, as well. Therefore, only a one-compartment model is usually applied to calculate pharmacokinetic parameters of drugs, but there are also two and multi-compartment models.

Figure 15. *One-compartment models*

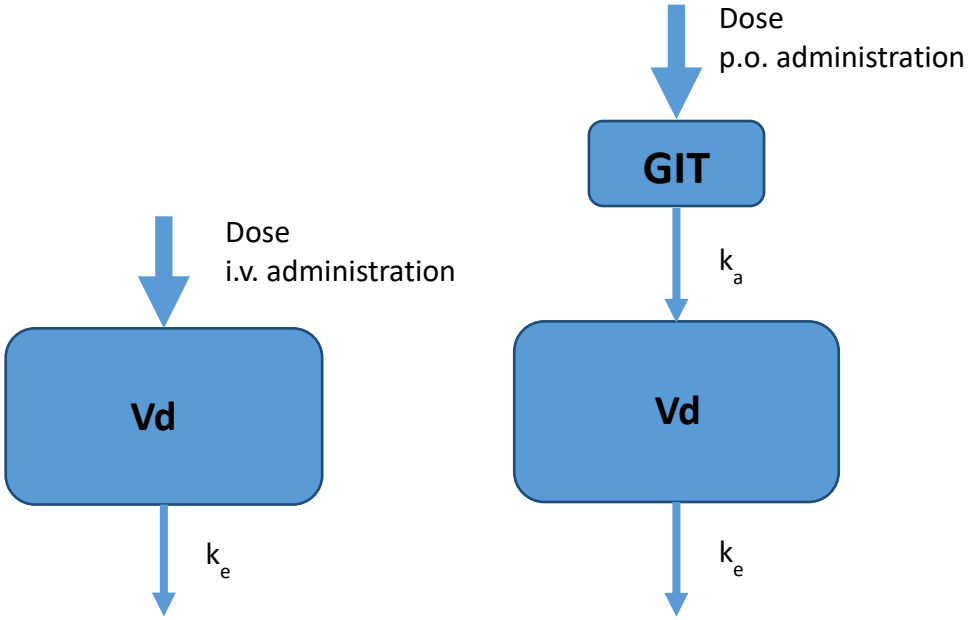
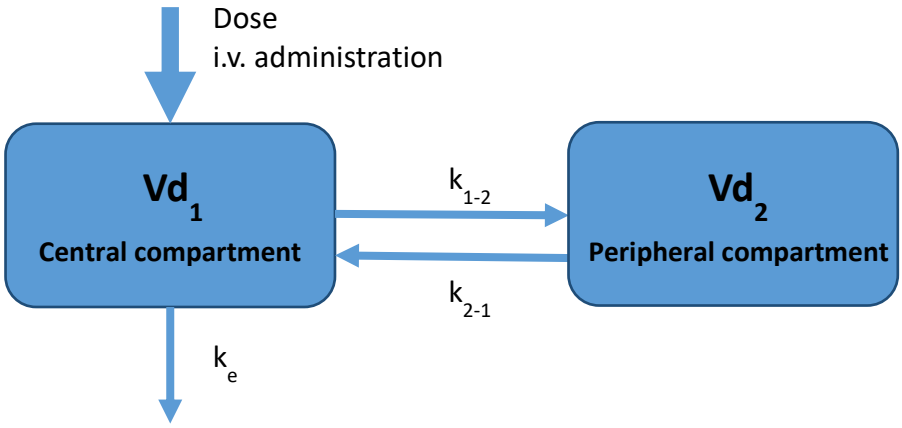
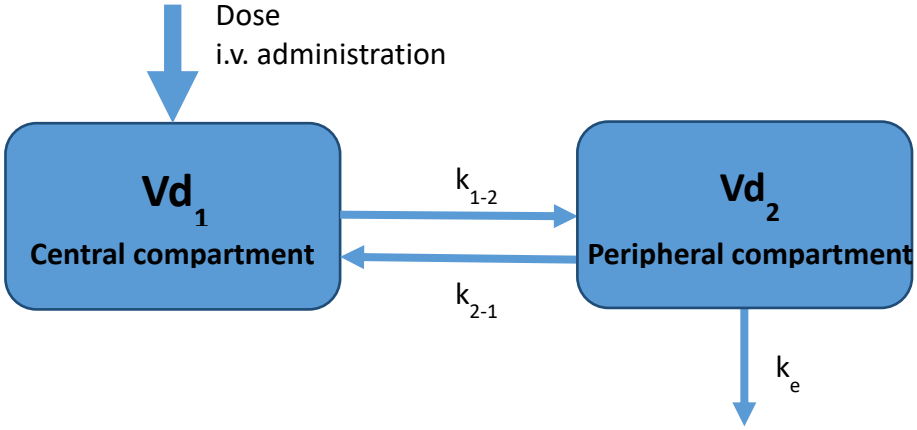
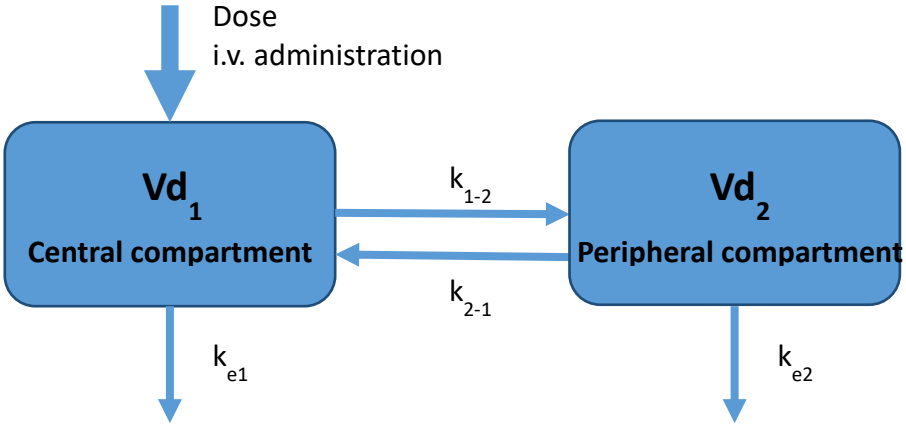
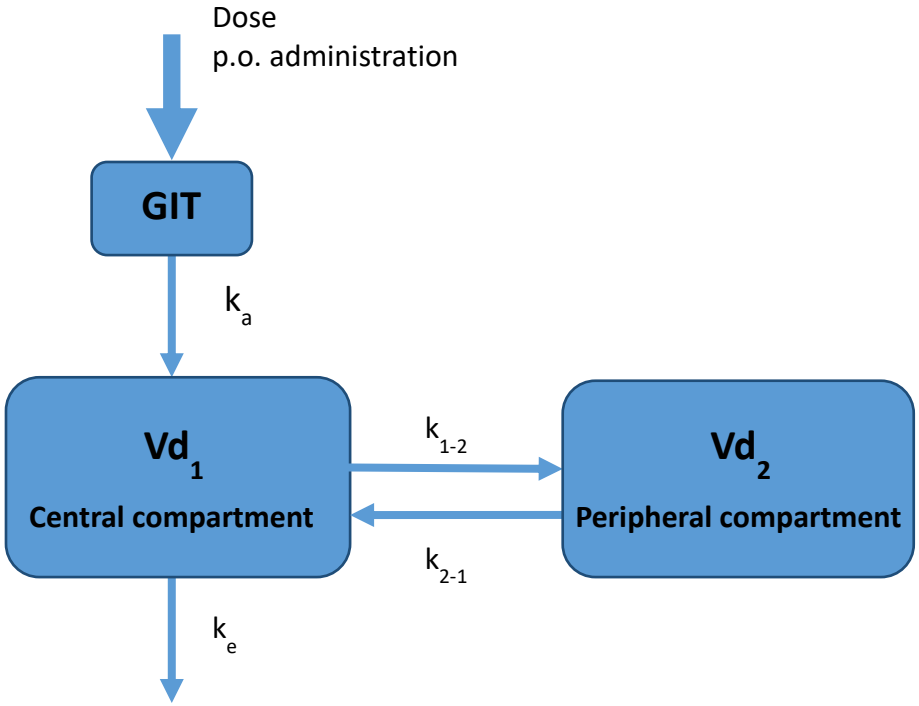


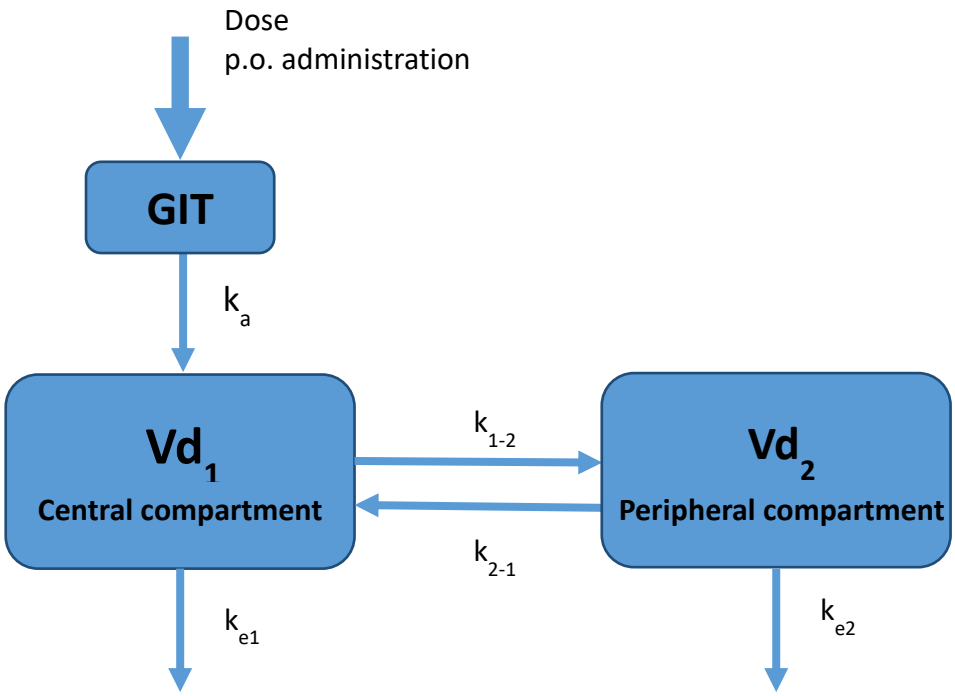
Figure 16. *Two-compartment models*




Dose
i.v. administration
Vd1
Central compartment
k1-2
k2-1
Vd2
Peripheral compartment
ke


Dose
i.v. administration
Vd1
Central compartment
k1-2
k2-1
Vd2
Peripheral compartment
ke1
ke2


Dose
p.o. administration
GIT
ka
Vd1
Central compartment
k1-2
k2-1
Vd2
Peripheral compartment
ke


Dose
p.o. administration
GIT
k_a
Vd_1
Central compartment
k_{1-2}
k_{2-1}
Vd_2
Peripheral compartment
k_{e1}
k_{e2}

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3. Routes of drug administration and drug dosage forms

The knowledge of a drug's mode of action and its pharmacokinetics are not the only determinants of safe and efficacious use of drugs. The route of drug administration and in some cases also drug dosage form (pharmaceutical form) could be essential for the final effect of a drug. Suitable selection of administration route and the pharmaceutical form of the drug can significantly influence the onset of the drug's action or its duration of effect. Moreover, it can diminish the risk of unwanted effects or increase the patient's adherence to therapy. In some situations, different means of drug administration can result in different effects of the same drug. For example, osmotically active mannitol administered orally is a laxative agent, whereas the same drug administered intravenously has diuretic effect. Both effects are based on the same mode of action. Another example of medications where the effect is dependent on the administration route are iodine-containing drugs. These, when applied on skin or mucosa, have only a local antiseptic effect at the site of administration based on the oxidative properties of iodine. On the other hand, when administered orally the iodine is trapped in the thyroid and influences the release of thyroid hormones. This effect can be used both at lower doses in the treatment of goitre or at higher doses for its thyreostatic effect.

Drug dosage forms and routes of drug administration along with their characteristic benefits and risks will be described in the following text.

3.1 A brief overview of drug dosage forms

Most drugs are in their pure form crystalline substances and must be dissolved or „diluted" with other substances, usually lacking their own pharmacological activity, called vehicles. Such mixtures of active drugs and vehicles are supplemented with other substances (pharmaceutical additives) to improve the stability or organoleptic characteristics of mixtures. The final physical form of the mixture of active substances, vehicles and additives in which they are given to the patient is called the pharmaceutical form or drug dosage form.

Pharmaceutical forms can be classified with respect to various characteristics, for example with respect to their shape. We recognize shape specific forms, which possess their own shape regardless of the external packaging (tablet, suppository). By contrast, shape non-specific forms adopt the final shape of the external packing (ointments, solutions, gases). Another classification criterion closely related to the previous is whether the form is divided into single doses with accurate content of the active substance or not (dose divided vs dose undivided). In the latter case, the dose of a drug is measured by the patient before each administration. An example of the divided form which is usually shape specific is again tablet or suppository, while ointments or solutions can be given as examples of non-divided forms.

The most common type of pharmaceutical form classification, which can also be found in the Czech pharmacopoeia, is organized with respect to the physical character of the dosage form. There are four basic groups: solid, semi-solid, liquid, and gaseous forms.

3.1.1 Solid drug dosage forms

Solid drug dosage forms represent a variable group of pharmaceutical forms, for which it is common that they are all formed or at least their external coating is formed by solid particles.

3.1.1.1 Powders

Powders are one of the simplest solid pharmaceutical forms. They can be composed of crystals of the drug alone or in combination with additives, both pulverized to particles of specified size. Typical representatives of undivided powders, in which the patient measures the dose of a drug before administration, are dusting powders or powder of potassium manganate used for the preparation of antiseptic solutions. Some ready-made preparations can be in the form of divided powders with single doses divided into paper sacks. The advantage of this drug dosage form is the simplicity of its production.

3.1.1.2 Granules

Other example of a relatively simple pharmaceutical form is granules. Granules are intermediate products in the production of tablets, but can be used as a unique drug form. Granules are produced by moistening the aforementioned powders with liquid

additives, the mixture is then pushed through a granulating sieve and dried. Granules, as well as powders, can be undivided or divided and their advantage is again the simplicity of their production and speed of onset of the drug effect in comparison with other solid drug dosage forms. The fact, that granules must be dissolved prior their administration can be both advantageous and disadvantageous under specific circumstances.

3.1.1.3 Tablets

Tablets are shape-specific, divided drug dosage forms that are prepared from granules by pressing them into tablet moulds. There are several administration routes for tablets used in clinical practice. Nevertheless, oral use is the most common way of administering tablets to patients. This pharmaceutical form is highly variable in its shape and size. Basic types of tablets are non-coated and can be manufactured with a scoring line. This enables the patient to split the pill into halves or quarters with corresponding decrease in the amount of active substance. Non-coated tablets disintegrate quickly in the stomach after oral use with quick release of the active substance. The process of dissolution can be significantly influenced by tablet coating. External coating can control the speed of drug release or the site where the drug is released. Coating with materials soluble under specific pH is used to guide the tablet to a specific part of the GIT to release the drug (e.g. enterosolvent coating). The control of the speed of drug release influences the speed of drug absorption and its plasma levels, and enables us to prolong the dosing interval with preserved drug efficacy. Splitting of the tablet disrupts the coating and its function. Therefore, tablets coated with functional film are never equipped with the scoring line. The tablet can be coated with a pigmented film-forming coating. Such a coating can improve the stability of active substances and mechanical integrity of the tablet during its manufacturing. It has no effect on drug release and often it is used together with the specific shape of the tablet for marketing purposes (to differentiate it from other pills on the market). Less common types of tablets are effervescent, vaginal or orally disintegrating tablets.

In some cases, lozenges are incorrectly called tablets, too. Their appearance can be tablet-like with a sugar coating. The difference is that lozenges don’t have a core produced from granules by pressing. Their whole body is formed by sequential drying of sugar solutions.

3.1.1.4 Gelatine capsules

Gelatine capsules are another common pharmaceutical form. Contrary to tablets, capsules are not produced by pressing of granules. The gelatine outer coating is filled with powders or the drug dissolved in a lipophilic vehicle. Capsules are classified into “soft” and “hard” with respect to their production and characteristics. The “hard” capsule coating consists always of two pieces (body and cap) and are filled mostly with a mixture of powders or other solid particles with different sizes. “Soft” capsules have a one-piece body containing the drug dissolved in oil. The gelatine coating dissolves in the aqueous environment of the GIT and the drug is released. Similarly to tablets, the gelatine coating can be supplied with a functional coating controlling release of the drug. Even non-coated capsules cannot be divided, because of their structure. Gelatine capsules are probably the most common pharmaceutical form for dose-divided solid individually prepared preparations because of the simplicity of their manufacture and low cost. Together with tablets, capsules represent another of the commonest forms of orally taken solid ready-made preparations.

3.1.1.5 Suppositories and vaginal globules

Suppositories are shape and size suitable forms for rectal/vaginal delivery of drug and are prepared by pressing (ready-made) or pouring (individually prepared) suppository mixture into the moulds. Suppositories are classified into lipophilic and hydrophilic types with respect to the additives and vehicles used. Because of a small amount of liquid present in the rectum, lipophilic suppositories are preferred for hydrophilic drugs. The lipophilic vehicles melt at body temperature and release the drug, which can be dissolved in an aqueous environment and become ready for absorption. Vaginal globules have similar characteristics, but differ from suppositories namely in shape, size, and additives. Lactic acid is used in globules as an additive for the restoring of pH of the vaginal environment making it suitable for vaginal microflora.

3.1.1.6 Tea mixtures

Today, tea mixtures are less frequently encountered pharmaceutical forms for the preparation of herbal infusions (mixture has hot water poured over) or decoctions

(mixture is boiled for app. 10 minutes). Tea mixtures consist of dried herbs shredded to a specified size of particles.

3.1.1.7 Implants

Implants are sterile solid drug dosage forms inserted into body cavities or subcutaneously. Drug is released from the implant continuously and the speed of its release is again controlled by a functional coating (membrane) or by the matrix structure of the body of implant. Some implants are degradable and under the physiological conditions of the human body are continuously broken down while releasing the drug. The great advantage of implants is constant and continuous drug release. On the other hand, implantation of the device is invasive, and the implant cannot be easily removed if needed. Sometimes local immune reaction to the implant resulting in its encapsulation is reported. The most common use of implants is for continuous hormone delivery.

3.1.2 Semi-solid drug dosage forms

By their consistency, semi-solid preparations are in between solid and liquid formulations. They are applied to skin or mucosa and their advantage is that they easily attach to these body parts and prolong the time for drug absorption in comparison to dusting powders or liquids administered in the same way. Semi-solids are frequently dispersions (emulsions or suspensions), and therefore must be stable and homogenous at least for the time necessary for administration of the preparation. Additives to increase the stability of suspensions (preventing sedimentation of particles) or emulsions (emulsifiers, that prevent separation of oil and water phase) are used, because the active principle is usually found only in one of the phases of the dispersion system. Additives can also significantly influence penetration of the drug through the skin.

3.1.2.1 Ointments

Ointments are formed either by lipophilic or hydrophilic bases in which the drug is dispersed. Chronic dermatologic defects are the main indication for these formulations because it enables the molecules of drug to penetrate deeply into the lower layers of the skin. Typical lipophilic bases include paraffin, vaselines, waxes, or silicones whereas typical hydrophilic bases include macrogols or gel-forming

substances (gelatine, methylcellulose). Ointments are characteristic for their one phase basis, that can adopt a limited amount of immiscible liquid to form an emulsion ointment. Ointments are simple drug dosage forms suitable also for individually prepared preparations.

3.1.2.2 Creams

Creams are different to ointments because their base consists of two phases (oil and water) and they are therefore emulsions. Creams are produced from ointment bases by adding bigger amount of immiscible liquids and emulsifiers what makes them more liquid in comparison to ointments. With respect to the character of the emulsion, creams can be classified into hydrophilic creams (oil in water emulsion type) and lipophilic creams (water in oil emulsion type). Creams have a cooling effect on the skin thanks to the higher water content and its evaporation from skin surface. The clinical use of creams lies namely in subchronic and acute phases of skin diseases. Because of the emulsion character of creams and the possible instability of these preparations their individual preparation is rare.

3.1.2.3 Gels

Gels are formed by liquids and gel-forming substances, which, under suitable conditions, create a three-dimensional structure in which the molecules of liquid are trapped. Similarly to previous semi-solid forms, gels can also be classified with respect to the characteristics of the continuous (external) phase to hydro- and oleogels. Because the preparation of gels is time consuming and technologically demanding, similarly to creams, gels are only a marginal pharmaceutical form for individually prepared formulations.

3.1.2.4 Pastes

Pastes are prepared by the addition of solid substances into an ointment or cream base. With regard to the type of base which is used, hydropastes, oleopastes, hydrocream pastes, and oleocream pastes can be prepared. The content of solid particles represents at least 25 % of the total weight of the preparation. One of the most common pastes used in dermatology is indifferent zinc paste containing zinc oxide.

3.1.2.5 Medicated patches

In contrast to previous semi-solid formulations patches are shape specific. They can contain a drug with local effect at the site of administration or a drug which penetrates into the hypodermis and passes into the capillaries where it can be absorbed and evoke a systemic effect. The body of the patch always consists of an adhesive and cover layer. Nevertheless, other parts of the patch can be different. The simplest patches contain drug dissolved directly in the adhesive layer. This construction is not suitable for controlled drug release. Therefore, some patches are equipped with a drug reservoir which is separated from the adhesive layer by a membrane regulating the release of the medicine. Similarly to implants, another possibility of controlled-release is a matrix structure of the drug reservoir. Patches combine the advantages of implants (controlled drug release) without the need to implant the device or complicated discontinuation of medication. Patches are pharmaceutical forms used only for ready-made preparations.

3.1.3 Liquid drug dosage forms

True solutions, liquid emulsions and suspensions, or different kinds of drops are examples of liquid pharmaceutical forms. Administration routes for these preparations vary from topical use to intravenous injections. Therefore, their composition and requirements for their quality vary too.

3.1.3.1 Liquid preparations for topical administration

All types of liquids can be administered on skin. Nevertheless, the requirement for homogeneity of the pharmaceutical form at least for the time of drug administration persists. There is a warning note on the external package of suspensions and emulsions to shake the preparation well before use. Except for the common vehicles for hydro- and lipophilic liquids, formulations often contain additives as emulsifiers, stabilizers or antimicrobials. Separation of phases in case of emulsions and suspensions is not disqualifying if a homogenous mixture can be easily reconstituted by shaking the preparation. Liquid formulations administered onto the skin contain almost exclusively locally active drugs and their effect is primarily determined by the concentration of drug in the medicine. Examples of such preparations are salicylic spirit or Iodine tincture. There are also preparations with sophisticated compositions. Their single components increase the stability of the formulation and a great example

of this is the liquid dusting powder. Its advantage over the classical dusting powders is its better adhesion to skin and therefore longer duration of the effect without a need of frequent administration.

3.1.3.2 Liquid preparations for peroral use

Liquids for oral use are usually available as undivided preparations. On one hand, this brings a great variability in their dosing on the other hand it also increases the risk of improper or inaccurate dosing. Patients measure the dose of the medicine themselves, usually with measuring cups in ready-made preparations and with tea or tablespoons in individually prepared medicines. The risk of improper dosing is high, and those forms are suitable mainly for drugs with high therapeutic index. For drugs requiring more accurate dosing the form of oral drops is used. Liquids for oral use are suitable for paediatric and geriatric patients. Children and elders can have a problem with oral intake of solid preparations. With respect to the bitter taste of most of drugs, namely if they are not administered in small volumes like drops, these preparations contain sweeteners and other taste and smell corrigents. Suitability of adjuvants and vehicles should be considered when selecting formulations for specific patients (syrups for diabetics or ethanol solutions for children).

Exceptional cases of peroral liquids are syrups (aqueous solutions of saccharose), tinctures (spirituous herbal extracts), and aromatic waters (aqueous saturated solutions of essential oils). Their clinical use is minimal today.

Liquids administered into oral cavity for use without swallowing are also available. This group of preparations contain gargles, oral and sublingual sprays, or solutions for irrigation.

3.1.3.3 Drops

Except for solutions for oral use with accurate dosing, drops are also used for drug delivery into the eye, nose, or ear. These preparations differ in requirements for their quality and in the types of active components. Eye drops must fulfil the highest quality requirements. They contain drugs for the local treatment of the eye. Therefore, these formulations should not irritate the eye to prevent lacrimation and removal of the preparation from the eye bulb. Because of that, eye drops should be isotonic and isoacid, if possible. Eye drops are the only drops for which Czech

pharmacopoeia requires sterility. The expiration of eye drops is four weeks from the first use with respect to sterility, if the preparation is not equipped by antibacterial membrane filter. Typical drugs administered in the eye drops are antiglaucomatics, mydriatics, H_1 antihistamines, antibiotics, or decongestants.

Nasal drops should also cause minimal irritation after their administration to prevent drug removal from the nasal cavities. Therefore, the requirement for isotonicity remains. Contrary to eye drops, nasal drops don't have to be sterile and can also be used for drugs with systemic effect, for instance for hormones (oxytocin, calcitonin). Among drugs with local action in the nasal cavity decongestants or H_1 antihistamines are used.

Ear drops are used for the treatment of the external ear duct. Drugs in ear drops do not get into contact with mucosa and neither osmotic pressure nor pH have to be adjusted. Most common active components of ear drops are antiphlogistics, local anaesthetics, or cerumenolytics (earwax softeners).

3.1.3.4 Injections and infusions

Solutions for parenteral use in the form of intravascular injections or infusions must be always sterile and apyrogenic. If it is also possible and it is not the therapeutic goal to change the plasma pH or oncotic pressure, they should also be isoacid and isotonic. True hydrophilic solutions and special microemulsions (oil in water type) with specified sizes of particles can be administered intravascularly due to possible risk of thromboembolism. For other types of injections lipophilic solutions, emulsion and suspensions can be used. These types of formulations can release the drug slowly and can extend the duration of their effect.

3.1.4 Gaseous drug dosage forms

With respect to state, gaseous formulations are available in pressurized cans (gaseous form at room temperature) or in containers that enable the release of an aerodispersion containing the drug which is in a liquid or solid state at room temperature (inhalers, mechanic sprays). An essential difference, except for the phase of drug, is the size of the particles of drug. Macroscopic dispersions are used for topical drug administration for instance for air disinfection, whereas microdispersions (aerosols) with size of particles up to 5 μm are used for inhalations.

Pressurized cans are used for formulation of aerodispersions from substances that are dissolved or suspended in a solution of propellant gas. Propellant quickly evaporates after its release from can. Hydrofluoroalkanes, a substitute for ozone layer destroying chlorofluorocarbons (CFC), are used today.

3.1.4.1 Inhalants

Preparations for inhalation contain a drug in solid or liquid form. Inhalation is possible thanks to a special device, usually a part of the external container (dry powder inhaler, metered dose inhaler etc.). Another possibility is electronic devices producing aerosols (nebulisers). The bigger the particles of inhaled drug are, the more proximal the place of their sedimentation in the airways. This can be used to target the effect of drug into specific parts of the airways. Inhaled drugs include various types of antiasthmatics.

3.1.4.2 Medicated foams

Medicated foams are formed by huge volumes of gas trapped in a liquid where a drug is also dissolved. It is a pharmaceutical form used in dermatology. In contrast to semi-solid preparations the foam is readily spreadable, and its administration doesn't irritate the skin at the site of its administration. A liquid in the foam can have a cooling effect itself. This effect is present in dexpanthenol-containing foams used in skin burns after sunbathing.

3.2 Routes of drug administration

Selection of the appropriate route of drug administration is as important as selection of the drug itself for successful pharmacotherapy. The means of administration of a drug given to a patient can influence the character of its effect as well as the speed of onset of its effect, duration of its effect, side effects and therefore the patient's willingness to continue with the pharmacotherapy.

3.2.1 Classification of routes of administration

Three basic aspects can be used for this classification: disruption of biological integrity, site of drug administration, and type of evoked effect.

3.2.1.1 Disruption of biological integrity (invasiveness)

In some types of drug administration, the natural barriers protecting human body from the negative effects of environment have to be overcome. Therefore, invasive routes of drug administration are risky because they break those natural barriers and the benefit to risk ratio of such types of drug administration should always be evaluated. Disruption of skin by the puncture of injection needle or parenteral administration of contaminated preparations increases the risk of infections of various aetiology. There is also a risk of organ damage by injection needle in some types of injections (conductional anaesthesia) and in case of implantation an immune reaction to the implanted device/material can develop. Because of that, invasive routes of drug administration are namely used in acute situations to achieve faster onset of the effects in comparison to other means of drug administration or in severe conditions when there is no alternative way to reach the desired therapeutic effect (aminoglycosides in the treatment of severe systemic bacterial infections). Disadvantages of invasive routes of administration are, except the abovementioned, the inability for self-administration of drugs by patients. Invasive drug administrations are performed by health care professionals (apart from s.c. delivery of hormones or heparin) which brings additional costs to the therapy. The review of invasive and non-invasive routes of drug administration is presented in Table 1.

Table 1. *Review of invasive and non-invasive routes of administration.*

Non- invasive	Invasive
peroral	intravascular
sublingual	intraosseous
rectal	intramuscular
inhalational	subcutaneous
intranasal	intracerebral/cerebroventricular
transdermal	intrathecal
vaginal	implantation

3.2.1.2 Site of administration and type of evoked effect

Sometimes “local” and “systemic” types of drug administration are used within pharmacology. An example is topical administration of glucocorticoids on skin (local) and peroral use (systemic). These words better represent not the type of

administration but the type of drug effect that can be either localized to the site of administration (local) or present in the whole body after drug absorption and distribution to various organs and tissues (systemic). Type of effect depends more on the specific drug and drug dosage form than on the means of administration. In general, both types of effects can be evoked by any method of drug administration. Intravenously administered heparin acts locally inside of the vessels whereas intravenously given morphine will evoke systemic analgesia.

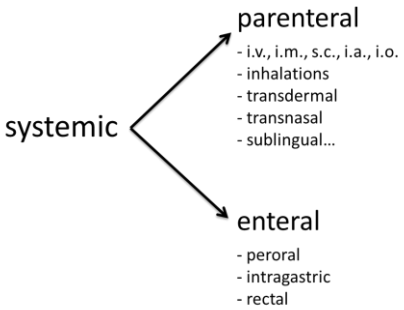
Drugs have to have limited possibilities of absorption from the site of administration to evoke a local effect only. In some cases, we actively prevent or slow down drug absorption from the site of its administration to prolong its effect or prevent its adverse effects (combination of local anaesthetics with vasoconstringents). An advantage of local use of drugs is the ability to target its effect only to the site where it is required together with minimization of possible adverse effects in other parts of the human body. An example of such drug use is the inhalational use of glucocorticoids with minimal risk of their systemic metabolic side effects. The final concentration of a drug at the site of administration and the time for which the drug is present at the site of administration are the major determinants of its effect.

Absorption, the process of penetration of a drug from the site of administration to systemic circulation, is followed by the distribution of a drug to its target structures in drugs with systemic effect. Theoretically, such a drug can influence any tissue or organ of human body, which can also evoke unwanted effects. The toxicity of a drug with systemic effects always depends on the pharmacodynamic and pharmacokinetic characteristics of each drug. The advantages of local administration are therefore applied also to the systemic use of drugs. A selection of drugs with the most selective mode of action or at least with limited/specific distribution in the body are used to minimize its effect on structures other than target ones. The latter drug characteristic can be supported with the use of 3rd generation drug dosage forms or with specific types of drug administration as can be shown in the case of intraarterial administration of chemotherapeutics into arteria hepatica in the treatment of liver metastases. The size of the effect and the time of its duration are determined by total dose together with the pharmacokinetics of the drug which determines the final concentration of agent at the site of its effect.

As was already mentioned, any type of drug administration can evoke a local effect of a drug. Nevertheless, not all ways of drug administration can evoke a systemic effect. The pharmacokinetic properties of each drug are essential, because in systemic effect a drug enters a body in a site different to the tissue or organ where the effect is required. Therefore, the drug has to pass from the site of administration to the target site and this process takes some time and includes factors that can significantly influence the portion of the drug that actually reaches the target site. It is necessary to realize that essential differences between administration routes leading to systemic effect are found in the pharmacokinetic processes of absorption and distribution. The size of effect and speed of its onset can therefore be different for the same drug administered via different routes.

Fundamental differences between routes of administration for systemic effect are the sites where the drug enters the body. With respect to that, routes of administration are classified as enteral and parenteral (see Scheme 1). Drug enters the organism via the gastrointestinal tract in enteral routes. This represents a natural and non-invasive way of drug administration, but on the other hand there are some disadvantages and risks that thwart this possibility for some types of drugs. Firstly, some kinds of drugs can be inactivated by gastric acid or degraded by digestive enzymes or gut microflora. Because of that, it is practically impossible to administer proteins e.g. insulin orally. Another problem is that drug absorbed from the GIT first enters through enterocytes to the portal system and arrives at the liver which is the main organ of drug metabolism. There is a high chance that a significant portion of a drug will be metabolized to inactive products prior to its arrival at the site of action. This phenomenon is called the first-pass effect and is further described in Chapter 2. Liver metabolism of an oral drug after its absorption can be so intensive, that it is practically impossible to use this route of administration in some cases. Delayed onset of effect should be also considered in orally given drugs in comparison to, for instance, i.v. injections, because the drug has to pass through the GIT to a part suitable for its absorption, then it has to pass the liver and accumulate at the site of action in a level sufficient to evoke the effect.

Scheme 1. *Classification of systemic routes of administration with respect to the site of administration.*



3.2.2 Routes of administration to evoke only a local effect of a drug

3.2.2.1 Intraurethral and intravesical administration

Intraurethral drug use is not very common. Sometimes it is used prior the catheterization of urinary bladder, when a local anaesthetic is applied to decrease the pain during the catheter insertion. Intravesical administration is used for both diagnostic purposes in the case of florescent cystoscopy and also to decrease the systemic toxicity of drugs. An example of this would be in the case of chemotherapeutic agent doxorubicin that is used in the therapy of urinary bladder tumours or the BCG vaccine that is administered intravesicaly in the prevention of the same tumours.

3.2.2.2 Intracavernous administration

Erectile dysfunction is the main indication for drug injection into the corpora cavernosa. To be more specific, the synthetic analogue of prostaglandin E1 alprostadil is used. With the same structure as the endogenous molecule, it is metabolized at the site of administration with minimal absorption to systemic circulation.

3.2.2.3 Dental and gingival administration

These routes of administration are characteristic for dentistry. Toothpastes applied directly to teeth with a high content of fluorides are used to prevent or treat tooth decay. A mixture of paraformaldehyde with lidocaine for devitalization of tooth pulp or

framycetin for antiseptic treatment of root canals prior to their filling are other examples of dentally administered drugs. Antiseptic and local anaesthetic solutions or semi-solid preparations are administered onto gingiva in cases of inflammatory disease like gingivitis or parodonditis.

3.2.2.4 Endotracheopulmonal administration

The only indication in which endotracheopulmonal drug administration is used is respiratory distress syndrome in preterm newborns when a suspension of phospholipids is given to substitute missing surfactant in the airways.

3.2.2.5 Intraaural administration

Various formulations can be administered into the external ear duct including drops, ointments and medicated tampons. The most common pharmacotherapeutic groups are antiphlogistics, antibiotics, and anaesthetics. Oil and water solutions for the softening and removal of ear wax are also available.

3.2.2.6 Intraamniotic administration

Intraamniotic injections are highly risky during physiological pregnancy. The only situation in which drug is delivered by this route is for the induction of abortion with dinoprostone (prostaglandin E2) in conditions of pathological development of the foetus.

3.2.2.7 Conjunctival administration

Administration of drugs to the conjunctiva is the most common method of drug delivery in ophthalmology. Nevertheless, only a portion of drugs administered via this route influence the conjunctiva itself, most drugs also influence other parts of the eye like *m. ciliaris* and *m. dilatator pupilae* or regulate the production of intraocular fluid. Conjunctival drug administration delivers the drug to the whole surface of the eye bulb in general. There is a multilayer barrier protecting the epithelium of cornea on the surface of eye ball. Individual layers of this barrier each have different characters to the lipid outer layer, with the aqueous phase representing the thickest part to the mucin tightly attached to corneal epithelium. Drugs like mydriatics, miotics or cycloplegics must have amphiphilic structure to penetrate through this complicated structure to the sites of their action. The eye bulb is permanently hydrated and washed with produced tears. Therefore, one of the essential requirements of

ophthalmologics is to be non-irritant. That can be achieved with isotonic and isoacidic preparations. In the opposite case, excessive lacrimation leads to fast drug removal and discontinuation or shortening of the drug's effect. Ointments can be used to prolong the time for which drugs stay on the eye surface. The ointment base slowly melts or dissolves which can cause blurred vision. Eye ointments are therefore suitable for administration before going to bed, while eye drops with the same active substance can be used during daytime. It should be stressed that eye drops are often administered improperly. The correct way to use these formulations is the following: 1. Wash your hands. 2. Heat the bottle with eye drops to body temperature to decrease its irritant effect. A few minutes in the clenched palm or in the pocket of clothes worn should be enough. 3. Give one drop to the eye, close it and gently press the tear duct for approximately 1 minute. Compression of the tear duct is important namely in preparations containing drugs capable of absorption via nasal mucosa. Because of high concentrations of drugs in ophthalmologics, even a small volume of preparation that gets to the nasal cavity via the tear duct can lead to significant systemic adverse effects. It is not rational to administer more than one drop to an eye because the volume of preparation in one drop is even higher than the volume that can be spread over the eye bulb. Typical drugs administered to eye are previously mentioned miotics and mydriatics, or antiglaucomatics, antihistamines, decongestants, antiinfectives, H_1 antihistamines, or artificial tears.

3.2.2.8 Intraocular (intravitreal) administration

Intraocular administration is an invasive type of drug administration when a solution of drug or implant is injected or inserted directly to the chamber of the eyeball. Such a measure is used to deliver monoclonal antibodies in the therapy of macular degeneration. These antibodies target the VEGF that plays an important role in the pathophysiology of this disease. This is also the only route of administration with the possibility of achieving a local effect of drug on the retina. Mydriatics and antiphlogistics are also injected intraocularly to induce post-operative mydriasis and to decrease pain after eye lens transplantation.

3.2.2.9 Intrathecal administration

Drug solutions infused or injected into the spinal cavity represent the intrathecal drug delivery route. This route of administration presents an opportunity for drugs

incapable of passing the hematoencephalic barrier to cross this structure. Except for drugs that do not cross the hematoencephalic barrier, this administration route can also be used to minimize the systemic side effects of drugs that target the spine and brain. The spinal cavity is usually accessed in the lumbal area (L3/L4 or L4/L5). It is appropriate to aspire the same volume of liquor as volume of administered drug prior to its intrathecal injection to maintain intracerebral pressure. Different solutions with respect to their oncotic pressure can be delivered. Apart from isotonic solutions, hypo- and hypertonic solutions can be also given. Suitable positioning of the patient then moves the solution to the specified part of the spine and also enables us to influence segments of the spine other than lumbal. This measure is used in spinal anesthesia. In some cases, namely when there is a need for repeated intrathecal administration of a drug, a subcutaneously implanted pump with a catheter inserted into the spinal canal can be used. This type of device is used for instance in chemotherapeutics or the central muscle relaxant baclofen.

3.2.2.10 Intraarticular administration

Drugs injected directly into the joints are used in degenerative disorders such as rheumatoid arthritis. Glucocorticoids with strong antiphlogistic effects, radionuclides or hyaluronic acid can be delivered in this way. This route of administration is also suitable for autologous transplantation of expanded chondrocytes. Drugs can be injected into big joints (shoulder, knee), but also to smaller ones (wrist, temporomandibular joint) if needed. Administration itself often requires appropriate positioning of the patient to facilitate the insertion of the injection needle into the joint cavity.

3.2.2.11 Oral administration

Oral administration in this section describes the administration of a drug into the oral cavity to obtain a local effect. Different formulations are used for this method of administration including solutions for gargling and irrigation, lozenges, mucoadhesive tablets, or oral sprays. It is suitable to use drugs that are not absorbable from the oral cavity and are safe enough even when accidentally swallowed. Typical groups of drugs fulfilling these requirements are local anaesthetics, antiseptics, and some anti-infectives.

3.2.3 Administration routes used for both local and systemic effect

3.2.3.1 Vaginal administration

The vaginal environment is characteristic in its microflora and mucosa, which can be used for the systemic delivery of drugs. Anti-infectives in the form of vaginal globules, suppositories or fluids for irrigation are the most common types of preparations for local use in the therapy of microflora disbalance. Uterotonic prostaglandins are used in local preparations in obstetrics. They are administered in the form of vaginal tablets to the external orifice with specialized applicators. Prostaglandins promote contractions of myometrium and enhance cervical ripening.

Systemic effects of vaginally delivered drugs are achieved with combined hormonal contraceptives. These are administered in the form of vaginal rings with controlled release of drug usually for 21 days. It is a type of continuous drug release and its advantage over classical oral contraceptives is a lower dose of oestrogen thanks to elimination of the first pass effect and increased adherence to therapy thanks to a simpler dosing schedule. On the other hand, some adverse effects including local irritation can develop.

A similar principle of continuous drug release is used in intrauterine devices. Monocomponent gestogen preparations containing levonorgestrel are used as hormonal contraception. Intrauterine devices are introduced with specialized applicators supplied with the preparations. The drug is released for a long time (3-5 years). Its disadvantage is complicated discontinuation of therapy and requirement of device removal after the end of its lifetime.

3.2.3.2 Topical administration on skin and transdermal drug delivery

Local administration of drugs to skin is used mainly in dermatology. The character of drugs administered in various semi-solid or liquid formulations is wide and contains drugs from antiseptics, anti-infectives, antiphlogistics, or drugs typical for dermatology like emollients, granulating and epithelizing agents. Adjuvants play an important role in topically administered drugs on skin where they can enhance the penetration of a drug to deeper layers of skin or can have therapeutic effects themselves (substitution of epidermal lipids, mechanical protection). Local irritation of the administration site is the most common complication of drugs administered

topically. Nevertheless, topical drugs administered chronically or on large areas of the body surface (glucocorticoids, boric acid) can evoke even systemic adverse effects.

Transdermal drug administration is a route of non-invasive drug delivery. The molecules of a drug must have suitable characteristics (small and lipophilic) to be able to penetrate the skin into blood capillaries and then be absorbed to evoke a systemic effect. Drugs can be administered continuously transdermally, patients adhere to this type of therapy well, and the drug can be simply discontinued. First pass effect is also eliminated in contrast to oral drug administration. Transdermal therapeutic systems (TTS) with controlled release of the drug are mostly represented by transdermal patches. A disadvantage of this method of drug administration is the slow onset of drug action and the higher cost of this type of pharmacotherapy.

Nicotine for substitution therapy in the smoking cessation, combined oral contraceptives, or opioid analgesics are available in TTS. Less often liquids, gels, or creams with a dose dispenser for accurate dose measurement are used for transdermal delivery. These are not used for continuous, but for intermittent drug administration and they are used for example, in hormonal substitution therapy with estrogens.

3.2.3.3 Intranasal administration

Nasal formulations with local effect mostly contain (similarly to ophthalmologics), decongestants, H_1 antihistamines, various antiphlogistics or anti-infectives. These are administered in the same pharmaceutical forms as intranasal drugs with systemic effects like nasal sprays, drops or ointments. Opioids (fentanyl, pentazocine), antivirals (acyclovir in liposomes), or hormones (oxytocin, ADH) are administered intranasally to produce a systemic effect. This type of drug application is non-invasive, with a fast onset of drug effect and with elimination of first pass effect.

3.2.3.4 Inhalational administration

Sizes of particles of the inhaled drugs are important in this route of application. The bigger the size of the particles the shorter the journey of the drug in the airways and the more proximal the site of its deposition. On the other hand, molecular dispersions can reach the alveoli and can penetrate into the bloodstream. Local drug

administration in the airway is used mainly in diseases of the respiratory system such as bronchial asthma. Inhalations themselves do not guarantee a local effect, therefore manifestations of systemic adverse effects should be expected after huge doses of drugs such as glucocorticoids or β_2 sympathomimetics. Inhalations are also the only possible method of administration of gaseous drugs under normal conditions. They are used namely in anaesthesiology for the administration of inhalational anaesthetics. A great advantage of these inhalations is easy regulation of the level of anaesthesia and its fast discontinuation in case of need. On the other hand, this administration route requires specific instrumentation in the case of volatile liquids (sevoflurane, isoflurane) that ensures accurate concentration of the drug in inhaled air. A gas container equipped with a reduction valve is necessary for the administration of gaseous anaesthetics such as nitrous oxide or xenon.

There is a possibility to use insulin in inhalations for the treatment of diabetes in outpatients. Only short-acting insulins for the control of postprandial glycaemia are available in this type of formulation today.

Correct technique of inhalation is essential to obtain the required effect of a drug. Problems with this route of administration can be seen in the elderly and children. It is necessary to carefully synchronize the release of drug with its inhalation, what can be complicated in these subcategories of the population. Various additional devices for inhalations like spacers or containers that are activated (releasing a measured dose of drug) by suction during aspiration can help in these patients. The most common complications of inhalations include: local irritation with cough and risk of bronchial spasms. Cold vapours of propellant released from pressurized containers can also increase the risk of bronchial spasms. Advantages of inhalations are similar to other parenteral types of drug delivery and include elimination of the first pass effect. Fast onset of the effect can be also of importance for instance in the case of quick-relief antiasthmatics.

3.2.3.5 Transbuccal, sublingual administration

Similarly to nasal mucosa, the oral cavity is richly perfused and is suitable for absorption of drugs with small lipophilic molecules. Fast onset of effect suitable for acute situations is obtained and first pass metabolism is eliminated after transbuccal or sublingual drug delivery. Drugs are applied in the form of sprays, mucoadhesive or

dispersible tablets. Nitro-glycerine for the treatment of myocardial ischemic pain, analgesic fentanyl for breakthrough pain in oncology, hypnotics (zolpidem), or antiemetics (ondansetron) are absorbed from the oral cavity. Sublingual administration is also used for the administration of sublingual tablets. These types of administration evoke only systemic effects. For a local effect of a drug in the oral cavity, oral formulations as described above can be used.

3.2.3.6 Rectal administration

Rectal drug administration can be a suitable alternative if oral drug administration is impossible (nausea, unconsciousness, or children). Only a part of the drug absorbed from the rectum enters portal circulation as most of the perfusing blood goes directly to systemic circulation via the vena cava inferior. The first pass effect decreases the dose by approximately 30 % in contrast to oral delivery. Rectally administered drugs with systemic effect are, for instance, antiemetics, antimigrenics, or diazepam. The speed of onset of effect after rectal administration is determined by pharmaceutical form. The absorption is fast from aqueous and spirituous solutions whereas delayed absorption caused by adjuvants can be seen in some types of suppositories. Examples of drugs administered for their local effect in the rectum are laxatives (glycerol), antiphlogistics (mesalazine), or local anaesthetics.

3.2.3.7 Peroral (oral) administration

Administration by mouth represents a natural method for the intake of various substances and it should be preferred every time it is possible. A variety of drugs and pharmaceutical forms for oral intake give us many possibilities for the selection of suitable pharmacotherapeutic strategies. On the other hand, the oral route of administration is highly variable with respect to interindividual differences in the conditions and functions of the gastrointestinal tract (GIT). That can be a reason for dose optimization, change in the drug dosage form or in exceptional cases for the change of the administration route. The first pass effect should be also stressed as an important factor influencing the bioavailability of orally administered drugs.

Some drugs, like antacids, laxatives, or antibiotics (rifaximin), are not absorbed after oral intake and evoke only local effects within the GIT. An advantage of these drugs is minimal adverse effects. Nevertheless, possible drug-drug interactions with co-administered drugs should always be evaluated. A typical example is concomitant

use of adsorbents in the treatment of diarrhoea (diosmectite or activated charcoal) together with other drugs.

Absorption of drugs from the GIT is not only determined by physico-chemical properties of the drug itself, but can also be significantly influenced by its localization within the GIT. Drugs can be ionized in specific parts of the GIT with respect to changes of pH in various segments of this system. Ionization also determines a drug's lipophilicity and therefore influences the process of absorption. Weak acids are absorbed from the stomach, if released readily from the formulation after use. Contrary, weak bases have to reach the duodenum and jejunum with a more alkaline pH to be absorbed. Therefore, a longer time delay until effect can be seen in drugs with a weak base character in comparison to acids.

An essential factor influencing absorption of a drug from the GIT is also diet and intestinal content. Decrease of intestinal passage should be expected after a drug is co-administered with food, whereas an increase is probable when a drug is administered on an empty stomach. This effect again influences the time delay which describes the delay from drug administration to the start of its absorption. Diet can even interfere with the absorption of some drugs. Tetracyclines and calcium ions, common in milk products or mineral waters, can form un-absorbable complexes. In these cases, patients should avoid specific types or food, or should be instructed to use the drug on an empty stomach, which means at least 30 minutes prior to or 120 minutes after the meal. Generally, it is better to use drugs together with a meal if the interaction of drug and food is not known, because of lower GIT irritation.

Drug dosage form is another substantial factor determining drug absorption from GIT. Two different groups of pharmaceutical forms can be described with respect to their influence on the time course of a drug's plasma level. The first group are "classical" forms that do not influence the release of the drug from the formulation. The drug is released at once and the process of absorption depends only on the properties of the drug itself (Fig. 17a). Examples of these forms are solutions, suspensions, non-coated capsules and tablets. The second type of these drug dosage forms are preparations with controlled release of the drug. Various reasons, why controlled release of active substance is advantageous, as well as various mechanisms by which drug release can be controlled, exist. One of the possibilities is the release of drug in pulses (Fig. 17b), where drug is released either in one or more pulses

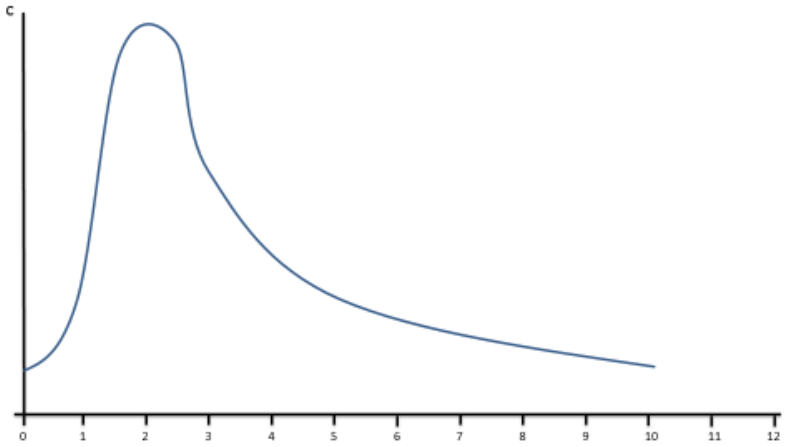
separated by a defined time interval. Contrary to “classical” forms, a latency from the administration of the preparation to the release of the first pulse is precisely defined. Antiasthmatics with delayed release can prevent nocturnal attacks that are most common in the early morning. The drug is used in the evening and is subsequently released in the required period. This principle allows us to decrease the total amount of the drug administered and therefore the risks of adverse effects. A similar principle can be used to prevent development of tachyphylaxis (nitrates).

Another type of drug dosage form with controlled release of active substance is drugs with prolonged, extended, or slow release. Contrary to the previous types of preparations, the drug is not released at once. Gradual release of the drug for a longer time ensures prolonged duration of its effect and dosing interval can be also prolonged. Finally, the patient’s adherence and compliance to the therapy increases. Mechanisms that can control extended release of a drug from the formulation involve semi-permeable membranes, matrix systems, osmotic, or microparticle systems. The time course of drug plasma levels in extended release preparations show less fluctuations than “classical” formulations and are more similar to preparations with continuous drug release (Fig. 17c). Diuretics in the treatment of hypertension (indapamide) or calcium channel blockers (verapamil) are examples of drugs used in these types of preparations.

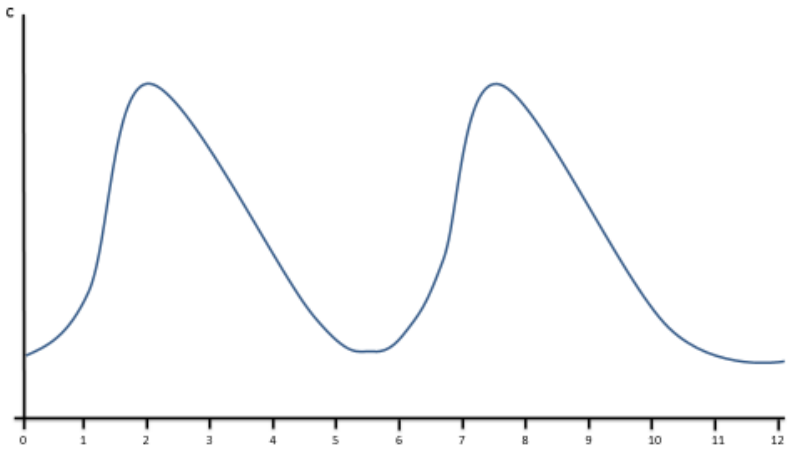
Drug dosage forms combining the abovementioned systems of drug release exist. A part of a drug can be released immediately after administration to insure fast onset of effect, whereas the rest of the drug is released slowly to prolong its efficacy (Fig. 17d).

Figure 17. *Time course of plasma levels of drug in peroral drug dosage forms with a) classical; b) pulse; c) prolonged; d) combined drug release*

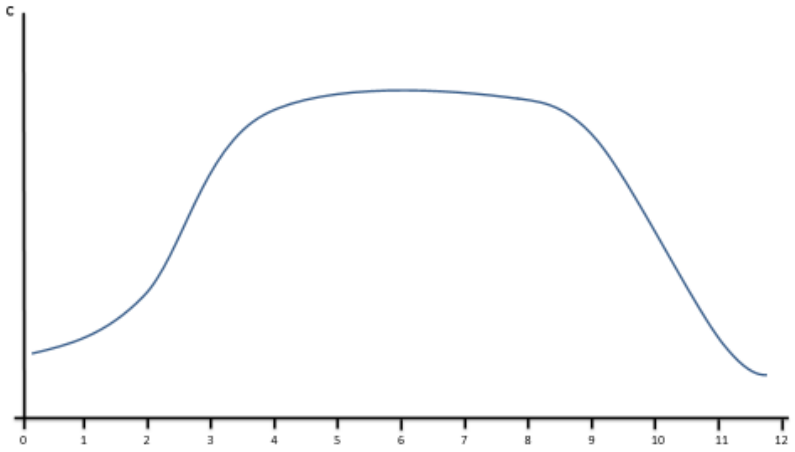
a)



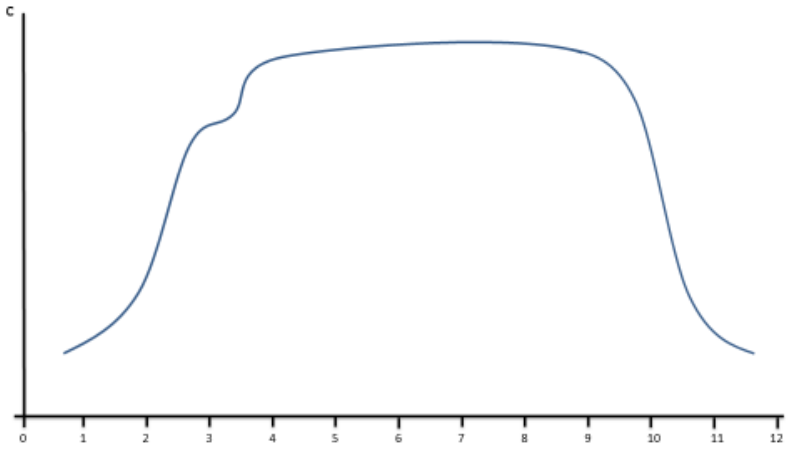
b)



c)



d)



3.2.3.8 Injectional types of drug administration

Individual types of injections differ namely in the speed of drug absorption, in the volume of preparation that can be administered and in the character of the liquid that can be used. With respect to invasivity of administration, injections are administered mostly by healthcare professionals and are used namely for inpatients. Exceptions are subcutaneous injections with minimal risk of improper drug administration and

related complications. They are used for the administration of insulins or low-molecular weight heparins.

True aqueous solutions are used for intravascular administration because of the risk of thromboembolism. In case of systemic toxicity of local anaesthetics microemulsions can also be used. Drugs injected directly to the bloodstream have an almost immediate onset of effect because of lack of absorption and fast distribution of active substance to its target sites. Superficial veins that are visible to the naked eye are easily accessible for injections in comparison to arteries hidden deeper in the tissues. Therefore, intravenous (i.v.) is preferred to intraarterial (i.a.) drug administration. Venepunction into the forearm of the non-dominant hand is the most common site of intravenous injections. In newborns, venepunction of the head veins is an alternative. Surgical preparation of a vein (*vena saphena magna*, *vena basilica*, or *vena mediana cubiti*) is an option in case venepunction is not possible. Intraarterial drug administration is rare and it is used in case we need to aim the effect of a drug towards an organ perfused by distinct artery. An example of such a measure can be intraarterial application of chemotherapeutics into *arteria hepatica* in the treatment of hepatocellular carcinoma or liver metastases. There are almost no limitations of administered volume in intravascular drug administration. Nevertheless, intravenous infusions should be used in case of big volumes or in case of continuous drug administration. Peripheral or central catheters are used in case of repeated intravascular administration to prevent traumatisation of the patient by repeated venepunctions. A subcutaneous venous port with catheterisation of jugular vein can be also used.

Typical drugs for intravenous administration are antibiotics (aminoglycosides, glycopeptides), chemotherapeutics (methotrexate, anthracyclines), or general anaesthetics (propofol). Examples of intravenous drugs with minimal distribution and practically only local effects within the bloodstream are unfractioned heparin or various blood derivates.

Disadvantages of intravascular drug administration are the risk of infection and in some cases difficulty in to finding suitable veins for venepunction (children, elderly, shock or polytrauma). In these cases, intraosseous (i.o.) drug delivery can be used as an alternative to intravenous administration in prehospital emergency care. Drug is delivered directly to the marrow of long bones (*tibia, humerus, femur, sternum*).

Intraosseous needles or catheters are firstly introduced with manual, semi-automatic, or automatic devices. The site of implantation can be pre-treated with local anaesthetic to prevent pain. The introduction of a needle is described as pain free contrary to the aspiration of marrow for the verification of correct position of needle.

Drugs that are insoluble in aqueous vehicles can be administered in oily injections (progesterone), or emulsions intramuscularly (i.m.). Similarly drugs soluble in water can be administered in suspensions to prolong their release, absorption, and effect (procaine penicillin). Intramuscular injections are administered mostly to *m. gluteus medius* or *maximus*, less often to *m. quadriceps femoris*. Risk of vein or nerve impairment is minimal at these sites. Nevertheless, aspiration to prevent venepunction prior to the drug being administered is required. The volume of a preparation injected intramuscularly is determined by the injection site and patient's status and it should not exceed 5 ml. Multiple injections to different target sites should be used in case bigger volumes have to be injected. The effect of intramuscularly injected drugs occurs usually 10-20 minutes after the injection. Venepunction, nerve injury, development of abscess, or infection at the injection site are the most common complications. Injection sites should vary in case of repeated i.m. injections.

Injections of true solutions, emulsions, or suspensions are administered subcutaneously (s.c.). A 25-35 mm needle is usually inserted into the skin fold under a 90°or 45° angle. The volume of injected drug is usually around 1 ml (2 ml is the maximum for one injection site). This type of injection is mostly used for chronic administration of drugs that cannot be delivered with non-invasive methods (proteins). Subcutaneous injections are safe and can be safely administered by outpatients themselves, in comparison to the previous types of injections. Subcutaneous implants or catheters (insulin pumps) can be used for continuous drug delivery. The most suitable site for s.c. injections is the later aspect of the upper arm and abdomen in the umbilical region. Alternatively, drugs can be subcutaneously injected in the area of the thighs. Absorption of a drug after s.c. delivery is influenced by physical activity. With respect to that, the absorption is the fastest and with the lowest variability after injection to the abdominal area. Similarly to i.m. injections, aspiration prior to drug administration is required to exclude accidental i.v. injection.

Intradermal injections are only of diagnostic importance. Solutions of allergens administered in tenths of millilitres are used in allergology to test sensitivity in the prick test.

3.3 Factors determining selection of administration routes

Selection of suitable administration routes can play an important role in the pharmacotherapy itself. Suitable route of drug delivery can lead not only to the desired therapeutic effect, but also to decreased risk of adverse effects or to simplification of the dosing schedule. These effects also increase the patient's adherence to prescribed therapy. Not all drugs are suitable to be delivered by all administration routes. Essential factors that determine the possibilities of drug administration involve its chemical-physical properties. There can be a limited number of pharmaceutical forms suitable for a drug. For instance, it is impossible to prepare tablet or ointment from a drug that is gaseous under room temperature. Each drug dosage form is also suitable for the specific route of administration and the effect of a drug can be totally different when the preparation is used incorrectly. For instance, it is hard to imagine that a TTS patch with hormonal contraceptives would be taken orally. It would be almost impossible to swallow the device and the amount of drug released and absorbed from the device would hardly be predictable. Another problem is that even if there is a possibility to prepare the required drug dosage form with the drug, the drug must also be suitable for the required route of administration. It is purposeless to deliver peptides orally or in TTS, although it is not a problem to prepare tablets, capsules, or patches with peptides. More about the influence of physico-chemical properties on the drug's pharmacokinetics can be found in Chapter 2.

Another factor significantly influencing the administration route is the drug indication. Local drug administration should be always preferred to systemic use to prevent possible toxicity. Therefore, the administration route of glucocorticoids will differ in the treatment of asthma (inhalational route preferred) and in the management of autoimmune diseases like *sclerosis multiplex*, when glucocorticoids are administered systemically. An important criterion for the selection of administration routes is the severity of the patient's condition. Administration with the fastest onset of drug effect

and a minimal delay in drug absorption (ideally i.v. administration) after application should be selected in acute or emergency situations. Intravenous administration doesn’t always guarantee fast onset of the effect. In some cases, the drug's mode of action delays its effect (warfarin) or the body must first deplete physiologic stores of the substances involved in pathophysiologic conditions. The latter case applies in thyrostatics (propylthiouracyl, metimazol). These drugs interfere with the synthesis of thyroid hormones, which are stored in the human body in amounts sufficient to cover its needs for approximately one month. It is always necessary to evaluate benefits and risks of individual administration routes. Based on this principle, it is logical to use “more risky” and namely invasive routes of administration that can harm the patient in serious and life-threatening situations.

The administration route can be significantly influenced by a patient’s comorbidities. Inflammation at the administration site plays an important role in locally acting drugs. The speed or extent of absorption can be modified due to a change in pH of the inflamed area. Orally administered drugs can be rapidly removed in cases of vomiting or diarrhoea. Another complication of peroral therapy is suppression of the first pass effect and increase of drug bioavailability due to the hepatopathy. Comorbidities with an impact on drug absorption include impaired peripheral perfusion in transdermal administration.

Co-administration of drugs can cause formation of un-absorbable complexes (activated charcoal + with other orally administered drugs). A simple solution to prevent these interactions is possible. Sufficient delay between administrations of individual drugs is advisable. Besides that, another mechanism of drug-drug interactions is described. One of the drugs may change the function of an organ important for the absorption of the other drugs. Simple time separation of these drugs would not be effective. An example of such an interaction is the use of laxatives or prokinetics together with other oral formulations or the use of vasoconstringents that decrease or slow down the absorption from TTS.

3.4 New trends in drug administration

Recent medicine has probably discovered all possibilities for drug delivery to the human body. Most of the innovations in the area of drug delivery are therefore targeted at drug dosage forms. Formulations of second (with controlled release) and third (with controlled distribution) generations are the results of such innovations. The goal of these inventions is to increase the safety and efficacy of administered drugs. Decreased fluctuations of a drug's plasma levels during repeated administration minimizes the risk of inefficacy or toxicity of the drug in the part of the dosing interval when the drug gets out of the therapeutic window. Targeted biodistribution with specific drug "carriers" enables us to target the effect of a drug towards specific tissues and again makes the pharmacotherapy safer. Limited toxicity and simplification of dosing regimens increases the adherence of the patient to prescribed pharmacotherapy. In some cases, the modification lies in drug release. Some of the formulations release the medicine "on demand" (triptans in treatment of migraine or opioids in the treatment of breakthrough pain). Last but not least, some modifications are aimed at the possibilities for non-invasive routes of administration and also how they can be extended for drugs that are available only as injections today.

The transdermal route of administration is an interesting prospect for innovative formulations. There are transdermal patches, that release the drug when needed, available for clinical use today. Those are suitable for the treatment of breakthrough pain in oncology. A patch is equipped with control mechanisms that allow the release of a specified amount of a drug in a time period to prevent the risk of drug overdosing. Another interesting possibility is to use transdermal administration of drugs that do not penetrate through skin under physiologic circumstances. It is necessary to disrupt the epidermis and create pores with microneedles or other suitable devices. The drug then diffuses through these micropores to the dermis with blood capillaries and is absorbed. An advantage of this "semi-invasive" method is the possibility to deliver drugs with a high molecular weight. It seems that this type of drug application could be an alternative to some types of injections (e.g. vaccination).

An interesting alternative to injectional administration is represented by intestinal patches that could be used to deliver macromolecules including peptides. Micropatches are millimetres or micrometres in size and are delivered in gelatine

capsules. The micropatch consists of a protective layer that protects the drug from destruction by intestinal juices, enzymes, and an adhesive layer that attaches it to the mucosa of the GIT and through which the drug is released.

Some research in this field is also concerned with the prospects of various particle and nanoparticle systems. They can be used to decrease the toxicity or enable targeted biodistribution of drugs. Biocompatible liposomes with a membrane formed from a phospholipid bilayer can be used as a carrier for both polar and nonpolar drugs. Liposomes are highly variable with respect to their size and membrane characteristics. Their surface can be pegylated – substituted with polyethylenglycol. This modification increases their hydrophilicity and the duration of their circulation in plasma. Nanoparticles are also highly variable with respect to material, size, and surface modifications. More about the problems of innovative drug dosage forms can be found elsewhere (Current Opinion in Pharmacology, 36, 2017).

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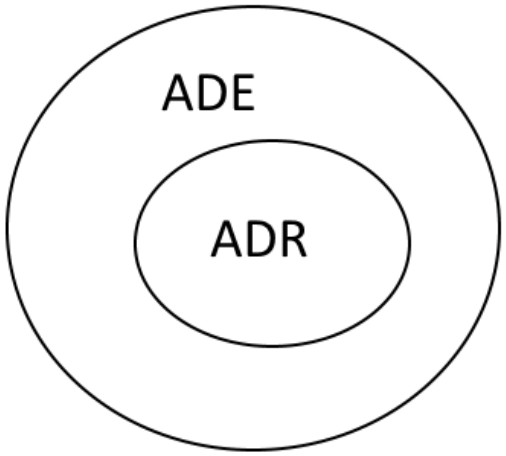
4. Adverse drug reactions

The adverse drug reaction (ADR) is an unintended adverse reaction to the administration of any dose of the drug. In developed countries, it is estimated that adverse drug reactions are the cause of up to 6-8 % of hospitalizations, and ADRs even occur in 10-20 % of hospitalized patients. According to some resources, adverse drug reactions are considered the 4th leading cause of death. Approximately 0.32% of hospitalized patients die due to an adverse effect in hospitals. Resolving the consequences of adverse drug reactions also significantly increases the overall cost of treatment. These costs could be utilized in more meaningful way, if at least some of these adverse reactions could be avoided by rational pharmacotherapy. Attention should be drawn to distinguishing Adverse Drug Event (ADE) from Adverse Drug Reaction. The WHO and EMA distinguishes ADE as any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In contrast, ADR describes in response to a drug that is harmful and unintentional and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of diseases or for the modification of physiological functions and a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Schematically, the relationship between ADE and ADR is shown in Figure 18.

Figure 18. *The relationship between ADE and ADR*



The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

Adverse drug reactions are closely monitored by national drug authorities. From the perspective of regulatory authorities, adverse reactions can be categorized according to their frequency of occurrence as defined by the SmPC. The most common side effects are reported as very common (with a frequency of ≥ 10%), followed by common (1% - 10%), uncommon (0.1% - 1%) rare (0.01% - 0 1%) or very rare (<0.01%). The SPC summarizes the ADRs into categories according to their occurrence on different organ systems (e.g. cardiovascular diseases, psychiatric disorders, eye disorders, etc.). **Pharmacovigilance** is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU. Within the framework of individual national or supranational regulatory authorities (SÚKL, EMA), specialized committees and departments are established to ensure safety and to monitor adverse effects. The Pharmacovigilance Department thus operates within the State Institute for Drug Control (SÚKL, Czech), and the European Medicines Agency has established a PRAC (Pharmacovigilance Risk Assessment Committee).

4.1 Classification of adverse reactions by nature and mechanism of origin

Depending on the nature and mechanism of the adverse reaction, adverse reactions can be divided into several groups:

4.1.1 Type A adverse reactions

Type A (augmented) side effects result from the enhanced 'normal' effects of drugs that are seen at the usual therapeutic doses. These side effects are dose-dependent and predictable. By appropriate use of drugs, in particular by an appropriately selected indication and dose, these adverse reactions are usually avoided. Examples

include opioid-induced respiratory depression, warfarin-induced bleeding, hypoglycaemia following insulin and sulphonylureas, or anticholinergic syndrome following tricyclic antidepressants or antipsychotics.

4.1.2 Type B adverse reactions

Type B ADR (B-bizarre) is an unexpected response to drug. It is not originated from the mechanism of action and is rare; these ADRs may therefore only appear for the first time after the medicinal product has been placed on the market. Type B NRCs include allergic reactions or idiosyncrasia - an abnormal drug response due to genetic variation in a particular patient (e.g. receptor, enzyme, transporter polymorphism, resulting in a qualitatively completely different response to drug administration).

An allergic reaction is an abnormal immune system response mediated by antibodies or T lymphocytes occurring after previous contact with an allergic substance (allergen). Thus, unlike idiosyncrasia, they appear at full intensity only after repeated drug administration.

4.1.3 Type C adverse reactions

Type C (continuing, continous, chronic) is a consequence of long-term administration of the substance and may have an additive character (cumulative effect, even at low therapeutic doses).

Examples of long-term ADRs include nephrotoxicity of some non-steroidal anti-inflammatory drugs or analgesics-antipyretics (mainly phenacetine) or osteonecrosis of the jaw bone following bisphosphonate administration.

4.1.4 Type D adverse reactions

Type D (delayed) adverse effects are also referred to as “late ADR”. These ADRs appear longer after drug administration (even several years) and are therefore sometimes difficult to be identified as adverse reactions; causality is difficult to be proved.

Examples of type D ADRs are leucopaenia following the administration of the cytostatic lomustine or the late procancerogenic and teratogenic effects of some

cytostatics or hormones. Another example is tardive dyskinesia after administration of neuroleptics.

4.1.5 Type E adverse reactions

This type of ADR occurs only after discontinuation of the drug (hence E-end-of-use).

Examples include insomnia and anxiety after discontinuation of benzodiazepines or hypertension upon abrupt withdrawal of beta-blockers. In the latter case, we refer to the so-called "rebound phenomenon" - the cause is the adaptation mechanisms on the receptors after long-term administration of receptor antagonists, which leads to up-regulation (i.e. increase in the number of receptors). Consequently, if this increased number of receptors is no longer occupied by the antagonist (drug) but by their natural ligand (noradrenaline = natural agonist), it may result in increased blood pressure and tachyarrhythmia.

4.1.6 Type F adverse reactions

Sometimes, a special type F is also classified, indicating therapeutic failure. A Type F side effect is an unexpected therapy failure. The cause may be unknown (e.g. primary resistance of microorganisms that should theoretically be susceptible to antibiotics), but it is also in unrecognized drug interaction where, for example, due to the induction of enzymatic biotransformation, effective drug concentrations decrease more rapidly and therapy fails.

Drugs that most often (considered as % ADR per number of uses) cause hospitalization due to an adverse effect include antitumor drugs (classical cytostatics and biological therapy), as well as vaccines, antibiotics, anticoagulants or drugs of the cardiovascular system.

4.2 Classification of adverse reactions by causality evidence

The causality of an adverse event is always studied very carefully, however, it is not always clear. According to causality evidence, the strength of evidence can be classified in several stages of causality (according to WHO). The highest degree of

causality is **“certain”** - when a clinical event (including an abnormality of one of the laboratory parameters) occurs with plausible time relationship to drug intake and cannot be explained by other circumstances (other disease, other drug or chemical substances) and, at the same time, response to withdrawal of the suspected drug is plausible (pharmacologically, pathologically). The adverse reaction is well described pharmacologically and phenomenologically and is verified by drug re-challenge.

The category is **"probable"**: A clinical event (including an abnormality of any of the laboratory parameters) occurs sequentially with drug administration and is unlikely to be attributed to disease or to other circumstances (other disease, other drug, or chemicals). The response to withdrawal of suspected drug is clinically reasonable. The rechallenge is not required. „**Possible"**: A clinical event (including an abnormality of one of the laboratory parameters) sequentially with drug administration, but may be explained by the disease or by the administration of another drug (chemical). Information on the follow-up after withdrawal is lacking or unclear.

“Unlikely”: A clinical event (including an abnormality of one of the laboratory parameters) occurs with a time to drug intake that makes a relationship improbable (but not impossible) and the event may be explained by disease or administration of another drug (chemical).

“Conditional/Unclassified”: A clinical event (including an abnormality in any of the laboratory parameters) that has been reported as an adverse reaction but more data for proper assessment is needed or additional data is under examination

“Unassessable/Unclassifiable”: Report suggesting the ADR that cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

There are more algorithms for assessing causality of adverse reactions, some of them are internationally recognized and used in pharmacovigilance studies, e.g. the so-called 10-item classification (scale, nomogram) Naranjo (according to the first author of published work from 1981), resp. a newer and more sophisticated Liverpool Adverse Drug Reaction Causality Assessment Tool.

4.3 Classification of ADR to serious / non-serious

Accordingly with the valid legislation (EMA Note for guidance on clinical safety data management: definitions and standards for expedited reporting (CPMP/ICH/377/95) or in the Czech Rep. Act on Pharmaceuticals No. 378/2007 Coll.), we have to distinguish between serious and non-serious ADRs and expected and unexpected ADRs.

A serious ADR is one that causes

- death or is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- cause a congenital anomaly/birth defect.

All other ADR are therefore non-serious

Unexpected side effects are those where the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

4.4 Reporting of adverse reactions

In the Czech Rep. (but also other European countries), pursuant to the Pharmaceuticals Act, (or pursuant to the EMA Note for guidance on clinical safety data management: definitions and standards for expedited reporting (CPMP/ICH/377/95), MAH is obliged to report **serious adverse reactions** within a period of 15 days, while **healthcare professionals are obliged to report immediately unexpected or serious adverse reactions** to the State Institute for Drug Control or distinct national regulatory authority (e.g. MHRA).

In addition, MAHs are required to report, at regular 3-year intervals, newly identified adverse reactions - all, including non-serious or expected, to specify their Periodic Safety Update Report (PSUR), which will then be reflected in the updated Summary of Information. (SPC).

Patients can report any suspicion of ADR to all mentioned subjects - MAH (a pharmaceutical company that authorized the product in the Czech Republic), who is legally obliged to process this information and report to SÚKL/national authority within a period of 15 days. Other option (for patients) is to report directly to the State Institute for Drug Control, also via the online form on its website. However, the **marketing authorization holder must also report suspected non-serious adverse reactions occurring in the European Union** within 90 days of the day on which he became aware of the suspicion.

National regulatory authority (MHRA/SÚKL) then passes information on ADR to the European Eudravigilance database. This database is managed by the Pharmacovigilance Risk Assessment Committee at the European Medicines Agency (EMA). The Committee then makes recommendations on the safety of medicinal products. A schematic representation of the reporting and transmission of information between subjects is shown in Figure 19. An example of the CIOMS form (for proffesionals) shown in Figure 20 and the Yellow card form (UK, MHRA) is shown is in the Figure 21. The regulatory authorities (EMA, MHRA etc.) can then decide on measures to ensure the safe use of medicines. These measures may result in reduced indications, reduced duration of administration, definition of a new contraindication, notification of a new interaction and, as a last possibility, suspension or withdrawal of a marketing authorization (i.e. withdrawal of the product from the market). The special adverse event reporting regime applies to the clinical trials (CT) on medicinal products. In case of suspicion of a serious unexpected ADR (Suspended Unexpected Serious Adverse Reaction; SUSAR) within the CT, the Sponsor of CT is obliged to report this ADR even within 7 days to National authority/SÚKL and to the relevant ethics committee, which approved the given CT.

Figure 19. *Scheme of obligatory and voluntary reports of adverse drug reactions to national authority (SUKL)*

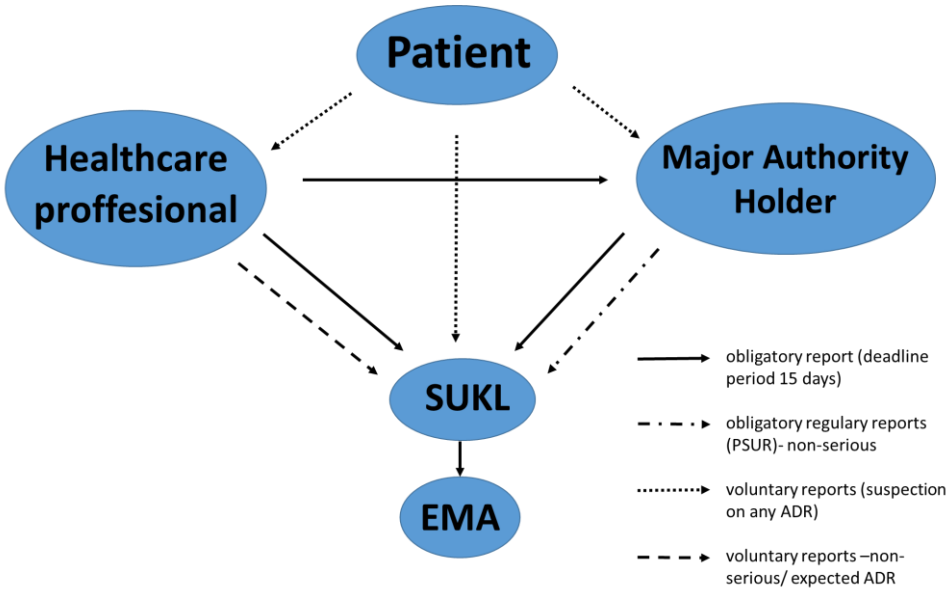


Figure 20. *Sample form for reporting ADR (CIOMS)*

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

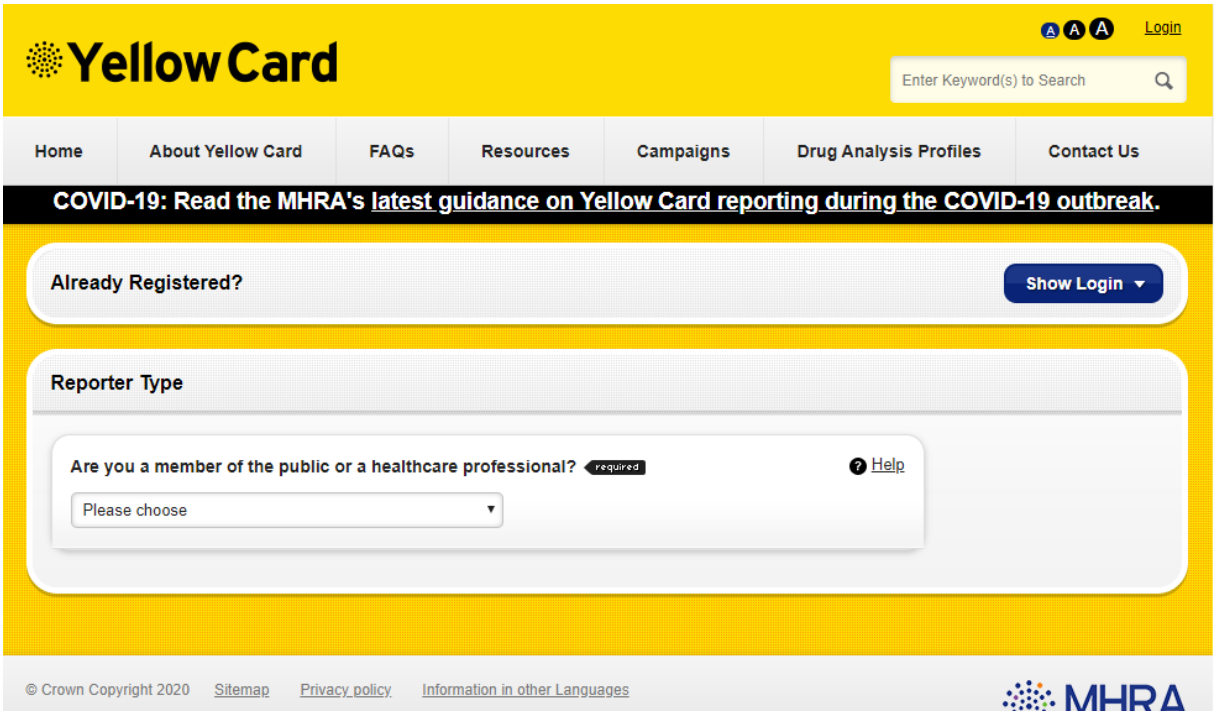
III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Figure 21. *Sample form for reporting ADR (MHRA)*



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Act No. 378/2007 Sb.

5. Drug interactions

Drug interactions are one of the factors influencing the overall efficacy and safety of pharmacotherapy. Concomitant administration of two or more drugs may affect the other's efficacy or frequency/severity of adverse effects. In a broader context, this also means interactions of drugs with food supplements or food ingredients.

A drug can increase the effect of another (or two drugs each other) and cause a so called **synergistic interaction** or, on the other hand, reduce the effect of another drug (or each other) and cause an **antagonistic interaction**.
Interactions do not always have to be percieved as negative - there are advantageous interactions between drugs which lead to an increase in efficacy or decrease of required dose of each drug and thus decreased risk and severity of adverse effects, respectively. Thanks to some beneficial combinations of antibiotics, the antimicrobial spectrum may be significantly broadened.

Another example of a beneficial interaction between 2 drugs is the use of specific antidotes (e.g. administration of naloxone in an overdose with opioids, flumazenil in an overdose with benzodiazepines, atropine in organophosphate poisoning, calcium chloride in overdose with calcium channel blockers or fomepizole or ethanol use in methanol poisoning). We call such interactions "**beneficial**" or "desirable"; on the contrary, a combination of drugs is described as an **adverse** (or undesirable) drug-drug interaction when the effect of one or both of the combined drugs is reduced or toxicity increased. Thus, interactions can be understood as synergistic or antagonistic and beneficial/desirable or adverse/undesirable.

Synergistic interactions may result from so-called **summation**, which is an increase in effect due to a combination of 2 or more drugs. Thus we preferably combine, for example, analgesics, antihypertensives or some cytostatics (e.g. bleomycin + etoposide + cisplatin, irinotecan + calcium folinate + 5-fluorouracil). In some combinations of antibiotics the effect is also increased, but the effect increase is not only a sum, but rather a multiplication of the effects of the individual drugs. We call this interaction **potentiation**. Examples include a combination of aminoglycosides with penicillin-type antibiotics, a combination of clarithromycin and

warfarin, when clarithromycin inhibits cytochrome P450 metabolic activity and potentiates its effect, or a combination of several sedative agents with different mechanisms of action (H_1 antihistamines, benzodiazepines and opioids).

Antagonistic interactions can be of the "**pharmacological**" type, where both administered substances compete for the same receptor/enzyme/protein (e.g. acetylcholine + atropine, noradrenaline and metoprolol). **Physiological antagonism** occurs when both substances do not have the same mechanism of action but interact with each other. For example, the vasoconstrictor effect of adrenaline or noradrenaline antagonizes the vasodilatory effect of histamine in the treatment of hypovolemic shock following an allergic reaction. Another type of antagonism used in the therapy of intoxication is chemical antagonism - in this situation there is a chemical reaction between two substances, which reaction can take place directly in the body. An example is the binding of heparin to protamine sulphate, free iron by deferoxamine or other chelating agents, or even the reaction of a specific antibody with a drug (idarucizumab + dabigatran, an anti-digoxin antibody).

The risk of interactions logically increases with the number of drugs used. The risk of interaction with a combination of 6 drugs is reported to be about 7%, but with a combination of 11 drugs it is almost 15%.

Interactions are also more dangerous for certain groups of patients - these are primarily the age groups of the elderly who are more likely to take more than one medication at the same time and are at risk of drug misuse (forgotten medication, incorrectly measured dose, failure to comply with recommendations to avoid certain combinations with food, time delay from food, etc.).

Elderly patients have logically lower compensatory capacities in terms of metabolism and excretion. While elimination may accelerate in younger patients when the drug levels are elevated (thanks to first-order kinetics), in elderly patients, due to the impaired renal or hepatic function a threshold may be reached where functional acceleration of elimination is not possible and first-order kinetics then change to 0. order kinetics. This may lead to drug accumulation and manifestations of drug toxicity.

Premature babies are also at high risk for interactions, factors which increase the overall risk include lower albumin levels, lower activity of biotransformation enzymes and significant changes in drug distribution due to higher body water content. Another group of patients at risk are cancer patients who also have disturbed homeostatic mechanisms and their physiological reserves are often exhausted by cancer or relatively aggressive treatment with cytostatics (nephrotoxicity, hepatotoxicity, anaemia, hypoalbuminaemia, impaired renal function – elevated creatinine and cystatin C levels, liver insufficiency, frequent ionic dysbalance). Interactions in these conditions are easier to manifest and can have more serious consequences. However, other specific groups are similar - for example, patients with GIT diorders (inflammatory bowel disease, irritable bowel syndrome, reflux disease), who are more likely to experience interactions at the level of absorption, or patients with cardiovascular disease or diabetics.

There are several mechanisms by which drug interactions occur; accordingly, the interactions can be classified as **(bio)pharmaceutical** (galenic), **pharmacokinetic** and **pharmacodynamic**. Any of these interactions can be dangerous; this is more often the case when a physician is unaware of these interactions. In some cases, however, there may be an interaction that can be used in a therapeutically advantageous way to increase bioavailability (e.g. ascorbic acid helps to reduce ferrous iron to the more soluble ferric iron), increasing drug efficacy (cytostatics: combination of calcium folinare + fluorouracil: 5-fluorouracil (5-FU) inhibits thymidylate synthetase (TS), a key enzyme involved in pyrimidine biosynthesis; calcium folinate promotes TS inhibition by increasing the intracellular folate reserve, thus stabilizing the 5-FU-TS complex and thus enhancing fluorouracil activity) .

Another example of a preferred antagonistic interaction is the reduction of drug toxicity (e.g., the mesna metabolite is excreted by the kidneys, where it is further metabolized to a product that binds to ifosfamide or cyclophosphamide metabolites and thus prevents their toxic effect on the bladder mucosa). The clinical consequences of adverse drug reactions may occur as adverse reactions (type A,C,D,E) or treatment failure - type F (failure) (see Chapter 4 - Adverse drug reactions).

5.1 Biopharmaceutical drug interactions

Biopharmaceutical drug interactions occur in the patient's body – i.e. before the drug is administered to the body or just at the moment of administration. Biopharmaceutical (sometimes also referred as Pharmaceutical or "galenic") interactions occur on the basis of chemical reactions between 2 or more components of medicinal products or administration aids or materials. Due to incompatible physicochemical properties, one drug's effect may abolished by reaction with another or an excipient, exceptionally both drugs may abolish each others effect. These interactions are almost all well identified, and do not occur in ready made drugs these preparations are manufactured according to pre-approved and tested technological procedures. Similarly, the pharmacist should solve potential problems by changing excipients or modifying IPP preparation technologies.

Thus, probably the greatest risk for pharmaceutical drug interactions is when medicines are mixed just before being administered to a patient by a nurse or nursing staff who may not be sufficiently experienced to identify and prevent such interactions properly. These risky procedures involve the mixing of more liquid drugs (injections with infusions to reduce the number of punctures) of crushing and mixing of some drugs with each other during swallowing or in gastric probes and so on.

An example of a pharmaceutical interaction, sometimes also referred to as incompatibility, is a combination of tannins (astringent, weakly antiseptic chemical compounds – active ingredients of some plants or black tea) with any alkaloid (morphine, codeine, galantamine, ergometrine, etc.) When combined together, the alkaloid is precipitated and rendered ineffective.

There are many incompatibilities known (aminoglycoside antibiotics are inactivated by penicillins and cephalosporins, tannin and zinc oxide in semi-solid dosage forms create very hard non-spreadable mixtures, etc.). Incompatibilities, however, are also called drug interactions between the drug (active ingredient) and the solution as a vehicle, and the active ingredient and the container, respectively. An example of a drug that interacts with a vehicle is furosemide, which may precipitate when the pH drops below 7 and according to the SPC it may not mix with substances that lower

the pH of the solution (noradrenaline, adrenaline, group B vitamins, ascorbate, local anesthetics, antihistamines) however, precipitation may also occur when combined with other drugs (amiodarone, ciprofloxacin, digoxin, morphine, proton pump inhibitors).

This type of interaction often occurs with drugs that are in the form of chloride salts and due to the common ion, the solubility may be reduced when diluted with saline (e.g. methylene blue must only be mixed with a 5% glucose solution, similarly oxaliplatin must be diluted to glucose solution and not saline). An example of drug-container (syringe, tubes) interaction is PVC-diazepam or insulin interaction, where adsorption leads to a decrease in concentration of the active ingredient.

5.2 Pharmacokinetic interactions

Pharmacokinetic interactions occur at the level of drug absorption, distribution, biotransformation or elimination. These interactions can be very harmful as in some cases the plasma concentrations may increase by several orders (or decrease, depending on the particular type of interaction) and thus lead to adverse effects, an increase in their severity or frequency, or treatment failure. There are many examples of pharmacokinetic interactions; in the following sections, examples of interactions at the level of individual pharmacokinetic processes are presented.

Absorbtion - The simultaneous administration of tetracyclines or some types of quinolone antibiotics and divalent ions (Ca^{2+}, Mg^{2+} in antacids, food supplements or milk, supplements containing Fe^{2+}), results in the formation of non-absorbable complexes thus causing the antibiotic to become ineffective.

Another example is influence of the efflux transporters (usually inhibition) in the intestinal wall (e.g., P-glycoprotein, P-gp or MRP1) which thereby increases the bioavailability of the drug. P-glycoprotein is the most important efflux transmembrane transport protein, expressed in the epithelial cells of organs involved in absorption and distribution such as enterocytes, the blood-brain and testicular barrier, as well as

at sites with a purely excretory function - in the canalicular membrane of hepatocytes, on the apical side bile duct cells and renal proximal tubule.

Another way in which drug-drug interactions occur at the level of absorption is by change of the motility of GIT by prokinetics (metoclopramide, itopride, cisapride). These substances accelerate the passage through the proximal part of the GIT and can thus speed up the absorption (shorten Tmax) and increase the bioavailability of some drugs, such as cyclosporine, levodopa, morphine, diazepam.

Conversely, anti-diarrheals, opioids, anticholinergic spasmolytics, or medical cannabis and its ingredients may slow down a drug's passage through the entire GIT and increase contact time with the intestinal wall. However, this may also increase the availability of some other drugs. Bioavailability may also be reduced by creating a mechanical barrier on the surface of the GIT mucosa by concurrent administration of sucralfate or by a direct drug interaction - thereby reducing the bioavailability of resins (hypolipidaemics), calcium ions, magnesium ions, iron or intestinal adsorbents (carbo medicinalis, diosmectite).

Another kind of interaction at the site of absorbtion occurs via altering of the pH in the stomach - weak acids are better absorbed from an acidic environment and their biovailability is significantly decreased when combined with proton pump inhibitors, antacids, or H_2 antihistamines. Such drugs include acetylsalicylic acid, atazanavir, itraconazole or ketoconazole.

Distribution - At the level of distribution, interactions occur when drugs bind to plasma proteins, especially albumin. A clinically relevant example includes the combination of warfarin with other drugs extensively bound to plasma proteins (e.g. diclofenac, some oral antidiabetics). In this case warfarin is displaced from its bond, thereby increasing the free warfarin fraction several times and causing bleeding. Although these interactions do not usually have clinically significant consequences, the warfarin example demonstrates that they may occur in drugs with a low therapeutic index.

In a broader context, interactions at the level of distribution can also be understood as those that affect the expression of efflux transporters, which affect the penetration of some drugs through the barriers of the hepatobiliary system, blood-brain barrier or renal tubules. The spectrum of P-glycoprotein substrates largely overlaps with CYP3A4 substrates. An example of the influencing of distribution equilibria is the interaction of statins with cyclosporine or HIV protease inhibitors – when (in addition to inhibition of CYP enzymes by statins) the effect of statins is reduced due to inhibition of the OATP1B1 transporter by cyclosporine or protease inhibitors.

This transporter (OATP1B1) is responsible for the transport of statins to the liver and thus, although their plasma concentrations are elevated, they cannot reach their site of action. Examples of P-gp substrates and other transport proteins are presented in Tables 2 and 3. Influencing P-gp is not only important for distribution but also for elimination as P-gp is found in the intestine, the blood-brain barrier, the placenta, and the hepatobiliary system. This is particularly important for drugs that are not metabolised but excreted unchanged into the bile.

Table 2. *Examples of P-gp substrates*

P-gp, *(product of the gene ABCB1)*	
Substrates	amitriptyline, ciprofloxacin, cisplatin, dabigatran, digoxin, fexofenadine, clarithromycin, cyclosporin, daunorubicin, erythromycin, docetaxel, domperidone, etoposide, fentanyl, fluorouracil, imatinib, lansoprazole, loperamide, losartan, levofloxacin, methadone, methotrexate, morphine nelfinavir, omeprazole, ondansetron, paclitaxel, pantoprazole, ritonavir, saquinavir, tacrolimus, tamoxifen, trimethoprim, vincristine, topotecan
Inhibitors	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir, ritonavir, propafenone, quinidine, ritonavir, saquinavir, telaprevir, tipranavir, verapamil
Inducers	amiodarone, bromocriptine, cisplatin, cyclosporine, dexamethasone, dilthiazem, doxorubicin, etoposide, fluorouracil, indinavir, clotrimazole, colchicine, methotrexate

Table 3. *Examples of substrates for other transport proteins*

Transporter	Gen	Substrate	Inhibitor
BCRP	*ABCG2*	rosuvastatin, sulfasalazine	curcumin, cyclosporin A
OATP1B1, OATP1B3	*SLCO1B1 SLCO1B3*	asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel, fexofenadine, nateglinide, paclitaxel, pravastatin, repaglinide, rosuvastatin, simvastatin	atazanavir, ritonavir, clarithromycin, cyclosporin, erythromycin, gemfibrozil, lopinavir, rifampicin, simeprevir
OAT1, OAT3	*SLC22A6, SLC22A8*	adefovir, cefaclor, ceftizoxime, famotidine, furosemide, ganciclovir, methotrexate, oseltamivir, penicillin G	p-aminohippuric acid, probenecid, teriflunomide
MATE1, MATE2-K	*SLC47A1, SLC47A2*	metformin	cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib

P-gp: P-glycoprotein 1, syn. multidrug resistance protein 1 (MDR1)

BCRP: Breast Cancer Resistance Protein;

OATP1B1, OATP1B3: Organic-anion-transporting polypeptide 1 and 3 transporters expressed on the basolateral (sinusoidal) membrane of hepatocytesOAT1, OAT3: organic anion transporter 1 a 3

MATE1, MATE2-K: multidrug and toxin extrusion-transport proteins expressed on the apical membrane of the proximal tubule

Biotransformation - The most common interactions are interactions at the level of cytochrome P450. This refers in particular to induction or inhibition. In the case of induction due to repeated administration of one drug (e.g. carbamazepine, rifampicin), there is a transient increase in the amount or activity of a cytochrome P450 form and consequently, a higher biotransformation rate decreases the plasma levels (and effect) of the drugs metabolized by the specific CYP enzyme more quickly. In the case of inhibition, the interaction may occur immediately, even after a single/simultaneous administration of the inhibitor. The consequences are the opposite in case of induction - the inhibitor (e.g. fluoxetine, ketoconazole) slows down biotransformation, increases plasma concentration and drug effects.

Conversely, a prodrug that is activated by biotransformation (clopidogrel, tamoxifen) may thus be less effective. Inhibition of enzymatic biotransformation is most often

reversible: the effect of the inhibitor does not persist after the inhibitor is cleared from the body. Types of reversible inhibition include simple competitive (drugs compete for enzyme binding), uncompetitive (inhibitor binds to enzyme-substrate complex) and non-competitive inhibition where inhibition cannot be overcome by increasing substrate concentration.

In contrast, irreversible or "quasi-irreversible" inhibition may persist even after the inhibitor has been removed from the body. The inhibitor binds to the enzyme via a covalent bond and complete de novo synthesis is required to restore its function. Examples of irreversible inhibitors are clarithromycin, erythromycin or protease inhibitors (HIV antivirals). In some databases, inhibitors are also classified according to the degree of inhibition as potent, moderate and weak inhibitors, according to the ability to increase the AUC of other drugs metabolised by the given CYP.

Strong inhibitors increase AUC by more than 5x, moderate by more than 2x and weak by 1.25x - 2x. Examples of substrates, inducers and inhibitors of CYP forms are given in Table 4. Information regarding ability to interact with P450 enzymes is very valuable for clinical practice. Therefore, during drug discovery and development, these interactions are monitored and considered clinically relevant when the ratio of maximum plasma concentration of inhibitor to its Ki (*in vitro* inhibitory constant) (Cmax/Ki) exceeds 1. It is also important to consider where the inhibition CYP occurs - whether during absorption (intestinal CYP) or in the liver. Another set of interactions concern the conjugation enzymes (NAT, UGT etc.), but these are quite rare and less relevant compared to CYP-mediated interactions.

Table 4. *Examples of substrates, inducers and inhibitors of CYP enzymes (next page).*

	Inducers	Inhibitors	Substrates
CYP1A2	omeprazole, phenobarbital, phenytoin, rifampicin, polyaromatic hydrocarbons (cigarette smoke, grilled meal)	cimetidine, ciprofloxacin, isoniazid, fluvoxamine, metronidazole, sertraline, macrolide antibiotics, paroxetine	amitriptyline, cyclobenzaprine, desipramine, diazepam, erythromycin, estradiol, naproxen, paracetamol, theophylline, warfarin
CYP2C9	rifampicin, carbamazepine, nevirapine, secobarbital, St. John's wort	amiodarone, chloramphenicol, cimetidine, fluvoxamine, zafirlukast	celecoxib, diclofenac, losartan, naproxen, phenobarbital, phenytoin, paracetamol, piroxicam, torsemide, S-warfarin
CYP2C19	rifampicin, St. John's Wort, ritonavir, carbamazepine	azole antifungals, fluvoxamine, omeprazole, topiramate	amitriptyline, citalopram, diazepam, lansoprazole, omeprazole, phenobarbital, propranolol, topiramate, R-warfarin
CYP2E1	alcohol (chronic), isoniazid	acute alcohol, disulfiram	alcohols, dapson, halogenated alkanes, isoflurane, paracetamol, theophylline
CYP2D6	dexamethasone, rifampicin	bupropion fluoxetine, paroxetine, quinidine, amiodarone, citalopram, methadone, midodrine, moclobemide, hydroxyzine, metoclopramide, ticlopidine, ritonavir	metoprolol, timolol, carvedilol, propafenone, TCA, venlafaxine, bufuralol, clonidine, donepezil duloxetine, lidocaine, dextromethorphan, codeine, metoclopramide, risperidone, tramadol
CYP3A4	carbamazepine, dexamethasone, etosuximide, phenobarbital, phenytoin, rifampicin / rifabutin, St. John's wort	amiodarone, aprepitant, netupitant, azole antifungals, cimetidine, cyclosporin, fluoxetine, macrolide antibiotics, metronidazole, nicardipine, propofol, protease inhibitors, quinine, sertraline, verapamil, voriconazole, boceprevir, delavirdine	alprazolam, amiodarone, amitriptyline, amlodipine, azole antifungals, budesonide, calcineurin inhibitors, carbamazepine, celecoxib, cisapride, clarithromycin, clindamycin, codeine, cortisol, dapson, diazepam, digoxin, diltiazem, donepezil, ethinylestradiol, fentanyl, fexofenadine, HMG-CoA reductase inhibitors, lansoprazole, loratadine, losartan, macrolides, methadone, omeprazole, propafenone, sertraline, tamoxifen, theophylline, verapamil, warfarin

Excretion - Drug interactions may occur due to the effects of urine pH on drug permeation across the microtubule membrane, on tubular secretion, on reabsorption and finally by its influence on the P-glycoprotein transporter. Examples include reduced digoxin excretion when amiodarone or clarithromycin are co-administered, or slowed lithium excretion after thiazide diuretic administration (increased sodium excretion causes increased reabsorption of lithium ions); or acceleration of barbiturate excretion by urine alkalinisation (forced alkali diuresis) in case of intoxication. Another example is uricosuric probenecid interactions, where tubular secretion is decreased and plasma concentrations (and possible toxicity) of methotrexate or penicillin are increased. This interaction was used therapeutically to prolong the elimination half-life of penicillin.

Renal excretion is also affected by catecholamines (or generally vasopressor agents) administered in hypovolemic postoperative circulatory failure, vasoplegia or septic shock. Catecholamines increase the tone of the arteries while maintaining circulation at the beginning, but may decrease splanchnic perfusion and through prolonged vasopressor effect they may decrease renal flow and drug excretion.

Excretion of drugs may also be affected by the general nephrotoxic effect of some drugs, which may subsequently result in delayed elimination of renally eliminated drugs. Nephrotoxic drugs commonly include aminoglycoside antibiotics, vancomycin, non-steroidal anti-inflammatory drugs, platinum derivatives (cytostatics), and furosemide.

5.3 Pharmacodynamic interactions

Pharmacodynamic interactions occur **at the target site of action**, or on the effector system (receptor, transporter, signaling pathway, enzyme). By this, an interaction may be categorised as **synergistic** or **antagonistic** in nature. Interactions may also occur at the same target site (e.g., the gamma aminobutyric acid receptor complex - GABA A) or may occur in two independent effector systems (e.g., opioid receptors and GABA A receptor complex).

A pharmacodynamic interaction is for example the interaction of beta-blockers and the antiarrhythmic drug and calcium channel blocker verapamil. Their concomitant administration may result in severe cardiac arrest by supression of the cardiac conduction system. Synergic (but undesirable) interactions also occur when

benzodiazepines and alcohol are co-administered - both substances inherently support the function of depressive endogenous systems (GABA-A and opioid) and therefore can lead to severe, even life-threatening CNS depression. These synergistic reactions are a common cause of the unexpected toxicity of a previously problem-free drug. Interactions may involve one-sided or both-sided increases in organ toxicity, such as combinations of multiple nephrotoxic drugs (e.g. vancomycin + gentamicin). Another example is the combination of several substances with anticholinergic activity and the onset of the so-called anticholinergic syndrome (e.g. in many psychoactive drugs and atropine), or the pro-arrhythmic effect of the whole group of antipsychotics, a number of antidepressants, fluorinated quinolones, prokinetics and antiemetics and some antihistamines. Their combination prolongs the corrected QT interval and *torsades de pointes* arrhythmias. Additionally, the factor of pharmacogenetics also affects this interaction, where patients with mutations in genes for potassium, resp. sodium channels (KCNQ1, SCN5A) are predisposed to an increased risk of long QT syndrome (LQTS). Another similar example is the combination of several drugs causing hyperkalaemia and subsequently their proarrhythmogenic effect (ACEi, potassium sparing diuretics).

In the case of a combination of diuretics and non-steroidal anti-inflammatory drugs, the antihypertensive effect of diuretics is reduced, since non-steroidal anti-inflammatory drugs tend to cause sodium retention. Thus, due to the different mechanisms of action, the variety of these interactions is wide.

Examples of pharmacodynamic-type drug interactions are presented in the Table 5.

Table 5. *Examples of drug interactions*

Drug 1	Drug 2	Mechanism of interaction	Consequence/ type of interaction
thiazide diuretics	NSAIDs	inhibition of prostaglandin synthesis, sodium retention	reducing the antihypertensive effect of thiazides
ASA	ibuprofen, metamizol, NSAID	competition for the COX1 binding site	competitive (reversible) COX1 inhibition, shorter, decreased anti-aggregative effects, antagonism
levodopa	neuroleptics	competition for dopamine receptors	reducing the effect of levodopa

warfarin	Vitamin K	substitution, competition	decreased anticoagulant effect of warfarin
beta blockers	clonidine	adaptation mechanisms on the receptor-level	hypertensive crisis after clonidine withdrawal
ACEi	spironolactone	synergistic effect at level of absorbtion	hyperkalemia, arrhythmia
quinolones	macrolide antibiotics	cardiotoxic effect	QTc interval prolongation, arrhythmia
neuroleptics	setrones	cardiotoxic effect	QTc interval prolongation, arrhythmia
SSRIs	prokinetics (metoclopramide, cisapride, itopride)	cardiotoxic effect	QTc interval prolongation, arrhythmia
ASA	SSRIs	antiplatelet effect - platelet depletion in serotonin + inhibition of COX1	bleeding, petechiae
SSRIs	triptans	activation of serotonin receptors	serotonin syndrome
tricyclic antidepressants (TCA)	neuroleptics (1st. generation)	synergies of anticholinergic effects	anticholinergic crisis, constipation, confusion, ileus, delirium
midazolam	thiopental	synergistic effect-potentiating depressant effects through the GABA A receptor complex; 2 different binding sites	severe sedation, respiratory center depression
SSRIs	tramadol	increase in serotonin concentration	serotonin syndrome
SSRIs	prokinetics (metoclopramide, cisapride, itopride)	increase in serotonin concentration	serotonin syndrome
opioids	Neurotropic spasmolytics	reduced GIT motility through opioid receptors and anticholinergic effects	constipation
TCA	antihypertensives	TCAs increase the availability of catecholamines, antagonizing the antihypertensive effect	hypertension

5.4 Interactions of drugs and food, food supplements

5.4.1 Influence of pharmacokinetics of drugs

Absorbtion

Food and its components may affect the bioavailability of a drug as well as the rate of absorption. Content of the GIT may present a simple **mechanical barrier** which reduces contact of drug with the mucosa and hence absorption rate. Therefore, some medicines (e.g. penicillins, levothyroxine, etc.) should be administered in the fasting state, 30-60 minutes before a meal or 2-3 hours after the meal. On the other hand, food can increase or facilitate the absorption of drugs, e.g. a fatty diet increases the absorption of lipophilic drugs (lipophilic vitamins, griseofulvin, cyclosporine etc.).

Food ingredients and drugs can react **chemically** to form undesirable compounds. Typically, for example, the chelation of bivalent and trivalent metal cations from food with a drug and the subsequent formation of non-absorbable and thus systemically inactive compounds. Thus, for example, fluoroquinolones or tetracyclines with Ca^{2+}, Mg^{2+}, Al^{3+}, Fe^{2+}, Fe^{3+} cations from the diet, or Fe^{2+} and Fe^{3+} ions used as supplements administered in anaemia may be chelated by polyphenols present in coffee, tea, etc. By altering the pH, it is possible to influence the absorption of some drugs and a typical example is iron supplementation, which requires the acidic environment of the stomach for good absorption, preferably in the fasted state.

Among food ingredients there are also substances that specifically **block transporters** located on the villous membrane. This may be, for example, an organic anion-transporting polypeptide (OATP) transporter. By inhibiting this transporter, the bioavailability of some drugs with organic anion nature may be reduced by preventing their influx into the enterocyte. An OATP blocker is for example the flavonoid narigenin, which citrus fruit species are rich in. The opposite example (from the perspective of bioavailability) is another transporter - efflux P glycoprotein. Its inhibition may increase the bioavailability of drugs by blocking the excretion of xenobiotics (drugs) from the enterocyte back into the lumen of the intestine.

Distribution

Naturally, dietary supplements can also affect the distribution of concomitantly administered drugs. When the components of a dietary supplement bind to plasma proteins, this may present a risk for drugs with a low therapeutic index, which are also bound to albumin and other plasma proteins. In fact, their displacement leads to an increase in their free fraction and thus an increase in their effect. This interaction may result in an increased free concentration of warfarin in the plasma and thus an increase in its effect. In addition, coumarins of natural origin alone have a slight anticoagulant effect and thus the whole interaction becomes even stronger.

Biotransformation

Phase I biotransformation processes include reactions mediated by the cytochrome P450 (CYP) enzyme system. Found on the membrane of the intestinal villi, some CYP enzymes are responsible for presystemic elimination, i.e. biotransformation of a drug which has not reached systemic circulation yet. Inhibition or induction of intestinal CYP may affect the plasma level of the drug and its effect. Inhibition leads to a decrease in presystemic elimination, a larger proportion of the drug is then available for absorption and the plasma concentration of the drug increases (risk of overdose, toxicity). Induction, on the other hand, leads to an increase in presystemic elimination, a decrease in plasma drug concentrations and a risk of low efficacy or treatment failure.

Some components of diet may also affect hepatic CYP metabolic activity. Induction of hepatic CYP results in decreased plasma drug concentrations; whereas inhibition of CYP leads to increased drug plasma levels. Clinically relevant **inhibitors** of intestinal CYP3A4 are **furanocoumarins** (dihydroxybergamotin, bergamotin) contained in grapefruit (*Citrus* × *paradisi*), pomelo (*Citrus* × *maxima*), Seville orange (*Citrus* × *aurantium*) and carambola (*Averrhoa carambola*). Some **flavonoids**, such as quercetin contained in high concentrations in pomegranate (*Punica granatum*) also have an inhibitory effect, but data on its interaction potential in humans are still limited to case reports. Well-established evidence exists for the effects of grapefruit juice however in the other fruit ingredients mentioned, reliable clinical studies are missing or have methodological concerns, or are only individual case reports.

Nevertheless, some flavonoids are considered to increase plasma concentrations and the effect of benzodiazepines, calcium blockers, some H_1 antihistamines, and generally CYP3A4 and P-gp substrates. Inhibition of hepatic CYP is not usually observed when furanocoumarin-containing foods are consumed.

Inducers of hepatic CYP1A include, for example, cruciferous vegetables and **polycyclic aromatic hydrocarbons** (PAHs) which originate from, for example, inappropriate cooking or tobacco smoking. Many medicinal plants that are consumed most often in the form of infusion also affect biotransformation processes.
Phase 2 biotransformation takes place in enterocytes with the help of various conjugation enzymes (e.g. glucuronyltransferases, sulphotransferases). Inducers of these enzymes include, for example, **cruciferous vegetables, ingredients of citrus species and soybean products**.

Excretion

Dietary composition affects urine pH. Vegetarians and vegans have alkaline urine, and thus it is easier to reabsorb weak-alkaline medicines (e.g. morphine, pethidine, amiloride, amphetamines etc.) back into the interstitium. Therefore these drugs remain in the body for longer, while excretion of weak-acid medicines is accelerated (methotrexate, sulphonamides, thiazide diuretics). Acidification of urine e.g. by sipping fruit juices helps the elimination of drugs of the weak base nature. On the contrary, acidic beverages may impair the solubility of some drugs and cause them to crystallize in tubules and manifest nephrotoxicity (methotrexate, sulphonamides).

5.4.2 Pharmacodynamic interactions of drugs and food supplements

Diet components and drugs may act synergistically (increase in effect) or antagonistically (decrease in effect). An example of a **synergistic effect** is the interaction of monoamine oxidase (MAO) inhibitors with a tyramine-rich diet. Tyramine is a biogenic amine present in significant levels in bananas, cheese (especially fermented), chocolate, coffee, fermented meat products, soybean sauce, red wine, etc., which is normally decomposed by intestinal MAO. When drugs that inhibit MAO are administered, tyramine from the diet is not metabolized and causes hypertension (even hypertensive crisis), increased diuresis, headache and

palpitations. Non-selective MAO inhibitors and MAO A inhibitors include tranylcypromine, phenelzine or moclobemide.

Another example of synergism is the interaction of antithrombotic drugs and anticoagulants with garlic extracts or simply garlic-rich meals. Antithrombotic agents and anticoagulants are drugs that interfere with the coagulation cascade and are used to prevent thrombotic events. Garlic contains the essential oils ajoene and allicin, which affect platelet aggregation, the binding of fibrinogen to activated platelets, and the production of prothrombotic thromboxane A2 for the reduction of blood clotting. Excessive consumption of uncooked garlic or garlic supplements with antithrombotic drugs or anticoagulants can cause bleeding disorders. A combination of ginkgo supplements and antithrombotic or anticoagulants may also result in a similar interaction.

An example of an antagonistic action is a combination of the oral anticoagulant warfarin and a vitamin K-rich food. Warfarin is a vitamin K antagonist - competing with its actions in the synthesis of new coagulation factors in the liver. By varying the plasma vitamin K concentration, warfarin can be displaced or replaced by vitamin K in biochemical processes, reversing its anticoagulant effect. Patients on anticoagulant therapy with warfarin should be properly instructed about the composition of their diet. Balanced intake of relatively lower amounts of vitamin K is recommended and caution should be given to potentially risky foods (vegetables, esp. cruciferous, rapeseed and olive oil, avocado, kiwi, parsley, spring onions, etc.). Vitamin K is also produced by intestinal bacteria and there are clinical studies which have evaluated the effect of diet as insignificant. However, routine clinical practice suggests monitoring and informing of the patient.

Food supplements are available in pharmacies, but also frequently in online stores. Any food supplements may cause some of the above-mentioned interactions. The situation is perhaps even more complicated than with administration of the drug, for the following reasons:

a) dietary supplements do not have a standardized and guaranteed content of active substances and therefore sometimes the interaction occurs and sometimes not

b) the quality (content of ingredients) may vary a lot, depending on the manufacturer
c) food supplements are not as extensively tested as drugs and their interactions are often not mentioned in the literature
d) patients do not always tell their physicians what dietary supplements they use and how frequently

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