Toxins and Poisons
Mechanisms of Action

Lecture for medical students

Prof. MUDr. Sixtus Hynie, DrSc.
Inst. of Medical Biochemistry,
1st Medical Faculty
Charles University in Prague

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Every natural or synthetic chemical can cause injury if the dose is high enough.

Potency of various poisons in terms of acute lethality

Dose	Poison
mg/kg body weight	
1,000,000	Water
10,000	Alcohol
100	Barbiturates
10	Morphine
1	Nicotine
0.1	Curare
0.01	Tetrodotoxin
<0.0001	Botulinum toxin

TCDD (dioxin) – Chloracne

Poisoning of Victor Yushchenko just before Ukraine presidential election

Definitions:

Poisons are chemicals that can injure or impair body functions.

Venoms are substances injected by one species into another.

Toxins are mostly described as drugs produced by microorganisms.

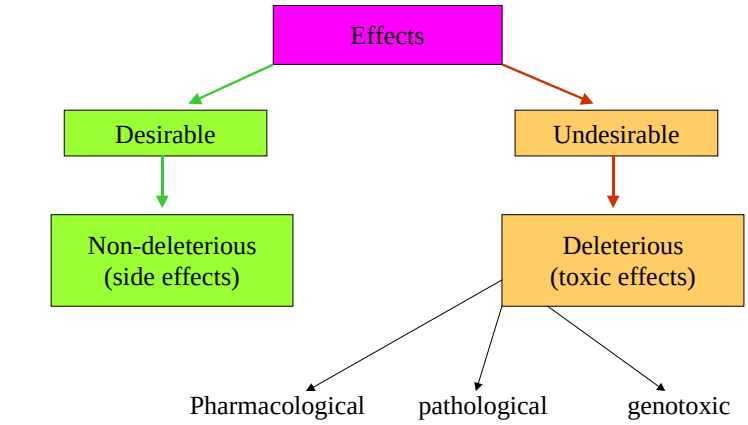
Venoms and toxins are mostly proteins or polypeptides.
Many of toxins and poisons are alkaloids (drugs of plant origin).

Toxikology

Medical discipline that has many parts:

Toxicology: Chemical
Biochemical
Pharmacological
Clinical
Industrial
of foodstuff
Veterinary
Agriculture
Military
Ekotoxicology

Classification of the effects of chemicals

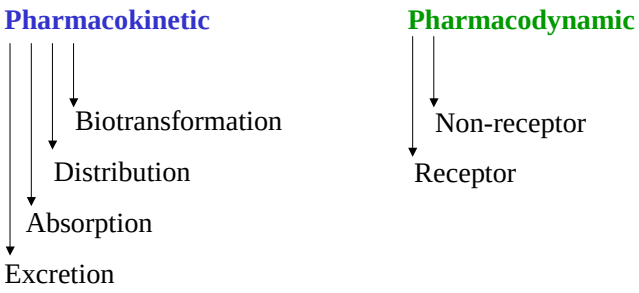


General toxicology

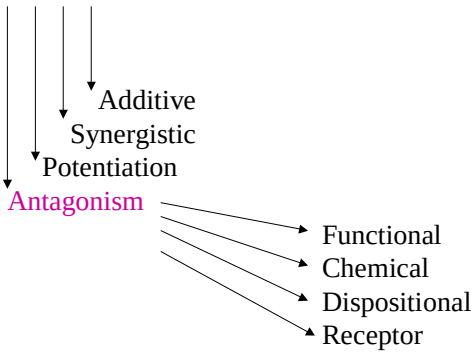
Subjects mostly discussed in pharmacology:

Biological availability
Distribution
Penetration into organs
Elimination
Accumulation
Relationship between dose and effect
Doses
Mechanisms of action
Factors influencing the effects of toxic drugs

Mechanisms of chemical interactions



Classification of type of interaction



Different Classifications of Toxic Agents:

Length of exposure:

- Acute toxicity – results from brief exposure.
- Chronic toxicity – exposure for months or years.
  - (Chronic low level exposure – common route in the workplace)

Route of exposure:

- Direct contact
- Ingestion
- Inhalation

Other classifications:

- Deteriorated function or tissue
- Mechanism of action
- Chemical structure

Toxins and poisons can have direct and indirect mechanisms of action

Most frequently influenced organs:

- Liver
- Kidney
- Brain
- Lung, intestine and other

Mechanism of action:

- Direct damage of tissue
- Effect on function
- Genetic defect

Consequences of action of toxic agents

Critical Factors:

Dose / Response

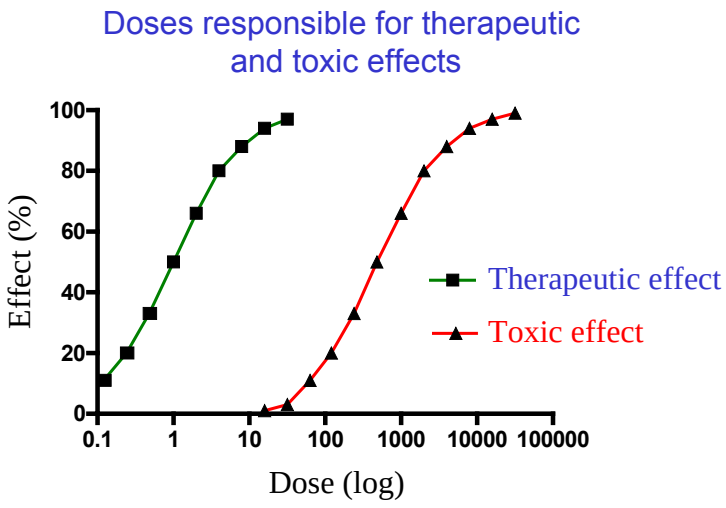
Risk = Hazard x Exposure

Individual sensitivity

Whether damage is reversible or irreversible often depends upon the repair and regenerative ability of the target tissue.

Exposure to neuropoisons may reduce the age at which neurologic and behavioral deficits appear.

Allergic reactions may develop to nearly all drugs.



Allergic reactions are one of the indirect reactions

Toxic effects may also be mediated by:

immunosupression

idiosyncratic reactions

Statistics of acute poisoning

The hazard due to exposure to toxins is regulated by various governmental committees and agencies.

A no-observed-adverse-effect level (NOAEL) can be determined in laboratory animals.

1/100th of this amount is considered acceptable for humans.

This accepts 1 death per milion individuals exposed as the maximum acceptable exposure.

In the USA 20,000 people die each year from the effects of illicit drugs.

Mechanism of action of some venoms and toxins

Toxin	Source	Mechanism
Tetrodotoxin	fish	Na^+ channel blocker
Cardiac glycosides	toad	ATPase inhibitor
Batrachotoxin	frog	Na-channel activator
Domoic acid	mussels	Activator of glutamate rec.
Cholera toxin	Vibrio cholerae	Activation of Gs proteins
Pertussis toxin	Bordetella pert.	Inactivation of Gi protein
Tetanus toxin	Clostridium tetani	Cell membrane ionophore
Botulinum toxin	Clostr. botulinum	Inactivation of synaptin for vesicular transport

Toxic plants can be found on many places

Foxglove purpurea	Datura	Oleander	Autumn crocus	Poison hemlock	Lantana	Ricinus communis (Castor bean)
digitalis	**atropine**	**cardiac glykosides**	**colchicine**	**coniine**	**lantadene**	**ricin**

Not visible: Lupine **(lupanine)**

Poisons from plants

Poison	Plant	Mechanism of action
Atropine	Atropa bella-donna	M receptor Inhibitor
Cardiac glycosides	Digitalis purpurea	ATPase inhibitor
Capsaicin	Peppers	Depletes P substance
Ricin	Castor bean	Protoplasmic poison
Emetin	Ipeca	Stimulates vomiting center
Curare	Strychnos sps.	Blockade of N receptor
Strychnine	Strychnos sps.	Stimulation of peripheral n.
Cocaine	Koka leaves	Blockade of NT transport

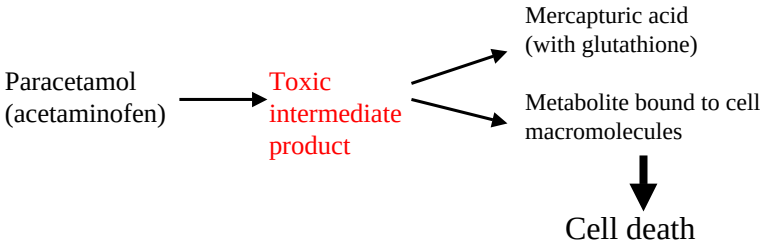
Some fungal toxins: muscarine, psilocybin, aflatoxins, ergot alkaloids etc.

Spectrum of unwanted effects

Chemical forms of drugs leading to toxicity

Maternal drugs have a required therapeutic effect.
Their metabolites are ineffective and are more easily excreted.

Some metabolites become more toxic.
Intermediate products can bind to nucleofils,
like glutathione; when it is depleted these metabolites can bind to macromolecules and the cells are killed.



Types of toxic reactions

(pharmacological, pathological, genotoxic – change of DNA)

Phototoxic and photoallergic reactions.
Formation of free oxygen radicals.
Further mechanisms dependent on the specific type of toxic drugs.

Local or systemic toxicity
(most drugs lead to systemic toxicity)
Reversible and irreversible effects
Chemical cancerogenesis
Malformations (teratogenesis)
Allergic reactions

Treatment of poisoning

Remove the source of poison

Minimize absorption of the poison

Supportive therapy (oxygen, ventilation etc.)

Specific therapy, if available
antivenins
antitoxins
chelators

For drugs: atropine
flumazenil
opioid antagonists
vitamin K

Toxicology of heavy metals

Heavy metals and their antagonists

Most important: lead, mercury, arsenic, cadmium, iron

Toxic effects are produced by binding to one or more reactive groups, which are essential for normal physiological functions.

Heavy metal antagonists (chelates) were prepared in order to compete with different radicals that are bound by heavy metals; By this mechanism they prevent the toxic effects and increase the excretion of heavy metals.

They react mainly with these groups:

-OH, $-COO^-$, $-PO_3H^-$, =C=O, -SH, -S-S-, $-NH_2$, =NH

Mechanism of action of heavy metal toxicity

Metal	Site and mech. of action	Tissue and organ
Mercury	Direct toxicity SH binding and disruption different macromolecules Binds amino & other groups	Corrosive damage of lung, GIT, CNS, kidney
Lead	SH binding, impaired heme synthesis	Damage to CNS, peripheral nerves, blood, kidney
Cadmium	Binds to macromolecules and disrupts function	Lung and renal damage
Arsenic	SH groups and uncoupling of oxidative metabolism	Peripheral n. syst., GIT, liver, CV system

Chelates

Compounds that are able to bind molecules of heavy metals and thus they inactivate them.

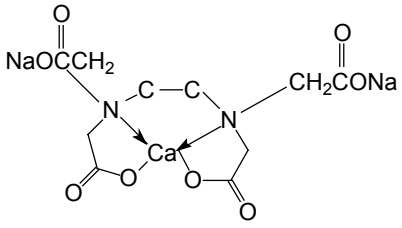
These complexes release heavy metals from tissues and enable their excretion.

EDTA

Edetate calcium disodium

Ethylene-diamin-tetraacetic acid

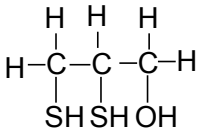
$CaNa_2EDTA$ is used primarily in the intoxication by lead



Further chelates

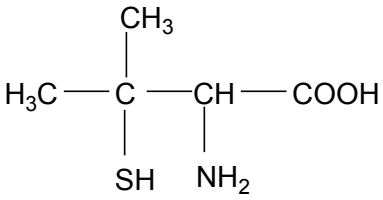
Dimercaprol

BAL



Used p.o. or i.m.
It binds heavy metals, mercury, arzen etc.

Penicilamin



Used p.o. in intoxication by Cu, Hg and Pb.

Succimer, Trietin and Deferoxamine

Environmental toxic drugs, Ecotoxicology

Industrial poisoning

Metals (elemental, salts and organic compounds)

Air pollutants and gases

Aromatic and aliphatic hydrocarbons

Insecticides, pesticides and herbicides

All produce acute and chronic toxicity

Mutagenesis and carcinogenesis are particular problems

Industrial poisons

Environmental poisons are those that reach the environment and they can cause acute or chronic poisoning or be carcinogens.

Frequently the concentrations are too low to produce acute intoxication, however, they are sufficient to produce chronic poisoning.

Environmetal toxic agents

Air pollutants

Source:

Most urban air pollution is due to carbon monoxide, sulfur oxides, hydrocarbons and nitrogen oxides.

Photochemical pollution (smog) contains mentioned drugs and photochemical oxidants.

Airborne particles account for 10 % of all air pollution.

Transport and transformation

air, water, soil

Exposition and Response of the organism

dependent on the properties of toxic drug, biotransformation, depositions, transfer by food

Population, response of ecosystem

Changes in population (reproduction, mortality etc.)

Basic air pollutants

Particles:

Fossil fuels, ashes, carbon particles, asbest etc.

Gases:

Carbon monoxide (CO)
Sulfurous oxide (SO_2)
Nitrogen dioxide (NO_2)
Aldehydes, gasoline burning
Metals
Ozone

$$Cl^- + O_3 \longrightarrow ClO^- + O_2$$
$$O_3 + photon \longrightarrow O_2 + O^-$$
$$ClO^- + O^- \longrightarrow Cl^- + O_2$$

Toxic drugs in the environment

Pesticides survive for years – chlorinated hydrocarbons,
DDT, hexachlorcyclohexanes etc.
- Triazine herbicides
- organophosphates etc.

Non-pesticidal agents in water

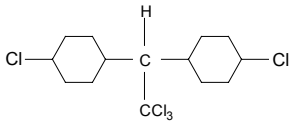
Aromatic hydrocarbons, polychlorinated biphenyls,

dioxin etc.

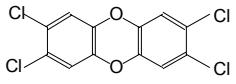
Metals

Nitrites, nitrates, phosphates

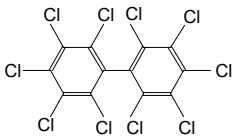
Chemical structures of most important polychlorinated drugs



DDT, Dichlorodiphenyltrichloroethane



TCCD, Tetrachlorodibenzodioxin



PCB, polychlorinated biphenyls

Symptoms of intoxications

Pupils – miosis, mydriasis (opioids, organophosphates)

Odour (arsenic – garlic)

Allopecia, hair loss (thallium)

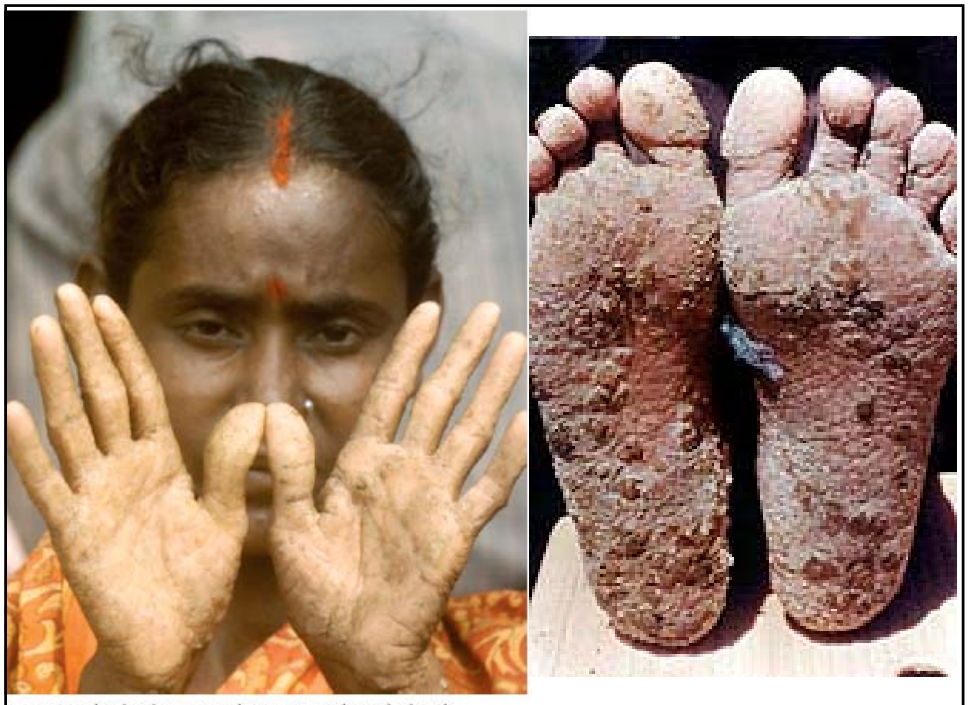
Convulsions (strychnine)

Paralyses (botulism)

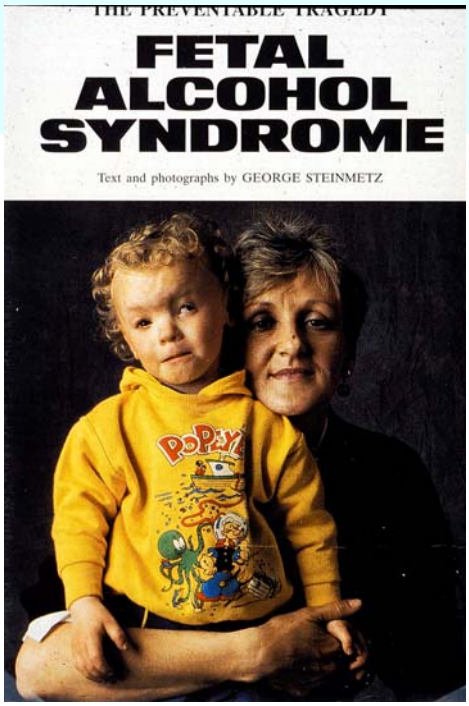
Coma (depressants, hypnotics)

Skin color changes (CO – cherry red; nitrates – blue)

Skin changes (arsenic – hyperkeratosis, blisters)
(dioxin – chloracne)



Arsenic in the drinking water leaves its mark on the hands.



FAS Child

Accidental Food Contamination

Iraq 1972: 5-6,000 people hospitalized, 10% died.
Seed grain donated with methyl mercury antifungal agent.
Distributed 100,000 tons to farmers, improperly identified.
Grain (wheat, barley) mistakenly used to make bread.

Michigan 1973: Nearly 2 million livestock destroyed.
Several hundred pounds PBBs mixed with dairy feed.
Coverup by company and state officials compounded problem.

Spain 1981: 11,000 people hospitalized, >500 died.
Industrial rapeseed oil from France containing aniline refined.
Refining process produced toxic components.
Resold fraudulently as cooking oil (59 tons) after mixing olive oil.

Adulturation of vegetable oils (soybean/canola in olive) frequent.
Biochemical components becoming available for detection.

Most important drugs causing tumors

Smoking	30 per cent
Alcohol	3
Dietary factors	35
Pollution	4
Infection	10

Drug addiction

Stimulating drugs – amphetamines, cocaine

Depressants – opioids, hypnotics

Halucinogens – LSD, marihuana, cannabinoids

Inhalation addictive drugs – chloroform etc.

Analysis of toxic agents

Tangible evidence in the surrounding of the victim:
- remedy, food, beverage etc.

Symptoms:
- Acute
- Chronic

Sample collection:
- Tissues, fluids
- Other materials

Detection:
- Analytic instruments
- HPLC, liquid chromaqtography,
- mass spectrometry

Motivation of suicide:
- letter etc.

Toxicological studies on laboratory animals

Short-lasting studies

Acute toxicity
Subchronic toxicity
Local effects on skin and eyes
Teratogenity and toxicity on reproduction
Further specific studies – histology, pyrogenity etc.

Long-lasting studies

Cancerogenity
Chronic toxicity

Prevention and Treatment of Poisoning

Prevention of further absorption of poison

- Gastric lavage
- Chemical absorption
- Chemical inactivation
- Purgation

Enhanced elimination of the poison

- Biotransformation
- Biliary excretion
- Urinary excretion
- Dialysis

Antagonism or chemical inactivation of an absorbed poison

Literature

Hardman J.G. a Limbird L.E.: Goodman and Gilman´s The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, 2001

Amdur et al.: Casarett and Doull´s Toxicology: The Basic Science of Poisons, McGraw-Hill, New York, 1991.

Hayes A.W. (ed.): Principles and Methods of Toxicology, Raven Press, 1989, New York.

Prokeš J. et al.: Základy toxikologie, Obecná toxikologie a ekotoxikologie, Galen, Praha, 2005.

The remaining literature at the author.