Toxicity, effects of noxious substances

Poisoning – intoxication

- Interaction of the poison with the organism, effect on metabolic processes, damage to organ functions, morphological changes
- Processing of the poison in the organism - toxicokinetics
- Effects of poison on the organism - toxicodynamics
- Poison metabolism - detoxification or bioactivation
- Acute intoxication
  - neurotoxic, hepatotoxic, nephrotoxic, cardiotoxic, embryotoxic,...
- Chronic intoxication: developmental damage, carcinogenicity, genotoxicity, development of allergies, etc.
  - Chronic abuse of drugs, development of tolerance

Poisons and damage mechanism

- Damaging the function of the target organ. Toxicity is a function of concentration at target organs, receptors.
- Damaging cells causing **cellular lesions**
- The degree of damage depends on reaching the concentration in the target organ (amanitins, mercury,...)
- Combined mechanisms, e.g. prolonged cellular hypoxia (CO, HCN), formation of cytotoxic metabolites (methanol, glycol,...). Chronic exposure

Toxicity, effects, toxicodynamics

- toxicity of the original form, chemical structure (QSAR studies)
- method of administration, application, exposure (bioavailability)
- exposure time, dose frequency
- bioavailability
- Individual susceptibility of the organism – genetic basis, physiological and external influences (age, diseases, diet, smoking, etc.)
- Inter and intra-individual variability of metabolism, variability of enzyme capacity during biotransformation

Physiological factors

- Sexual differences – hormonal influences, differences in enzyme capacity (biotransformation of ethanol), isoenzyme representation in women and men (e.g. P450)
- Age differences, cell changes, cell development, development of enzyme activity in a specific way, increase and decrease (aromatic hydroxylation, N-demethylation, ability to form glucosiduronates....)
- External influences, diet, lifestyle, diseases
- Interaction of substances – induction and inhibition of enzymes
- Chronic doses – cellular changes, receptor adaptation (alcoholism, addictive substances, development of tolerance)

Substance toxicity

- **Acute**
- **Chronic**

Information about the toxicity of substances:

1. "case studies" - completeness and reliability of anamnestic data, filtering out interfering influences, e.g. mixed poisoning, unknown factors
2. *epidemiological studies* - side effects of drugs and therapeutic effectiveness - statistical evaluation. Unknown influencing factors
3. *controlled experimental studies*, *clinical studies* - strict ethical restrictions

Drugs'

- clinical studies on human volunteers
- Ethical considerations, microdoses, major limitations
- Informed consent of the volunteer

Other substances - experimental studies on animals

Testing regulations:

- Czech pharmacopoeia (drugs, medical supplies)
- "OECD Guidelines for Testing of Chemicals"
- Guidelines determine which animals and in what quantity to use for a certain test; what dose and method of application
- The goal is harmonization, generalization of study results

- What animal? – as close to the human model as possible
- Animal size - repeated sampling - study cost

Experimental toxicity studies

1. short term
2. long term

- Effect *versus* dose
- non-linear relationship
- semi-logarithmic dependence

- effect vs. log dose
- toxicity vs. log dose
- LD_{50} – median lethal dose

Therapeutic drug index

- Effective dose ED
- Toxic dose TD
- T-INDEX = LD50 / ED50
- higher value, high toxic dose
  - i.e. safer drug and less risk of poisoning

Classification of toxic substances according to LD_{50} size

Chemical substance	**LD_{50}**
Super toxic	less than 5 mg/kg
Extremely toxic	5–50 mg/kg
Highly toxic	50–500 mg/kg
Moderately toxic	0.5-5 g/kg
Slightly toxic	5-15 g/kg

LD_{50} for humans when administered orally – e.g.:

Chemical substance	**LD_{50} (mg/kg)**
Ethanol	7000
Sodium Chloride	3000
Morphine	900
Phenobarbital	150
Strychnine	2
Nicotine	1
Dioxin (TCDD)	0.01
Botulotoxin	0.00001

Short-term toxicity studies

- Acute toxicity – LD50 – histological examination of organs
- **Subchronic toxicity**, includes e.g. accumulation of poison, repeated doses lasting 10% of the life of the laboratory animal
- Local effects on skin, eyes (soaps, ophthalmology) – rabbit, guinea pig, mouse – irritation tests
- Teratogenicity, embryotoxicity – administration to females during pregnancy, histological examination of fetal soft tissues, skeletal examination
- Reproductive toxicity, administration to the parent pair, monitoring of litter size, offspring size, after weaning, parent necropsy, histopathological examination of reproductive organs

Long-term toxicity studies

- Carcinogenicity - repeated doses, 3 dosages, 18-24 months, haematological examination, necropsy and histopathological examination
- Chemical structure of the substance vs. carcinogenicity
- Different sensitivity of animals to chemical induction of tumors
- Chronic toxicity – minimum period of 12 months
- Both rodent and non-rodent (dog, primate)

Individual susceptibility to toxicity

Variability - mainly genetically determined (genotypes)

- between animal species
- within an animal species
- physiological and temporal influences (sex, age, diseases,...)
- variability of the metabolic capacity of enzymes
- polymorphism of enzymes, alternative forms, isoenzymes

Alcohol	Minimal i.v. lethal dose (g/kg)	
	Rabbit	Cat
Methanol	15.9	4.7
Ethanol	9.4	3.9
Propanol	4.0	1.6
Isobutanol	2.6	0.72
Isoamyl alcohol	1.6	0.21

Cross-species susceptibility to dichlorophenoxyacetic acid toxicity

LD_{50} of the herbicide 2,4-D – p.o.	
Animal species	(mg/kg)
Mouse	360–710
Rat	900–1500
Guinea pig	400–800
Rabbit	420
Dog	100
Monkey	214

Interspecies variability in phenol conjugation metabolism

	Excreted proportion (%) – glucuronide	Excreted proportion (%) – sulfate
Cat	0	87
Man	23	71
Rat	25	68
Rabbit	46	45
Pig	100	0

Interspecies variability in benzoic acid conjugation metabolism

Animal species	Dose p.o. (mg/kg)	Urine elimination in 24 hours (%)	Proportion of dose in urine in 24 hours		
			benzoic acid (%)	hippuric acid (%)	benzoyl glucuronide (%)
Mouse	56	55		95	5
Rat	50	100	1	99	
Hamster	52	99	1	97	
Rabbit	49	60		100	
Pig	50	49	15	85	
Cat	51	30		100	
Dog	51	94		82	18
Chimpanzee	20	47		100	
Human	1	100		100	
Human	42			50 – 85	

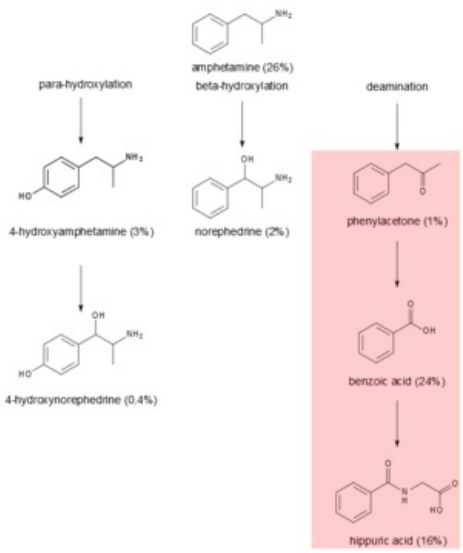
Člověk: amfetamin, 4-OH-amfetamin a konjugace, dále oxidativní deaminace až kys. hippurová

Králík: amfetamin, oxidativní deaminace; ale redukce fenylacetonu, výsledný alkohol je vylučován konjugovaný močí

Interspecies variability in methamphetamine metabolism

Human: amphetamine, 4-OH-amphetamine and conjugation, then oxidative deamination to hippuric acid

Rabbit: amphetamine, oxidative deamination; but reduction of phenylacetone, the resulting alcohol is excreted conjugated in urine



Amphetamine metabolism

Genetic variability of toxicity

- E.g. isoniazid (treatment for tuberculosis)
- Genetic polymorphism of N-acetylation, the metabolite is more polar, excreted more quickly
- Europeans: **40% of the population acetylates rapidly**
- **Asians:** 80% of the population acetylates rapidly
- **Eskimos:** 96% of the population acetylates rapidly
- The acetylation phenotype of an individual determines toxic manifestations:
  - neuropathy with slow acetylation
  - hepatotoxicity with rapid acetylation

Development of toxic manifestations

- Sequence of processes, interaction with macromolecules, disruption of physiological processes – change in toxicity
- Factors influencing toxic manifestations, dynamics:

1. Chemical effects, substance structure:
2. Genetic factors
3. Physiological factors (sex, age, state of health)
4. Toxicokinetic factors
5. External factors, diet, environment, lifestyle

Links

Related Articles

- The fate of xenobiotics in the organism
- Introduction to Toxicology
- Abuse and intoxication

Sources

- BALÍKOVÁ, Marie. *Toxicita, účinky nox* [online]. [cit. 2012-03-13]. <https://el.lf1.cuni.cz/p78927861/>
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