ABBREVIATIONS USED IN THE TEXT

ACE – angiotensin converting enzyme
ADHD – attention deficit hyperactivity disorder
ADP – adenosine diphosphate
ATP – adenosine triphosphate
BDNF – brain-derived neurotrophic factor
BP – blood pressure
cAMP – cyclic adenosine monophosphate
cGMP – cyclic guanosine monophosphate
CNS – central nervous system
COMT – catechol-O-methyltransferase
COPD – chronic obstructive pulmonary disease
CYP – cytochrome P450
DAG – diacylglycerol
DMARD – disease-modifying anti-rheumatic drug
GA – general anesthetic
GABA – gamma-aminobutyric acid
GIT – gastrointestinal tract
GUT – genitourinary tract
HCV – hepatitis C Virus
HSV – herpes simplex virus
IFN – interferon
IL – interleukin
IM – intramuscularly
INN – International Nonproprietary Name
IP_3 – inositol-triphosphate
IV – intravenously
MAC – minimal alveolar concentration
MAO – monoamine oxidase
MRSA – methicillin-resistant Staphylococcus aureus
NMDA – N-methyl-D-aspartate
NO – nitric oxide
NSAIDs – non-steroidal anti-inflammatory drugs
PABA – para-aminobenzoic acid
PD – Parkinson’s disease
PTT – partial thromboplastin time
RSV – respiratory syncytial virus
SC – subcutaneously
SNS – sympathetic nervous system
SSNRIs – selective serotonin and norepinephrine reuptake inhibitors
SSRIs – selective serotonin reuptake inhibitors
TCA – tricyclic antidepressant
TNF – tumor necrosis factor
USAN – United States adopted name
V_d – volume of distribution

SECTION 1

PHARMACOLOGY: BASIC PRINCIPLES

INTRODUCTION

Pharmacology can be defined as the science studying interaction of the chemical substances (i.e. drugs) with living systems, which is revealed as a change (activation or inhibition) of natural reactions in the organism.

A **drug** in pharmacology (pharmaceutical drug) is a chemical substance of any origin (natural or synthetic) which is used for treatment, prevention or diagnosis of diseases. Drugs also include oral contraceptives.

Each drug possesses International Nonproprietary Name (INN) and trade name.

Drugs can be divided into *original* (the drug which is done by the company which developed the drug and which is the owner of the brand name) and *generic* (i.e. copy of the original drug that is produced by other pharmaceutical company after the expiry of the patent of the original drug).

Pharmacology consists of ***pharmacokinetics*** and ***pharmacodynamics***.

Pharmacology is also divided into basic pharmacology and clinical pharmacology. ***Basic pharmacology*** covers mainly mechanisms and effects of drugs at a molecular, cellular, tissue and organ level, whereas clinical pharmacology applies the knowledge of basic pharmacology in clinical situations.

Clinical pharmacology is the science about the clinical use of drugs. It is underpinned by the basic science of pharmacology, with the added focus on the application of pharmacological principles and methods in the real world. It has a broad scope, from the discovery of new target molecules to the effects of drug usage on the whole populations.

Types of drug therapy **(*medications*):**

- *etiotropic* (*causal*), when the action of the drug is directed at the cause of the disease (for example, antibiotics in infectious diseases);
- *pathogenetic*, when the action of the drug is directed at the processes of pathogenesis of the disease (for example, clonidine causes reduction of the tone of vasomotor center in the treatment of essential hypertension);
- *symptomatic*, when the action of the drug is directed at the elimination of some symptoms (manifestations) of the disease (for example, the elimination of cancer pain with opioid analgesics);

- *replacement*, when the action of the drug is directed at compensate shortage in the body of the hormone, enzyme, etc. (for example, the therapy of diabetes mellitus with insulin);
- *prophylactic*, when the action of the drug is directed at the prevention of the occurrence of disease (for example, the seasonal appointment of salicylates and antibiotics for the prevention of exacerbations of rheumatism).

PHARMACOKINETICS

Basic Concepts and Terms

Pharmacokinetics (literally "movements of the drugs") consists of 1) absorption, 2) distribution and 3) elimination of the drugs. These processes determine how rapidly the drug will appear at the target organ and how long it will be there. Elimination can be subdivided on metabolism and excretion.

Absorption – the transfer of the drug from the site of administration to systemic circulation.

Distribution – the transfer of the drug from the systemic circulation into different organs and tissues of the body.

Elimination – the removal of the drug from the body which involves either (or both) metabolism or excretion.

Routes of Drug Administration

There are following routes of drug administration:

- enteral (via GIT):
  - – oral;
  - – sublingual;
  - – transbuccal;
  - – rectal;
- parenteral (bypassing GIT):
  - – subcutaneous;
  - – intramuscular;
  - – intravenous;
  - – inhalation;
  - – transdermal;
  - – intrathecal (subarachnoid);
  - – topical.

Oral administration.

Advantages:

- convenient;

- safe;
- economic.

Disadvantages:

- slow development of effect due to:
  - – slow absorption in the GIT;
  - – passage of drugs through the liver;
- low bioavailability due to:
  - – incomplete absorption;
  - – the first-pass effect in the liver;
  - – destruction of drugs by gastric acid and enzymes;
- some drugs can irritate gastric mucosa.

Sublingual administration. Rapid action is characteristic because a drug is absorbed directly to the systemic blood circulation without passage through the liver. So this route is used in emergent states.

Rectal administration. It may be used when drug absorption in the GIT is impaired, in children or unconscious patients. The most of a drug does not pass through the liver. The area of absorption is relatively small, so not all drugs are well absorbed from the rectum.

Subcutaneous and intramuscular administration. The rapid development of action is characteristic for aqueous solutions, but there are so-called slow-released preparations, that are absorbed slowly, so effect develops slowly but lasts for a long time. Suspensions or oil solutions may be administered by this route. It is not possible to use large volumes of solutions. Irritating drugs can not be injected, especially by subcutaneous route.

Intravenous administration. The effect develops very rapidly (almost immediately); bioavailability is 100%; duration of action is relatively short; only aqueous solutions may be administered, not suspensions or oil solutions.

Inhalation administration. Development of an effect is almost immediate; only gases, volatile fluids or aerosols are administered.

Transdermal administration. In this case, a drug is applied on the skin and is absorbed to the systemic blood circulation through the skin. Slow development and long duration of an effect are typical. The transdermal patch is the most commonly used dosage form.

Topical administration. A drug is used directly to the site of its action, for example, a drug is administered as an ointment on the skin for treatment of some skin disease.

Absorption of Drugs

Mechanisms of absorption (Fig. 1). Absorption (excluding intravenous or intra-arterial route) involves passage through the cell membrane.

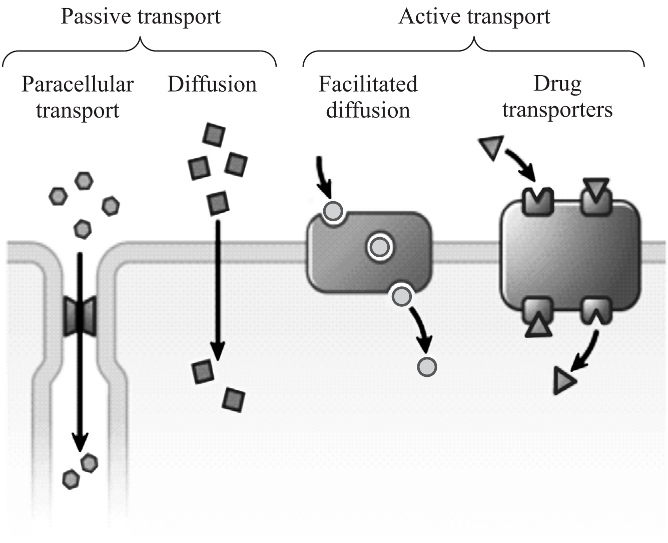

Fig. 1. Mechanisms of absorption

Passive diffusion **(*passive transport*)** is the most common mechanism of transportation of drugs. It is realized through the membrane's phospholipid bilayer according to the concentration gradient, i.e. from the area with the higher concentration of the drug to the area with the lower concentration of the drug.

Paracellular transport **(*filtration through membrane pores or through intercellular spaces*)** – only for small (< 100 Da) water-soluble molecules (for example, lithium). It is a subtype of passive diffusion.

Active transport needs the carrier (i.e. protein) and energy (ATP) and follows against a concentration gradient (for example, 5-fluorouracil).

Facilitated diffusion is a subtype of active transport when a drug penetrates through the cell membrane with the help of carrier proteins but without requiring energy.

Pinocytosis exists only for some macromolecules (like phagocytosis or amoeba feeding).

These mechanisms can be applied not only to the absorption of drugs but also to the transportation of drugs through a cell membrane and other biological barriers.

Bioavailability **(F)** is a fraction (calculated in %) of a drug, which reaches systemic circulation in an unchanged form. The bioavailability indicates the extent of absorption of a drug into the systemic circulation. The highest bioavailability is for intravenous route of administration (100%).

The term *bioequivalence* is used to compare two preparations that contain the same active compound (e.g. generic and original preparation). Two preparations are *bioequivalent* when they have the same bioavailability, the same peak concentration in plasma, and the same time to achieve this peak concentration.

Distribution of Drugs

Volume of distribution (V_d) is a hypothetical volume of body fluids in which the drug is distributed in the same concentration as in the blood. V_d can be calculated as:

$$V_d = \frac{\text{amount of drug in the body}}{C}$$

where C – concentration of the drug after distribution.

If a drug is administered intravenously, the amount of the drug is equal to the dose (D), so the above-mentioned formula can be expressed as:

$$V_d = \frac{D}{C}.$$

V_d may be much more than the real volume of fluid in the body (1000 l and even more), so it is often called as *apparent volume of distribution*. Large V_d means that the drug is accumulated in some tissues. On the other hand, if a drug has extremely low V_d (approximately 3 l in human of the average body weight), distribution of this drug is restricted only to plasma, because it does not penetrate through vessels.

Using V_d it is possible to calculate loading dose (D_l) of the drug:

$$D_l = V_d \times C_t$$

where C_t is the target concentration, i.e. the desired plasma concentration of the drug that is necessary to produce the therapeutic effect.

Compartments are the tissues and organs of the body where the concentration of the drug is equal (where central compartment is blood and peripheral compartment is body tissues – *a bicompartmental model* of the distribution). But the simplest model is *a monocompartmental model*, when the body is only one homogenous compartment which presupposes that blood is a true reflection of the drug's concentration in other fluids or tissues and that the elimination of the drug is directly proportional to the drug's concentration in the organism (first-order kinetics – see below).

Influence of plasma protein binding on the distribution of drugs. Drug + circulating plasma proteins (albumins, etc.) = reversible drug-protein complex. The drugs bound with albumins of plasma can not penetrate through the vessels and do not induce the effect. On the other hand, a relation between bound and free fractions of the drug is a constant value, so when some amount of a free drug leaves the bloodstream, some amount of a bound drug dissociates. Nevertheless, the plasma protein binding slows down the distribution of drugs, and, in general, reduces the rate of development of the effect and its magnitude. The decrease of binding with plasma proteins (in case of hypoproteinemia or due to interaction with other drugs binding with the same proteins) leads to the increase of the effect of a drug and can cause toxic reactions.

Elimination of Drugs

After absorption in the GIT, the drugs are metabolized in the liver (*first-pass effect* or *presystemic elimination*). Therefore, the oral administration of the drug which undergoes to intensive first-pass effect (if metabolites of the drug are pharmacologically inactive) is impossible.

First-order kinetics (a feature of the majority of drugs) is a process of elimination when a *fixed percentage of the drug* is eliminated per one time unit.

Zero-order kinetics (features of just some drugs: ethanol, phenytoin, aspirin, heparin, etc.) is a process of elimination when a *fixed amount of the drug* is eliminated per one time unit (Fig. 2).

Elimination of drugs includes two processes: metabolism and excretion.

Metabolism converts lipid-soluble drugs, which would be reabsorbed from the kidney tubule, into a water-soluble form, which is not reabsorbed,

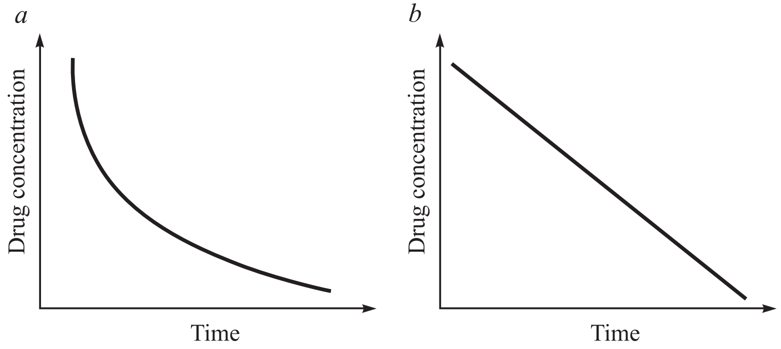

Fig. 2. Plots of zero-order (*a*) and first-order (*b*) drug elimination versus time

capable of being rapidly eliminated in the urine. In the majority of cases, the increase of polarity (of the ionization) is observed as well.

The drug metabolism is divided into two phases: Phase I – non-synthetic reactions (cytochrome P450 mediated reactions: oxidation, reduction, hydrolysis, and hydration); Phase II – synthetic reactions: conjugation with glucuronic acid, acetic acid, etc.).

Excretion is a removal of a drug (or its metabolites) from the organism. The most important route of excretion is excretion via urine by glomerular filtration or by tubular secretion. The most important process that regulates drug excretion by kidneys is reabsorption. Non-polar (lipophilic) molecules are easily reabsorbed and return to the blood. Polar (hydrophilic) molecules are not reabsorbed and easily excreted via urine. So, to be excreted, a drug must be metabolized to a polar water-soluble metabolite.

Other routes of excretion include excretion *via feces* (for drugs that are secreted via bile), *via lungs* (for gases or volatile fluids), *via milk*. Some drugs are reabsorbed in guts and re-enter the hepatic portal vein (enterohepatic circulation).

The most important parameters of the drug elimination are half-life and clearance.

Half-life **($T_{1/2}$)** is the amount of time required to reduce the amount of the drug in the body by half during elimination. $T_{1/2}$ is linked to a) V_d (the higher V_d, the greater $T_{1/2}$ is) and b) clearance (Cl) (the greater the clearance, the lower the $T_{1/2}$):

$$T_{1/2} = \frac{0.7 \times V_d}{Cl}.$$

In this equation 0.7 is an approximation to the natural logarithm of 2 (this is because the elimination is characterized by exponential curve, so twofold decrease of the drug concentration is proportional to ln2).

Clearance is a volume of plasma completely cleared from the drug per time units (ml/min or l/h):

$$Cl = C_{el} \times V_d$$

where C_{el} – an elimination rate constant.

An elimination rate constant reflects the rate of disappearance of the drug from the organism due to metabolism and excretion, namely this coefficient shows the fraction of the drug which is eliminated from the blood per time unit.

Dosing of Drugs on the Base of Pharmacokinetic Parameters

Parameters of distribution and elimination of drugs are used for the calculation of doses.

If a drug is administered with a *constant rate* (e.g. as intravenous infusion), the plasma concentration of the drug increases gradually without significant hesitation. After some time the rate of elimination becomes to be the same as the rate of administration, and the drug concentration becomes to be stable. This is a ***steady-state concentration*** (Css) (Fig. 3):

$$\text{Css} = \frac{\text{rate of administration}}{\text{Cl}}$$

where Cl is drug clearance.

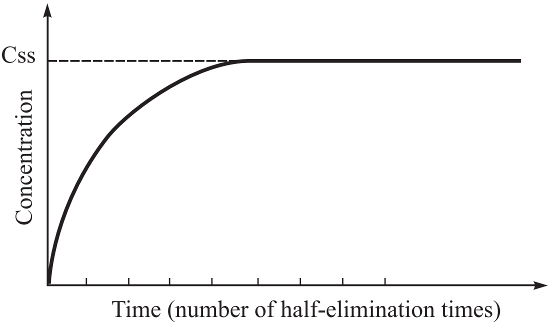

Fig. 3. Concentration-time curve if a drug is administered as intravenous infusion with a constant rate

To calculate the rate which is necessary for the administration of the drug (as intravenous infusion) to achieve Css that corresponds to certain therapeutic concentration, we use the formula:

$$\text{Rate of administration} = \text{Cl} \times \text{Css}.$$

In most cases *discrete dosing* (*fixed-dose regimen*) is used, i.e. a drug is administered in a certain dose (***maintenance dose*** – D_m) after certain periods of time (t). In this case, we observe the increase of the plasma concentration of the drug after taking of every dose during the processes of absorption and decrease of the concentration after reaching some peak concentration when processes of elimination prevail. During steady state certain maximal (Css_{max}) and minimal (Css_{min}) concentrations are observed after each dose (Fig. 4).

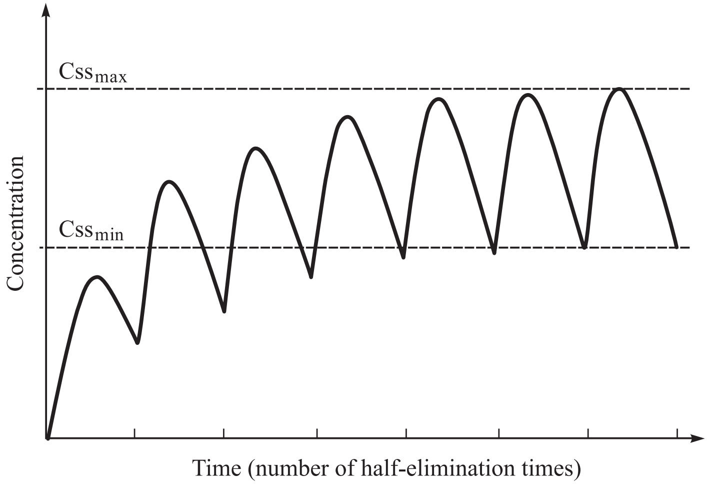

Fig. 4. Concentration-time curve if a drug is administered in accordance with fixed-dose regimen

The maintenance dose that should be administered to achieve the certain steady-state concentration can be calculated by the formula:

$$D_m = \frac{Cl \times Css}{F/100} \times t$$

where t is the time interval between doses; F is bioavailability.

The time that is required to achieve steady-state concentration is approximately 4–5 $T_{1/2}$.

If it is necessary to achieve the target therapeutic concentration (C_t) very rapidly, we must give ***loading dose*** (D_l), which can be calculated in case of intravenous administration by the formula:

$$D_l = V_d \times C_t.$$

For other ways of administration this formula is:

$$D_l = \frac{V_d \times C_t}{F/100}.$$

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