The fate of xenobiotics in the body

Xenobiotic

- A substance that causes pathological changes in the body after absorption into the bloodstream
- in other words also noxious substance or poison
- Toxic effects:

    1. transient
    2. permanently damaging
    3. fatal

The fate of a drug in the body

Pharmacodynamics - what the poison does to the organism (effects)

Pharmacokinetics - what the organism does with the poison (toxicological analyses)

- it includes following processes:

1. Administration – a way xenobiotic enters the body: Inhalation – snorting – injection – per os – dermal....

    Potential release of the bound active ingredient in the drug

1. **Absorption** - the process of diffusion into the bloodstream
2. **Distribution** - between blood and tissues and vice versa
3. **Biotransformation** - a transformation of chemical structure, formation of active and inactive metabolites
4. **Elimination** Routes of excretion - depend on a substance polarity: Kidneys - Intestines - Skin - Saliva - Lungs - Hair - Nails

Absorption of a drug

- passive by diffusion or
- by active transport

Speed of absorbance and absorbance rate - route of administration

1. Intravenous – rapid and complete absorption (100%)
2. Pulmonary inhalation – rapid and reduced absorption
3. Parenteral administration - absorption from tissues - circulation
4. Oral – first pass effect

Extent of xenobiotics absorption in the digestive tract

1. Environment pH influences the drug absorption
2. Absorption according to the acid-base properties of the drug

Stomach	pH 1–3	pole B1	< 5 m^2	acidic substances (aspirin)
Small intestine S_1	pH 5–7	pole B2	200 m^2	
Small intestine S_2	pH 7–8	pole B3	< 5 m^2	
Colon	pH 7–8	pole B3	< 5 m^2	base (ephedrine)

The absorbed proportion of the drug - depends on the method of administration

- Biological availability (Bioavailability)

  Proportion (%) of the drug absorbed into the bloodstream by a certain administration route in infinite time relative to i.v. administration (100%)

- „First pass metabolism“ – „First pass effect“
    - Proportion of the drug that reaches the liver before entering the circulation, and therefore is metabolized before it expresses its pharmacological effect - reduction in bioavailability
    - Pre-systemic metabolite formation in oral administration compared to subcutaneous administration (sc.)

Distribution

Model of the body as a set of compartments

Distribution depends on

- The polarity and size of the drug molecule
- Binding of the drug and its metabolites to plasma proteins
- Extent of ionization at given plasma pH
- Blood supply to tissues, transport of the drug
- Distribution between blood and tissues - water content of tissues

e.g.

- *Alcohol is dissolved evenly in the water throughout the body*
- *Warfarin is strongly bound to plasma proteins and is only found in plasma and extracellular fluid*

TISSUE	% of water
muscle	76
fat	10
liver	68
kidneys	83
lungs	79
brain	75

	Volume of water /body mass (l/kg)
plasma	0,04
blood	0,08
extracellular water	0,2
total body water	0,6
fat	0,2–0,35

- The volume of total water decreases in course of individual's development.
- **Distribution volume** - hypothetical quantity after distribution equilibrium is reached. Substances strongly bound to tissue proteins have high Vd and reduced plasma concentration

$V_d = D/c_0$ nebo $V_d = a/c$
D – absorbed dose of a drug/chemical (i. v. dose)
c_0 – initial plasma concentration (after i. v. dose)

(see reading from the semi-logarithmic kinetic curve below)

a – the current amount of the drug in the body
c – current plasma concentration

Distribution volume of substances

V_d (l)	Place of occurrence of the drug
5	remains in plasma
5–20	distribution into the extracellular space
20–40	distribution into all body fluids
>40	depot in peripheral tissues

Elimination

The vast majority of xenobiotics is metabolized in the liver and excreted in the urine. Ethanol is eliminated according to zero- order kinetics. First-order kinetics mainly applies to drugs:

$-dc/dt = k_{el}. c$

Plasma elimination half-life:

$-dc/dt = k_{el}. c$
$c = \exp(-k_{el}. dt)$
$\ln c = -k_{el}. t$

Half-life when, $c = ½\ c_0$

$\ln ½ = - k_{el}. t_{½}$

$\ln 2 = k_{el} \cdot t_{½}$
$t_{½} = 0{,}693 / k_{el}$

- In general: after 5 half-lives, 96.875% of the drug is eliminated, i.e. the organism is practically clean of the substance
- Clearance – volume of plasma from which a substance is completely removed per unit time

$[Cl] = [\ volume/(mass.time)\ ]$

- Total clearance and clearance of individual organs - dependent on the health condition of the individual
- Substances bound in tissues with high Vd are eliminated for a long time at a given clearance, they have a long half-life

$t_{½} = 0{,}693.V_d/Cl$ or $k_{el} = Cl/V_d$

- SUMMARY - Important pharmacokinetic data:

k_{el}; $t_{½}$; V_d; Cl

Enterohepatic circulation

- Xenobiotics and metabolites excreted by the bile into the intestines are reabsorbed, then they pass the liver and are again excreted into the bile, then again into the intestines.....
- This cycle is repeated until complete elimination
- Circulation prolongs the stay of a xenobiotic in the organism and can prolong or delay toxic manifestations
- Chemicals which are proved to enter enterohepatic circulation are found in the intestines even after parenteral administration (e.g. opiates, benzodiazepines)

Release from tissues

- Tissue blood supply
- Adipose tissue - little blood supply
- Slow re-release of an accumulated drug into the blood
- Extended elimination

> *e.g. Chronic marijuana abuse - depot in adipose tissue - long-term metabolite excretion*

Links

Related articles

- Toxicity, effects of noxious substances
- Introduction to toxicology
- Pharmacodynamics
- Pharmacokinetics

Source

- BALÍKOVÁ, Marie. *Osud xenobiotik a biotransformace* [online]. [cit. 2012-03-13]. <https://el.lf1.cuni.cz/p88978866/>.
- PROKEŠ, Jaroslav. *Základy toxikologie : obecná toxikologie a ekotoxikologie.* 1. edition. Prague : Galén : Karolinum, c2005. ISBN 80-7262-30-1X.