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GENERAL PHARMACOLOGY

An outline for 3rd year students of dental medicine

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1. General Pharmacology

1.1. Basic Principles

What is the nature of the drugs? The drug is a molecule that is able to change the function of an organism. Thus it cures or prevents a disease(s).

How does a drug act? In general, drug molecules bind to the surface of cells or to macromolecules within the cells. These macromolecules are receptors that couple with an effector system(s) generating a signal(s) for altering the function of the cell. Most of the drugs are water soluble weak electrolytes. However, the non-ionized lipophilic fraction of drugs is valuable for the therapy. The action of the drug on the organism is the subject of pharmacodynamics (*What does the drug do with the body?*)

How does the drug reach the target ? Drugs should pass through several membranes in order to reach the target receptor. Once a drug had produced the therapeutic effect, the body got rid off the drug, a foreign material. The mechanisms by which the organism handles the drug is the subject of pharmacokinetics (*What does the body do with the drug?*)

1.2. Pharmacodynamics

In general, drugs bind to macromolecules in tissues and cells, and drugs act following binding to receptors. The binding is a prerequisite for the biological effects of drugs (latin: 'Corpora non agunt nisi fixata'-a particle does not act without binding).

Exceptions:

A/ those drugs that exert physical effect on the body, e.g. osmotically acting diuretic drugs

B/ those drugs that neutralize other compounds chemically, e.g. basic protamine neutralizes acidic heparin or desferroxamine chelate complex with ferric compounds

1.2.1. Receptors for drugs

Receptors are macromolecules (e.g. lipo-or glycoproteins) that, in the majority of cases, couple with effector systems generating biological signals.

Classification of receptors:

A/ Transmembrane enzymes

Proteins embedded the cell membrane are the transmembrane proteins that have an extracellular part (receptor) and an intracellular part (enzyme). Drugs or endogenous hormones bind to the extracellular part and change the conformation of the receptor. This change activates the intracellular enzyme. *E.g. insulin binds to its receptor, activates tyrosine kinase and then phosphorylates intracellular amino acids.*

B/ G-protein coupled receptors

These receptors are also transmembrane receptors, however in contrast to the transmembrane enzymes, the intracellular part is not an enzyme but a signal-amplifier, G-protein. The amplified signal activates an intracellular enzyme. *E.g. adrenaline binds to adrenergic beta-receptors then the G-protein activates the intracellular adenylyl cyclase converting ATP to cyclic AMP. Cyclic AMP, the so-called 'second messenger', modifies intracellular biochemical reactions.*

C/ Ionic channels

Proteins or glycoproteins form ionic channels in the cell membrane and enable to pass certain ions. In most of the cases, drugs bind to the extracellular part of the ionic channel (except *e.g. local anaesthetics act intracellularly*) and modify the ionic flow through the channel. *E.g. the neurotransmitter gamma-aminobutyric acid enhances the flow of the chloride ion into the intraneuronal space causing hyperpolarization of the neuronal membrane.* In general, no second messenger is produced because the ion directly modifies the potential of the membrane.

D/ Intracellular receptors

Drugs and certain hormones having high lipid solubility diffuse into the cell and further to cell organelles and bind to intracellular receptors. *E.g. glucocorticoids reach the intranuclear DNA (receptor) and induce lipocortin production (effector) responsible for the decrease of inflammatory mediator production.*

E/ Other receptors: intracellular enzymes, structural proteins, ion pumps

In these cases, there are no second messengers because the change in the conformation of the receptor by the drug is the effect by itself. *E.g. intracellular enzyme: a monoamino-oxidase inhibitory drug, selegiline, inhibits the degradation of serotonin in the brain resulting in an antidepressive effect; structural protein: colchicin inhibits the polymerization of tubulin thus inhibiting migration of immunocompetent cells; ion pump: digoxin inhibits Na/K-ATP-ase resulting membrane depolarization and excitation of cardiac cell membrane.*

1.2.2. Effectors of drugs

Effectors are, in most cases, intracellular signal messengers: *e.g. calcium ion, cyclic AMP, inozitol-1,4,5-triphosphate (IP3), diacyl-glycerol (DG)*. A messenger activates intracellular kinases that phosphorylate proteins. The result is the modification of a certain function in the cell, e.g. muscle contraction.

1.2.3. Dose-response curves

1.2.3.1. Agonists

The effect of drugs is characterized by dose-response curves. The drug that binds to the receptor and produces an effect is called: agonist. When the drug binds to receptor and inhibits the binding of another drug or hormone (neurotransmitter) the drug is called: antagonist. The antagonist alone has no effect, that is, an antagonist by itself does not generate a biological signal.

Depicting the effect of an agonist, first, the dose or concentration of the drug is on the abscissa in a logarithmic scale. The ordinate shows the magnitude of the effect produced by the agonist, in most cases, in percentage. Enhancing the dose the agonist produces increase in the effect, and the dose-response curve has an S-shape. The maximum of the S-shaped curve (E_{max}) asymptotically fits to 100 % in the ordinate. This E_{max} is labelled with alpha (α) and also called: efficacy. The known most effective drug has $\alpha = 1$.

Besides the efficacy, another important parameter of the agonist drug: potency. This is the dose or concentration of the drug that produces 50 % of E_{max} effect and abbreviated as ED_{50} (50 % effective dose) or EC_{50} (50% effective concentration). The negativ logarithm of ED_{50} is pD_2 ,

the most frequently used value for characterization of the potency of a drug. The pD_2 points to the strength of agonist binding to the receptor, that is, the affinity of the drug.

Examples: acetylcholine contracts the smooth muscle of the guinea pig isolated ileum. Butyrylcholine exerted only 40 % of the maximum contraction (E_{max}) induced by acetylcholine. Thus acetylcholine is an agonist (full) with an $\alpha=1.0$, butyrylcholine is a partial agonist with $\alpha=0.4$. Acetylthiocholine produced the same E_{max} as acetylcholine. Acetylthiocholine is also a full agonist with $\alpha=1.0$. However, the pD_2 value of acetylcholine is 7 and 5 in the case of acetylthiocholine. This means that the EC_{50} , that is the concentration produced 50 % of E_{max} , is smaller in the case of acetylcholine (10^{-7} mol/l) than that of acetylthiocholine (10^{-5} mol/l). Thus acetylcholine possesses 100 times more affinity to the ileal muscarinic receptors than acetylthiocholine.

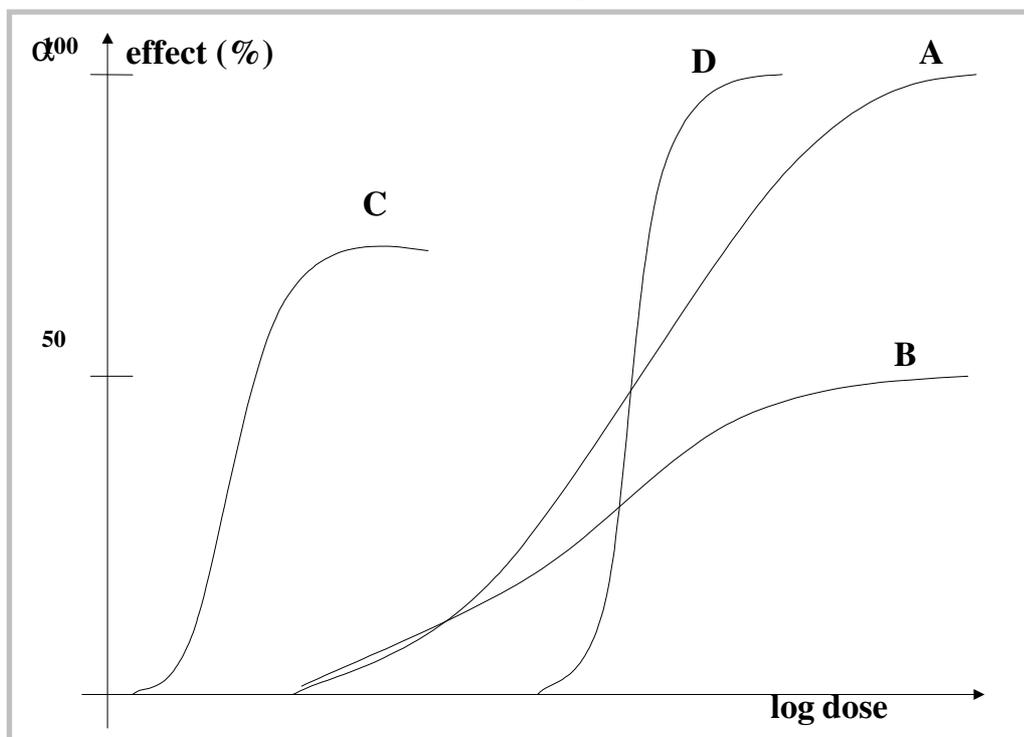


Fig 1. Compare the four dose-response curves! Answer: drug A is an agonist, drug B is a partial agonist. Drug A and B have similar potency (similar EC_{50} or PD_2), however, drug A has higher efficacy (E_{max} or α) than drug B. The potency of drug C is larger than drug A and B. The efficacy and potency values of drug D are similar to drug A, while the dose-response curve of drug D is steeper.

1.2.3.2. Antagonists

Antagonists –by definition- have potency but lack of efficacy. Competitive antagonists reversibly bind to the receptor and the enhancement of the dose of agonists displaces the antagonists from the receptor.

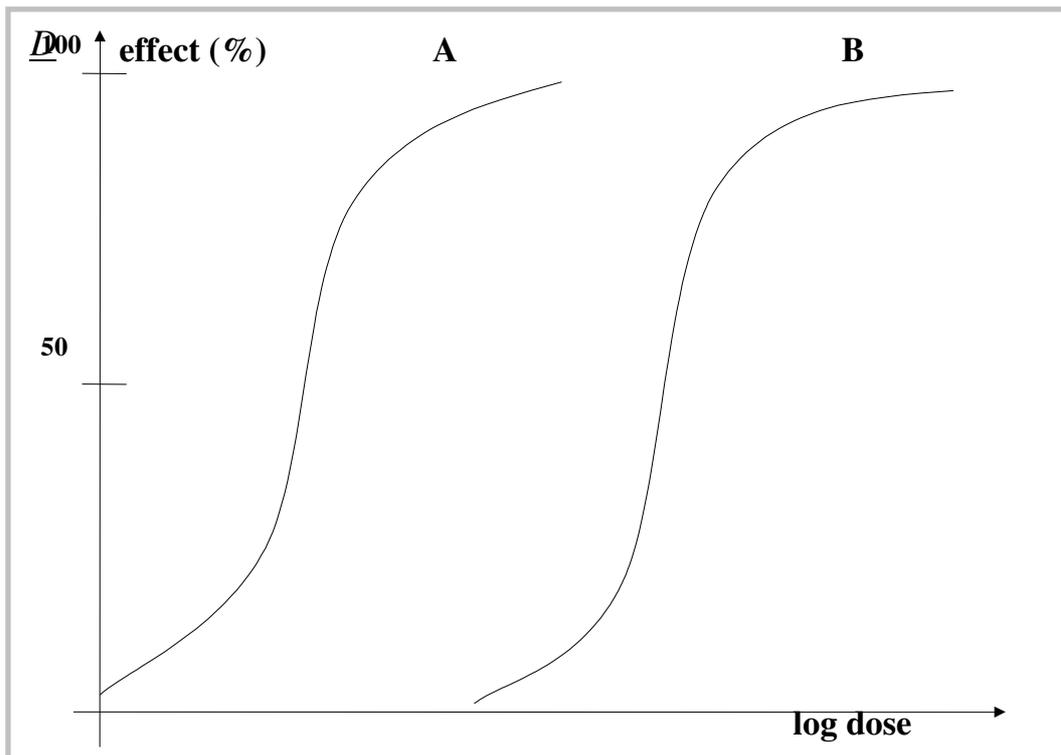
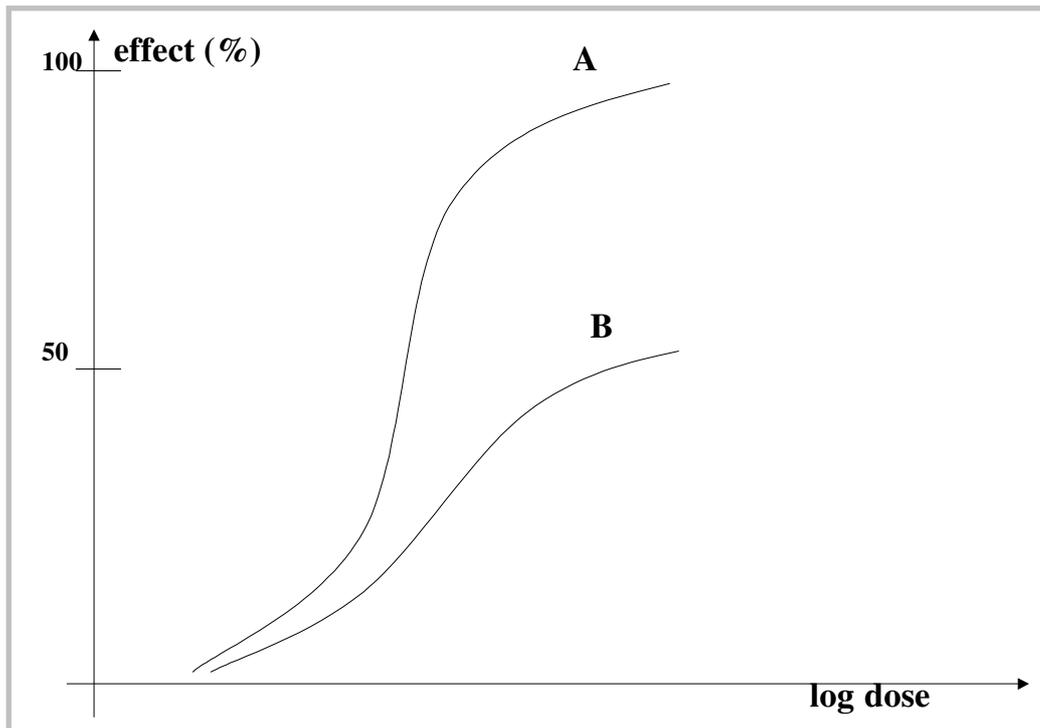


Fig 2. In the presence of a competitive antagonist (B) the dose-response curve of agonist (A) is displaced PARALLEL to the right. E.g. adrenaline (agonist) dose dependently enhances the frequency of the heart (A). In the presence of a beta receptor antagonist, propranolol (antagonista), the effect of adrenaline on the frequency is the same but only at higher doses (B). Important: in the case of curve B the Emax value is the same as in curve A that is, higher doses of the agonist is able to produce the same maximum effect when a competitive antagonist is present.

Non-competitive antagonists bind strongly- in a partly or completely irreversible manner- to the receptor. In the presence of a non-competitive antagonist even the higher doses of an agonist are not able to produce maximum effects.



3. In the presence of a non-competitive antagonist (B) the dose-response curve of the agonist (A) is displaced in a NON-PARALLEL fashion. E.g. histamine (agonist) dose dependently enhances the acid production of the gastric mucosa (A). In the presence of omeprazole (antagonist) even the largest doses of histamine are not able to produce maximum acid production (B).

1.2.3.3. Therapeutic index

Large doses of drugs may produce adverse or toxic effects. The safety of a drug depends upon the size of the margin between the effective dose (ED) and lethal dose (LD), the latter of which can be measured only in animals. The results are then drawn on two graphs: one for effectiveness and one for lethality. From these graphs the amount of drug required to produce the desired effect in 50 % of animals (ED_{50} , see above), and the amount required to kill 50 % of the animals (LD_{50}), can be read. The safety, or therapeutic index (TI) can be obtained by determining the ratio LD_{50}/ED_{50} . The larger the value of this ratio, the safer is the drug. Alternatively, therapeutic window or margin of safety are also used as terms instead of TI. TI should be larger than 1 and is valid with a note: the route of administration of the drug (e.g. oral, parenteral). *Drugs with large TIs are: penicillin (antibiotic), beta adrenergic receptor blockers, thiazide-type diuretic drugs. Drugs with small TIs: digoxin (cardiotonic), fenitoin (antiepileptic), theophyllin (antiasthmatic), lithium (antimaniac drug).*

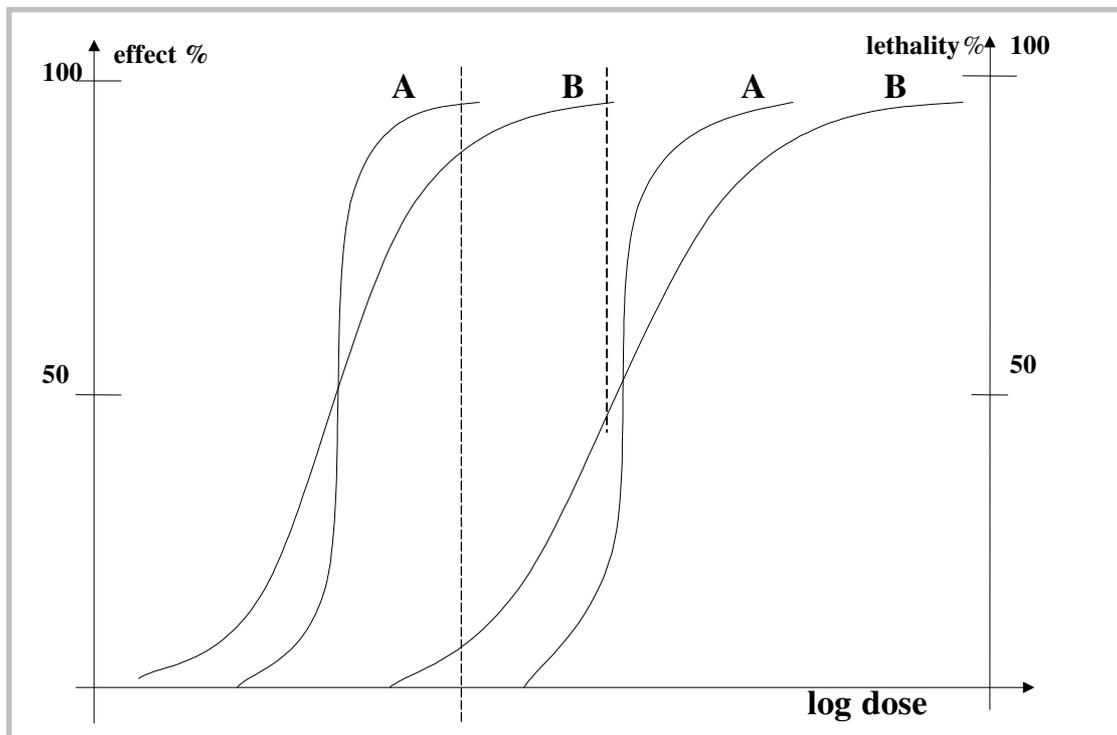


Fig 4. Compare the dose-response and dose-lethality curves of drugs A and B ! It can be seen that the therapeutic index of drugs A and B are similar based on the ratio of LD_{50}/ED_{50} . This TI ratio has limitation because the effective (therapeutic) concentrations of drug A cause no death while doses of B –close to E_{max} values– exert considerable lethality (see dashed line). Therefore, as a TI, the ratios of LD_{25}/ED_{75} and/or LD_1/ED_{99} for determining the safety of drugs are also used.

1.2.4. Individual differences in response to drugs

Different individuals have different amounts of endogenous hormones and neurotransmitters. In addition to this, their concentrations may change in time in a given person. Possibly, this is an important reason for alteration the number/activity of target receptors/effectors by drugs. Statistically, the majority of individuals responds with the desired effects, in a minority the given drug may produce too small or too large effect. The frequency distribution curve for

the responses of a population to a drug shows a Gaussian-type distribution. However, the reason of these altered reactions is still not exactly known. Large doses of agonists and antagonists can result in long-lasting changes in the receptor/effector systems. Experimentally, agonists cause a decrease (down-regulation) while antagonists cause an increase (up-regulation) of receptor/effector systems.

In general, chronic (long-lasting) administration of drugs may produce down-regulation with decreased biological effect, as a consequence. In another word, this is tolerance that can be pharmacodynamic or pharmacokinetic (pharmaceutical and psychologic tolerance is not discussed here). Pharmacodynamic tolerance can arise from 1/ decreased endogenous concentration of ligand/s, 2/ decreased number of receptors or 3/ decreased effector signal. *The mechanism 1/ is rare and occurs when the effect of a drug is mediated by an endogenous ligand. The exhaustion of noradrenaline in the sympathetic nerves following repeated administration of ephedrine is an acute pharmacodynamic tolerance (tachyphylaxis). Mechanism 2/ is more common. Decreased number of gamma-aminobutyric acid receptors can be detected following long-term use of benzodiazepine-type anxiolytic drugs. In this latter case more and more amount of drug is necessary for producing the same anxiolytic effect. Mechanism 3/: as an effector, cyclic AMP is decreased in a morphine abuser, the number of opiate receptors are unchanged. This type of drug tolerance can be so 'severe' that a morphinist (heroinist) may take the narcotic over the lethal dose for achieving an euphoric state.*

Up-regulation is relatively uncommon. *E.g. Chronic use of beta-receptor blocking drugs may result in the enhancement of the receptors in the heart. Sudden stop of the drug is dangerous when the endogenous sympathetic tone is enhanced and the so-called 'rebound hypertension' threatens the patient's life.*

The above-mentioned changes in the individual responses to drugs are of pharmacodynamic types. The pharmacokinetic differences are discussed later (Chapter 1.3).

1.2.5. Dependence

Drug dependence describes the state when drug-taking becomes compulsive and the patient can not 'get rid off' the drug for some psychological or somatic reasons. Upon sudden withdrawal of the drug psychological and/or somatic symptoms arise. Most often, drugs acting on the central nervous system cause psychological or somatic dependence. Although it is clear that these drugs change the concentrations of endogenous neurotransmitters/mediators in the brain, the exact mechanisms of dependence is not known. Drugs causing

somatic dependence are: *e.g. sedative-hypnotics, anxiolytics, opiate analgesics*; those are associated with psychological dependence: *e.g. amphetamines, cocaine, tetrahydrocannabinol (mostly not drugs but illegal narcotics)*. Almost all drugs that induce dependence are associated with tolerance, and possibly, this one important factor that results in dependence and abuse of drugs.

1.3. Pharmacokinetics

Pharmacokinetics is defined as 'what does the body do with the drug'. The body directs the drug to the receptor site and then eliminates the drug from the site of action. Most often the drugs are administered orally (per os). Other routes of administration: transcutaneous, intracutaneous, subcutaneous, intramuscular, intravenous, intraarterial injections, and also can be rectal, sublingual, rarely intralumbal, epi-or peridural, subarachnoideal. In the dental practice, localanaesthetics are added in a form of a special submucosal injection and, according to the type of application, it can be infiltrative or conductive type of anaesthesia.

Following administration, two main pharmacokinetic events determine the route of a drug: invasion and evasion. Invasion involves the absorption and distribution, evasion involves biotransformation and excretion of the drug. Instead of evasion, the term 'elimination' is more frequently used in the literature.

1.3.1. Absorption

Most of the drugs act systemically, therefore, the drug should diffuse from the site of administration to the blood and then to the target receptor. This is the classical definition of absorption. However, some drugs are administered close to the receptor site and these drugs do not reach the circulation. These are local (topical) drugs: *e.g. ocular drops, some inhalational anaesthetic drugs, localanaesthetics, dermatological ointments*.

Drugs must pass the membranes of different cells (intestinal mucosa, vascular endothelium, neurilemma) in order to achieve the target receptor. The lipid solubility of the drug determines this passage. The fraction of the drug that passes through a membrane depends on the amount of lipid soluble non-ionized concentration of the drug at a particular proton concentration in the surroundings of the membrane. The majority of drugs are either weak acids or weak bases thus, at different pH, the ratio of ionized and non-ionized forms of a certain drug is different. It should be emphasized again that the lipid soluble non-ionized form of a drug crosses the membranes.

Calculate the lipid soluble, non-ionized fraction of a drug!

pKa value of a drug means the pH at which half of the drug is present in ionized and the other half is in non-ionized form.

According to the Henderson-Hasselbalch equations

For a weak acid :

$$\text{pH} = \text{pKa} + \log \left(\frac{\text{ionized concentration}}{\text{non-ionized concentration}} \right)$$

E.g. aspirin has a pKa of 3.5, the pH of the gastric juice is 2.5. The ratio of log ionized/non-ionized concentration is 0.1 (antilog -1). This means that about one-tenth (10 %) of the total aspirin is in ionized form and the remaining 90 % is in the non-ionized form. Because the non-ionized form is the lipid soluble form, aspirin is well absorbed from the gastric mucosa.

For a weak base:

$$\text{pH} = \text{pKa} + \log \left(\frac{\text{non ionized concentration}}{\text{ionized concentration}} \right)$$

E.g. pKa of lidocaine is 8, the pH of gastric lavage is 2.5. The ratio of log non-ionized/ionized concentration is 0,000003 (antilog-5,5). This means that the fraction of non-ionized lidocaine is only about 1/billion in relation to the ionized form of the drug. Therefore, lidocaine is practically not absorbed from the gastric mucosa.

Besides lipid solubility absorption of drugs is determined by 1/ the magnitude of the surface participating in absorption (intestinal larger than gastric and thus intestinal absorption is faster), 2/ the time of contact with the absorptive surface (in enteral inflammation smaller, thus less drugs are absorbed), 3/ the speed of blood flow (in enteral ischaemia smaller, thus less amount of drug is absorbed), 4/ bioavailability of the drug (the fraction of the drug reaching the systemic circulation).

1.3.2. Distribution

1.3.2.1. Binding of drugs to plasma proteins

Following absorption drugs are distributed in the body and reach not only the target receptor but other sites in the tissues. After peroral administration, a drug is absorbed first, and as a result, it appears in the blood (except e.g. some drugs used to treat obstipation). In the blood stream acidic drugs mainly bind to albumin and those with basic characters, to alpha-1 acid glycoproteins. These bindings are called 'silent bindings' without causing effect and serve as stores

for drugs. The free and protein-bound fractions of drugs are in a dynamic equilibrium. This practically means that when the concentration of the free drug is gradually diminished in the blood (the drug leaves the blood and diffuses toward the target receptors) new drug molecules are liberated from protein binding. When the proteins are decreased under pathological conditions (albumin in liver cirrhosis) or increased (alpha-1 acid glycoprotein in infections), the bound fraction of the drug is decreased or increased, respectively. An important consequence is that the effective free concentration of a particular drug may change while the sum (free+bound) remains unchanged. Diagnostic means can measure the sum, and thus, the protein concentration should be measured in order to assess the free concentration of the drug. The amount of the free concentration of the drug is valuable for the therapeutic effect, that is, the fraction of the drug in the blood plasma that diffuses into the tissues toward the target receptor.

Drugs bound more than 90% to plasma proteins are: e.g. warfarin (anticoagulant), diazepam (anxiolytic), phenytoin (antiepileptic). Drugs that do not bind considerably to plasma proteins are: digoxin (cardiotonic), gentamycin (antibiotic), theophylline (antiasthmatic).

1.3.2.2. Tissue distribution

The fraction of free drug (not bound to plasma proteins) diffuses in the intercellular spaces and then gains access in the surroundings of the receptor. The amount of the drug accumulating in a certain tissue can be assessed from the lipid solubility of the drug and from the magnitude of circulation in the tissue. *E.g. a hypnotic/anaesthetic drug, thiopental is highly lipophilic and concentrated in the brain known to have large lipid content and high speed of blood flow. In contrast, gentamycin is a hydrophilic, polar compound and hardly penetrates the cell membranes. Gentamycin accumulates in the skeletal muscle being rich in porous capillaries through which small and non-lipophilic compounds can easily pass.*

In the tissues drugs bind to different macromolecules among which the so-called 'primary binding site' is the target receptor. There are 'secondary binding sites' (structural proteins) that do not necessarily mediate effects. These are also considered as 'non-specific binding sites' (similar to plasma protein binding). E.g. some antidepressive drugs –upon leaving the blood stream– strongly bind to 'non-specific binding sites' in the tissues. This kind of binding can be so strong that the concentration of the antidepressive drugs remains high in the tissues while they completely disappear from the blood. Practically, the free (unbound) concentrations in the blood will not be proportional to the therapeutic effect of the drug. For estimating the therapeutic effect in these cases the 'apparent volume of distribution' (V_D) is used. This pharmacokinetic parameter is the virtual amount of fluid in that the drug is equally distributed in relation to the

concentration in the blood plasma. This water space is virtual because the equal distribution is only an assumption and not a measured variable. As you see later, V_D is a calculated value that overwhelms even the total amount of body fluid (50-60 liters).

Calculation of V_D

V_D (apparent volume of distribution) = amount of the drug added (mg) divided by the concentration of the drug in blood plasma (mg/l).

V_D is a virtual amount of fluid expressed in liter in that the distribution of a drug is homogenous. *E.g. heparin stays in the blood stream because V_D of heparin equals to the amount of the blood (3-5 liters), lidocaine has a V_D of 10 liters (it is distributed in the inter/intracellular space with fast displacing kinetics from the receptor and quick metabolism). Some antidepressants and antimalarial drugs strongly bind to tissues with V_D s more than 200 liters supporting the virtual nature of this pharmacokinetic parameter.*

Example: 5 g ethanol results in 0.1 g/l maximum concentration in the blood (1 per ten thousand part ethanol equals 10 ml beer; 8 times of this amount is at the border of penalty on the Hungarian road). Using the equation this corresponds to 50 l V_D for ethanol (5 g divided by 0,1 g/l). Consequently, ethanol is equally distributed in the total body water.

Another example: the antimalarial chloroquine strongly binds to tissues. 3 mg of chloroquine results in 30 microgramm/l concentration in the blood. $V_D=3 \text{ mg}/0,03 \text{ mg per liter}$. V_D value of chloroquin is 100 liters. Chloroquine binds to proteins outside the blood and this means that, in the case of poisoning with chloroquine, removal of the drug from the blood (dialysis) will be unsuccessful. In contrast, poisoning with sodium salicylate can be successfully treated with dialysis, because the V_D of this antiinflammatory drug is 7, that is, most of the drug is in the blood.

1.3.3. Metabolism of drugs (biotransformation)

Most of the drugs are xenobiotics and the organism 'intends to get rid off' them by converting lipid soluble drugs to water soluble products. Following this biotransformation the drugs are more easily excreted from the body. The main site of biotransformation is the liver, others sites are *e.g. gut wall for contraceptive steroids, blood plasma for suxamethonium (neuromuscular blocking drug).*

Metabolism of drugs in the liver takes place in the Phase I. and Phase II. metabolic reactions. *There are some drugs- e.g. gentamycin- that are excreted*

without metabolisms. *Theophylline is converted only in the Phase I, morphine only in the Phase II. reactions.* The majority of drugs are transformed in both the Phase I. and Phase II. reactions.

Phase I. chemical reactions are: e.g. oxidation, reduction, hydrolysis. Oxidation is one of the most frequent reactions in that a cytochrom P450 family of enzymes plays the major catalytic role. Phase II. reactions are mostly conjugations. In these reactions, endogenous glucuronate, sulfate, acetyl groups are transferred to drugs.

Both Phase I. and Phase II. metabolic reactions result in more polar compounds but this does not necessary mean a decrease of the effect compared to the 'parent' compound. *Morphine is an example that retains its analgesic effect following conjugation.* Sometimes drugs become effective only after biotransformation. These are 'prodrugs' (e.g. *enalapril is oxidized into an effective antihypertensive drug*). Others are transformed into toxic metabolites such as the antipyretic drug, *paracetamol (by a Phase I. chemical reaction)*.

In general, the drugs become inactive and less lipophylic compounds following biotransformation in Phase I. and II. metabolic reactions.

1.3.3.1. Genetic differences in enzyme activities

Some metabolizing enzymes show considerable variations among individuals. Individual differences in metabolic activity are called as genetic polymorphism. *The antituberculosic drug, isoniazid, is metabolized by acetylation. In some patients this reaction is so fast that they are called as 'fast acetylators' while others are 'slow acetylators'. In the latter case the elimination of isoniazid is slow and the appearance of toxic neuropathy, a severe adverse effect of the 'parent' compound, is frequent. Suxamethonium is a skeletal muscle relaxant and metabolized by plasma (pseudo) cholinesterase enzyme. Prolonged apnea may occur after the administration of this neuromuscular blocking drug because of the presence of an abnormal cholinesterase. It has been estimated that about 1 in 2800 persons possess this atypical esterase which hydrolyses suxamethonium much more slowly than normal cholinesterase.*

1.3.3.2. Effect of liver diseases on biotransformation

In hepatic failure, drugs may be metabolized more slowly than normal, and as a result, the amount of active drug in the body declines more slowly than usual. This leads to an increased and prolonged effect. *The above mentioned plasma cholinesterase is again a good example. Plasma cholinesterase is synthesized by the liver and responsible for the hydrolysis of suxamethonium. Since the presence of liver disease reduces the production of cholinesterase, it also affects the rate of breakdown of suxamethonium. Hence, the duration of*

neuromuscular block including apnea is prolonged. Another example is the toxic effect of morphine. The decreased metabolism of morphine enhances the danger of life-threatening respiratory depression.

1.3.3.3. Induction and inhibition of metabolic enzymes

Some drugs can enhance or diminish the activity of enzymes responsible for biotransformation of the drugs. These are independent of the main therapeutic effects of the drugs. Examples: 1/ *Phenobarbital (hypnotic drug) induces Phase I. and II. metabolic enzymes in the liver. Consider that situation when the patient is treated with phenobarbital and warfarin at the same time. As a consequence, the inactivation of warfarin (anticoagulant) will be enhanced resulting in an ineffective anticoagulation at normal doses and, the risk of thrombosis is augmented.* 2/ *Cimetidine (antiulcer drug in the gastrointestinal tract) inhibits metabolic enzymes and increases the risk of warfarin overdose when the two drugs are added together. Bleeding appears as an adverse effect. Although, drug-induced changes in metabolism are considered as unwanted effects, both induction and inhibition of drug metabolisms may be used therapeutically. E.g. 1/ jaundice of premature infants can be treated with phenobarbital by enhancing the conjugation of bilirubin with glucuronate. Bilirubin glucuronate is more water soluble than bilirubin and excreted easily through the kidney.* 2/ *Combination of drugs may contain enzyme inhibitors. Treatment of Parkinson disease requires L-dopa and the concentration of L-dopa in the brain can be increased by combining it with a dopa decarboxylase enzyme inhibitor. The inhibitor, carbidopa, decreases the metabolism of L-dopa outside the central nervous system. In the brain, however, L-dopa is freely converted to its active metabolite, dopamine, that is necessary for the treatment of Parkinson disease. Other enzyme inductors: e.g. rifampin (antibiotic), carbamazepine (antiepileptic), phenytoin (antiepileptic); other inhibitors: e.g. erythromycin (antibiotic), ciprofloxacin (antibiotic), ketoconazole (antimycotic).*

1.3.4. Excretion of drugs

In general, drugs are excreted by the kidney with or without biotransformation. Molecules with lower than 70 kD are freely excreted via the filtration mechanism. *Aminoglycoside antibiotics or the cardiotonic digoxin are excreted without metabolic conversions.* The rate of glomerular filtration largely influences the excretion of drugs without metabolic conversion. Failure of renal function may decrease the excretion of these drugs to such a great extent that toxic effects appear even at normal therapeutic doses. Conversely, the majority

of drugs considerably lose their effectiveness during metabolism and thus, the decrease in the rate of glomerular filtration may not significantly influence the therapeutic effects.

The mechanism of excretion in the kidney also involves tubular secretion and tubular reabsorption. Strongly acidic or basic drugs are actively secreted in the tubuli (*e.g. penicillin*). Tubular reabsorption helps the diffusion of lipid soluble, non-ionized molecules back to the circulation. *E.g. overdose with acidic drugs (e.g. salicylates) can be treated with sodium bicarbonate. Bicarbonate ion turns the urine pH to more basic and increases the ionized fraction of salicylate. This treatment inhibits the tubular reabsorption of acidic salicylate and prevents the development of severe salicylate poisoning.*

Some drugs are excreted through the biliary tract. Oestradiol (component of contraceptive pill), ampicillin (antibiotic) are excreted in this way and finally, these drugs appear in the stool. Intestinal bacteria may split down conjugates (glucuronate, sulfate) from the drugs rendering them lipophilic again and thus, the drugs can be reabsorbed into the blood through the mucosa of the bowel. This is the 'enterohepatic recirculation', a mechanism that is able to delay the elimination of drugs from the body. Broad spectrum antibiotics decrease the physiological bacterial flora in the bowel that are necessary for an effective 'enterohepatic recirculation'. *When amoxicillin (antibiotic) is used together with oral contraceptives, the oestrogen component of the combined contraceptive pills is decreased in the blood leading to ineffective contraception and, sometimes, to pregnancy.*

Rarely, drugs are excreted *e.g.* into the saliva (*metronidazole-chemotherapeutic*), into the exhaled air (*halothan-general anaesthetic*) or into the breast milk (*diazepam-anxiolytic*). The fetus is more sensitive to drugs than the mother. A drug that causes only a mild sedative-anxiolytic effect in the mother may cause severe respiratory depression in a breast-feeding child.

1.3.5. Pharmacokinetic parameters; adjusting the dose of drugs

Before prescription, it is important to consider the reactions of an individual to a certain dose of a drug. In most cases, however, it is not necessary to calculate the exact dose: textbooks contain the usual doses, the frequency and the duration of administration. It is relatively infrequent that a patient develops an unusual extreme reaction to a drug except when a severe allergic reaction appears: an anaphylactic shock. In practice, the elder and very young patients may develop larger effects to the usual doses of drugs. They require the calculation of the exact dose. Similarly, liver and kidney diseases may also require the adjustment of drug doses. This is especially important in the case of drugs with low therapeutic index (*e.g. digoxin-cardiotonic*) and, in these cases, the calculation of the dose is obligatory. The following pharmacokinetic

parameters are used : half life, bioavailability and the V_D (the latter is discussed in Chapter 1.3.2.2. (Tissue distribution)).

1.3.5.1. Half life

Half life ($t_{1/2}$) is the duration expressed in minutes or hours that is necessary for the decrease of plasma concentration of a drug to the half. It is evident from this determination that this half life is an elimination half life (others: half lives of absorption, distribution are not used in the following calculations). Half life gives the information about the frequency of the administration of the drug, that is, once a day, twice a day etc. In most cases the frequency of administration is more than once a day in order to provide stable therapeutic concentration in the blood. Using this method the physician avoids subtherapeutic or –the opposite- toxic level of drugs in the organism.

Elimination half life shows the speed of disappearance of a drug from the body and this pharmacokinetic phase follows the distribution phase in time. The phase of elimination following the peroral administration of a drug can be seen in the time-plasma concentration curve.

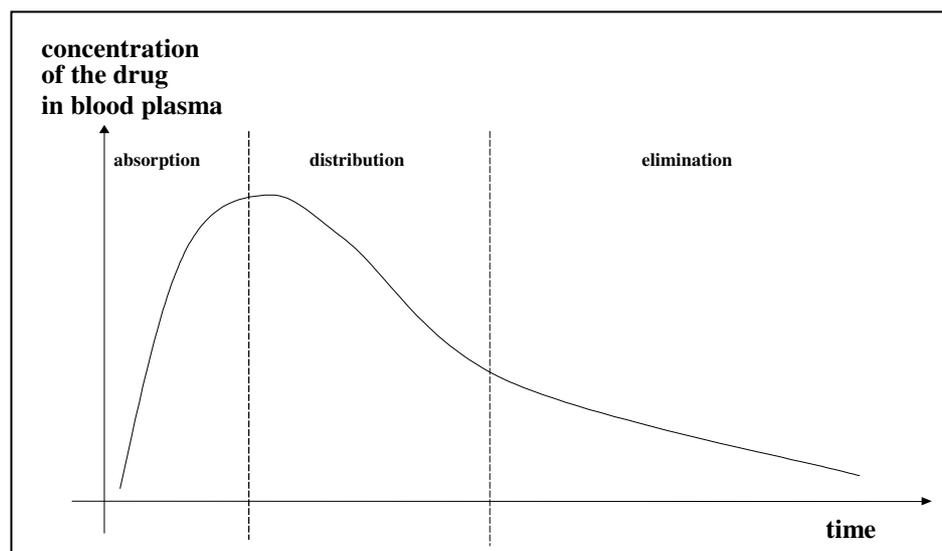


Fig 5. Changes of plasma concentration in relation to the time after peroral administration of a drug. Absorption increases the concentration of the drug in the blood. Then the distribution in the tissues decreases the concentration. The third phase (elimination) represents a slower disappearance of the drug from the blood (involving biotransformation and excretion).

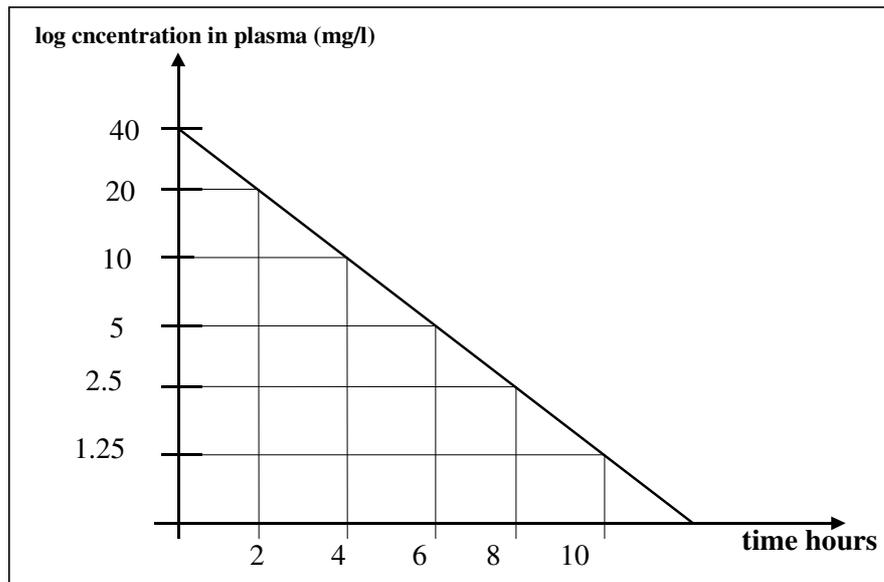


Fig 6. Elimination phase (the third phase) from Fig 5. is depicted by the logarithmic conversion of the scale in the ordinate. $t_{1/2}$ can be easily read and constant. The elimination half life of this drug is 2 hours.

As it is evident from Fig 5., elimination is the third phase of the curve. Fig 6. shows that the exponential characteristics of the elimination phase can be converted into linear if the ordinate contains logarithm of concentrations. With this conversion, the elimination $t_{1/2}$ of the drug can be easily calculated.

Comparing the plasma concentration of two drugs with different $t_{1/2}$, the drug with larger half life produces larger peak plasma concentration. Important: both drugs are added at the same time interval in Fig 7! A and B drugs are administered 5 times. Drug B has larger $t_{1/2}$ than drug A and hence, the peak concentration of drug B is larger than drug A following all the five administration. Consider that after the 5. administration, the peak plasma concentration is similar to that obtained after the 4. administration. It is true for both drugs. This means that any drug reaches the steady-state plasma concentration after the 5. dose.

Steady-state plasma concentration is a constant level of the therapeutic concentration at around the concentration fluctuates after the 4.-5. dose (see dashed lines in Fig7.). If we repeat the administration of a drug every $t_{1/2}$, the rule is: after the 1. dose 50 % of steady state concentration is completed, after the 2. dose 75%, after the 3. dose 88%, after the 4. dose 94%, after the 5. dose 97 %. Important: this rule is independent of the magnitude of the dose. Practically: for achieving the steady-state plasma concentration we should wait 5

times $t_{1/2}$ of the given drug. Steady-state can not be reached sooner by increasing the dose or frequency of administration.

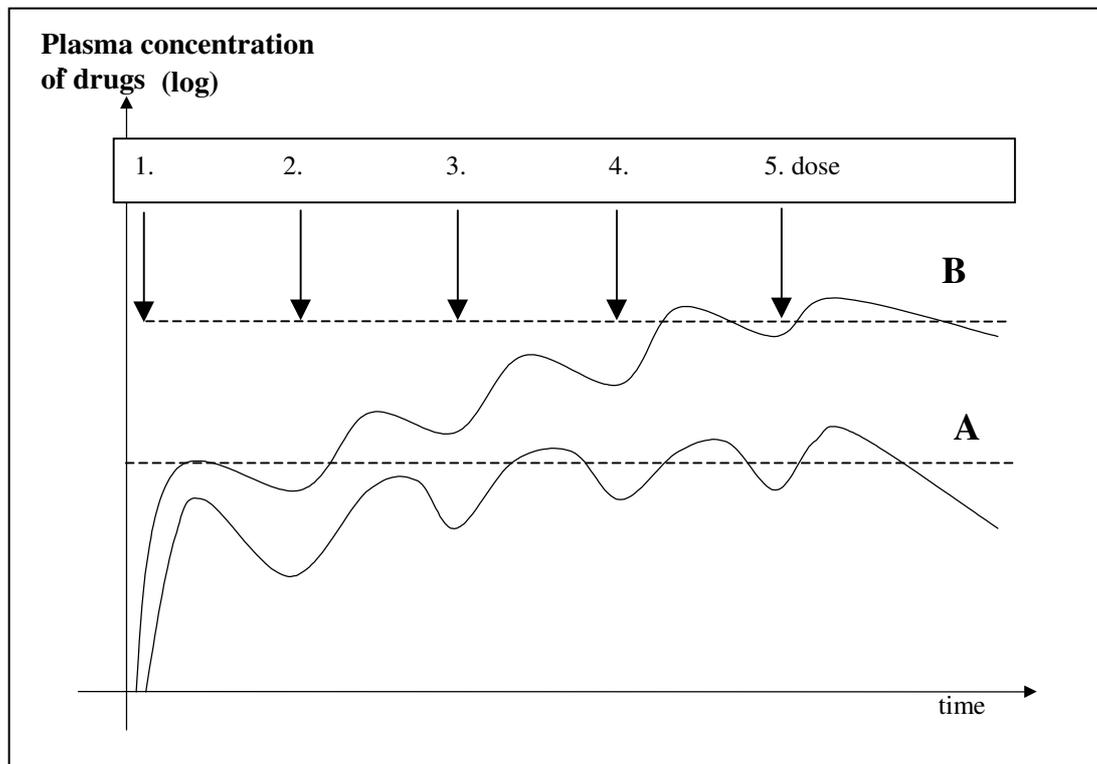


Fig 7. Drug A has smaller $t_{1/2}$ than drug B. When both drugs are administered at the same time, drug B with larger $t_{1/2}$ reaches always larger peak concentration compared to drug A. Both drugs reaches the steady-state concentration after the 5. dose (dashed lines represent the estimated steady-state concentrations, further comment, see text)

1.3.5.2. Clearance

Clearance (Cl) is the volume of blood or plasma that is cleared from the drug per unit of time.

Equation:

$Cl = V_D \times K_{el}$, where V_D is the apparent (virtual) volume of distribution, K_{el} is the elimination constant of the drug.

Because $t_{1/2} = 0,693/K_{el}$, inserting the above equation:

$$t_{1/2} = 0,693 \times VD / Cl$$

If a drug is excreted via the kidney after metabolization, Cl is the sum of metabolic clearance (Cl_m) and renal clearance (Cl_r).

1.3.5.3. Bioavailability

Bioavailability (abbreviated by F) means the fraction of the drug that reaches the systemic circulation. Logically, F value is 1 following injection of a drug directly into the blood stream (intravenous or intraarterial). In this case 100% of the drug appears in the systemic circulation.

Peroral (per os) administration of a drug results in F lower than 1. In this case F shows some inter- and intraindividual variability depending on the actual pH in the gastrointestinal tract and on the blood flow, especially in the liver. In general, the pharmacodynamic property of a drug is constant while the pharmaceutical properties –that is, other constituents such as diluents, granulating, lubricating, coating materials- may influence bioavailability. One of the most important parameter that profoundly influence F is the 'first pass' effect. This 'first pass' is related to metabolism that affects the blood concentration of a drug administered per os. (peroral administration is the most important type of drug intake: approximately 80 % of all the treatments are carried out with oral drugs). 'First pass' involves a passage through the liver and an immediate metabolism of a certain fraction of drugs before reaching the systemic circulation. *E.g. lidocaine and nitroglycerin (antianginal drug) are largely eliminated by liver metabolism. The extent of 'first pass' metabolism is so expressed in the case of these drugs that the F value is close to zero. Therefore, lidocaine has no peroral formulation and nitroglycerin can be administered only as a sublingual tablet. Nitroglycerin is highly lipid soluble and quickly absorbed from the buccal mucosa bypassing the portal circulation of the liver. Sublingual nitroglycerin directly reaches the vena cava, that is the systemic circulation. Rectal administration of drugs also bypasses the portal circulation because the circulation of the lower two-third of the rectum is not connected anatomically to the vena portae.*

Bioavailability (F) is calculated by using the dose of the drug and the amount that reached the systemic circulation. F value is important for

determining the interval between two doses, that is, the frequency of drug administration.

Interval between two doses of a drug = $F \times \text{dose} / Cl \times \text{plasma concentration of the drug}$

1.4 Adverse effects of drugs

Any substance which exerts useful therapeutic effects may also produce adverse (unwanted) effects. Indeed, adverse reaction to drugs are directly responsible for about 5 % of hospital admissions (~0.5 % death). In dental practice, adverse reactions to drugs appear to be less common than in medical practice, but they can still represent a significant problem. The dentist may be the first to observe an adverse effect produced by a drug prescribed by a general practitioner; *e.g. ulceration in the mouth that accompanies agranulocytosis*. On the other hand, as part of dental treatment, the dentist may prescribe a drug to which the patient reacts adversely, *e.g. antibiotics*. The drugs most often involved are *e.g. anticoagulants, antihypertensives, non-steroidal antiinflammatory drugs, digoxin, corticosteroids, cytotoxic drugs*.

Adverse effects are commoner in neonates and the elderly, and women appear to be more at risk than men (reason is not known). Patients with a history of allergy are prone to develop allergy to several different drugs. Reduced elimination of drugs (*e.g. liver or kidney diseases*) and even racial and genetic factors may predispose to adverse reactions.

There are two main types of adverse reactions to drugs : type A and type B reactions. As discussed in Chapter 1.2.3.3. (Therapeutic index), overdose of a drug may produce adverse or even severe toxic effects (or the most severe: lethality). These are type A, dose-dependent adverse/toxic/lethal effects. Type B adverse reactions are relatively rare –but often more severe– and they are dose-independent.

Type A reactions are reaction that would be expected from the known pharmacology of the drug; *e.g. antihistamines (H₁ blockers) prevent or cure allergic responses. In addition, in larger doses, antihistamines have sedative effect in central nervous system, and this may be unwanted. Intolerant patients (see Ch. 1.2.4) may develop sedation to small, therapeutic doses of antihistamines*. There are not only pharmacodynamic type A adverse effects. Pharmaceutical manufacturing (differences in formulations of drugs) or pharmacokinetic variabilities (differences in absorption, distribution, biotransformation, excretion) are also responsible for dose-dependent adverse reactions.

Although type A adverse effects are dose-dependent and predictable, the diagnosis of these effects is relatively difficult. Because organs have limited

number of responses to noxious stimulæ, physical examination rarely allows distinction between disease or drug-induced adverse reactions. Certain forms of discolouration of teeth or mucosal tissues are associated with *e.g. chlorhexidine*(disinfectant), *iron preparations*, *tetracyclines* (antibiotics), *oral contraceptives*, *metals* (copper, mercury, lead, silver).Gingival overgrowth can be a frequent adverse effect of *e.g. cylosporin* (anticancer drug), *calcium-channel blockers* (antihypertensives), *phenytoin* (antiepileptic).

Type B reactions are bizarre, so-called 'idiosyncratic' reactions. This kind of drug effects are apparently unrelated to the known pharmacology of the drug. The most often adverse reaction is allergy that arises following the second exposure to the drug. Less frequent is when the patient suffers from a genetic deficiency, *e.g. haemolysis caused by dapsons* (antileprous drug) is commoner in patients with *glucose 6-phosphate dehydrogenase deficiency*. Reaction of such a patient differs from the response of an allergic patient in that, the adverse reaction appears following the first exposure to a drug.

For a dentist, the most urgent treatment is a severe, acute allergic reaction: the anaphylaxis. The clinical picture starts with flushing and itching of the skin, followed by severe difficulty in breathing due to laryngospasm and bronchospasm, and severe fall in blood pressure. The pulse is rapid, weak, and may be almost imperceptible. The condition may be rapidly fatal unless immediate steps are taken to administer adrenaline (epinephrine).

The therapy of an anaphylactic shock require some routine procedures. The patient should be placed horizontally either by adjusting the dental chair or by placing the patient on the floor. If respiratory depression is present, oxygen should be administered or mouth-to-mouth respiration given. Then 0.5 ml of 1:1000 (1 mg/ml) adrenaline solution should be injected subcutaneously or intramuscularly (NEVER INTRAVENOUSLY). This should be followed by *hydrocortisone sodium succinate*, 100 mg intravenously. Further doses of adrenaline can be given as required at intervals of 5 minutes until the symptoms begin to subside. The maximum safe dose is about 1.5 ml over a period of 15 minutes-a substantial dose that is not without its own risk. Great care must be taken to see that adrenaline is not injected into the blood vessel because it may produce a fatal ventricular fibrillation if given intravenously.

1.5. Interactions between the drugs

A drug may change the pharmacodynamic or pharmacokinetic properties of another drug when administered two drugs together. Pharmacodynamic interactions involve antagonism or synergism of the effects at the level of the receptor/effector systems of drugs. Pharmacokinetic interactions occur in absorption, distribution, biotransformation and excretion phases of drugs.

Pharmacodynamic synergism is additive *between e.g. two analgesic drugs or between an aminoglycoside antibiotic and a non-depolarizing neuromuscular blocker (skeletal muscle tone is decreased considerably)*. Potentiation means that two drugs produce an effect that is larger than the sum of the two drugs when applied them separately. *E.g. digoxin and glucocorticoids (potassium in the blood decreases), anticoagulants and acetylsalicylic acid (bleeding time is prolonged)*.

Pharmacodynamic antagonism (competitive and non-competitive) is discussed in Chapter 1.2.3.2. Functional antagonism is a type of pharmacodynamic interactions – not discussed in Chapter 1.2.3.2. This antagonism between two drugs results in opposite effects while the two drugs act on different receptors (*e.g. between sympathomimetic and parasympathomimetic drugs, between cardiac glycosides and potassium sparing diuretics*).

Pharmacokinetic interactions -at the level of absorption- can occur with the diet. Meals enhance the absorption (*e.g. metoprolol a beta blocker or spironolactone a diuretic*) or decrease the absorption (*e.g. captopril an antihypertensive drug or glibenclamide an antidiabeticum*). pH in the stomach also affects absorption (*e.g. antacids inhibits absorption of acidic drugs*). Two drugs can form a non-absorbable complex (*e.g. cholestyramine a lipid lowering drug makes complex with acetylsalicylic acid*).

Pharmacokinetic interactions at the level of distribution frequently occur with those drugs that strongly bind to plasma proteins. A drug displaces another drug from plasma protein binding (*e.g. chemotherapeutic sulfonamide displaces the anticoagulant warfarin, antiepileptic phenytoin displaces the anticancer methotrexate*).

Pharmacokinetic interactions during the metabolic processes are discussed in Chapter 1.3.3.3.

Pharmacokinetic interactions at the level of excretion involve competition of drugs for active tubular secretion (*e.g. penicillin competes with salicylates, dopamine competes with the neuromuscular blocker, neostigmine*). A decrease in urinary pH inhibits the reabsorption of basic drugs (*e.g. psychostimulant amphetamine or morphine*), an increase in urinary pH inhibits the reabsorption of acidic drugs (*e.g. barbiturate-hypnotic or salicylates*)