Toxins and Poisons
Mechanisms of Action

Lecture for medical students

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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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Poison</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg body weight</td>
<td></td>
</tr>
<tr>
<td>1,000,000</td>
<td>Water</td>
</tr>
<tr>
<td>10,000</td>
<td>Alcohol</td>
</tr>
<tr>
<td>100</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>10</td>
<td>Morphine</td>
</tr>
<tr>
<td>1</td>
<td>Nicotine</td>
</tr>
<tr>
<td>0.1</td>
<td>Curare</td>
</tr>
<tr>
<td>0.01</td>
<td>Tetrodotoxin</td>
</tr>
<tr>
<td>&lt;0.0001</td>
<td>Botulinum toxin</td>
</tr>
</tbody>
</table>

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

- **Effects**
  - **Desirable**
    - Non-deleterious (side effects)
  - **Undesirable**
    - Deleterious (toxic effects)

- Pharmacological
- Pathological
- Genotoxic

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

Pharmacokinetic
- Biotransformation
- Distribution
- Absorption
- Excretion

Pharmacodynamic
- Non-receptor
- Receptor

Classification of type of interaction

Interaction
- Additive
- Synergistic
- Potentiation
- Antagonism

Functional
- Chemical
- Dispositional
- Receptor
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.

Doses responsible for therapeutic and toxic effects

- Therapeutic effect
- Toxic effect
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 million 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

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

Toxic plants can be found on many places

<table>
<thead>
<tr>
<th>Foxglove purpurea</th>
<th>Datura</th>
<th>Oleander</th>
<th>Autumn crocus</th>
<th>Poison hemlock</th>
<th>Lantana</th>
<th>Ricinus communis (Castor bean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>digitalis</td>
<td>atropine</td>
<td>cardiac colchicine</td>
<td>conine</td>
<td>lantadene</td>
<td>ricin</td>
<td></td>
</tr>
</tbody>
</table>

Not visible: Lupine (lupanine)
**Poisons from plants**

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

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

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**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.

**Paracetamol** (acetaminofen) → **Toxic intermediate product** → **Mercapturic acid** (with glutathione) → **Metabolite bound to cell macromolecules** → **Cell death**
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:

-\text{-OH}, -\text{COO}^-, -\text{POO}_3\text{H}^-, =\text{C=O}, -\text{SH}, -\text{S-S}, -\text{NH}_2, =\text{NH}
### Mechanism of action of heavy metal toxicity

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

### 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

CaNa₂EDTA 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.)

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**Basic air pollutants**

Particles:
Fossil fuels, ashes, carbon particles, asbest etc.

Gases:
Carbon monoxide (CO)
Sulfurous oxide (SO₂)
Nitrogen dioxide (NO₂)
Aldehydes, gasoline burning
Metals
Ozone

\[
\begin{align*}
\text{Cl}^- + \text{O}_3 & \rightarrow \text{ClO}^- + \text{O}_2 \\
\text{O}_3 + \text{photon} & \rightarrow \text{O}_2 + \text{O}^- \\
\text{ClO}^- + \text{O}^- & \rightarrow \text{Cl}^- + \text{O}_2
\end{align*}
\]
Toxic drugs in the environment

Pesticides survive for years – chlorinated hydrocarbons,
  DDT, hexachlorocyclohexanes 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, Tetrachlorodibenzo-dioxin

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)
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.


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 chromatography, 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


The remaining literature at the author.