General Principles of Pharmacology and Toxicology

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Introduction to Toxicology

Are all substances toxic? YES! Look at these:

- Sugar has an LD$_{50}$ of 30,000 mg/kg
- Ethanol has an LD$_{50}$ of 13,700 mg/kg
- Table salt has an LD$_{50}$ of 3,750 mg/kg
- Water has an LD$_{50}$ of slightly greater than 80,000 mg/kg

“Synthetic” does not mean toxic or poisonous
“Natural” does not mean safe or even low risk
## Approximate Lethal Doses of Common Chemicals
(Calculated for a 160 lb. human from data on rats)

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Lethal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar (sucrose)</td>
<td>3 quarts</td>
</tr>
<tr>
<td>Alcohol (ethyl alcohol)</td>
<td>3 quarts</td>
</tr>
<tr>
<td>Salt (sodium chloride)</td>
<td>1 quart</td>
</tr>
<tr>
<td>Herbicide (2, 4-D)</td>
<td>one half cup</td>
</tr>
<tr>
<td>Arsenic (arsenic acid)</td>
<td>1-2 teaspoons</td>
</tr>
<tr>
<td>Nicotine</td>
<td>one half teaspoon</td>
</tr>
<tr>
<td>Food poison (botulism)</td>
<td>microscopic</td>
</tr>
</tbody>
</table>

Did you know that....

- 92% of all poisonings happen at home.

- The household products implicated in most poisonings are: cleaning solutions, fuels, medicines, and other materials such as glue and cosmetics.

- Certain animals secrete a xenobiotic poison called venom, usually injected with a bite or a sting, and others animals harbor infectious bacteria.

- Some household plants are poisonous to humans and animals.
Did you know that....

• About 4 million toxic exposures annually

• Fewer than 1% of overdose patients that reach the hospital result in fatality
  • But 13-35% mortality if arrive in deep coma

• One fourth of suicide attempts are via drugs
Leading causes of pharmaceutical death

- Analgesics
- Tricyclic antidepressants
- Sedative/hypnotics
- Stimulants and street drugs
- Cardiovascular drugs
- Alcohols
Toxicology, an old field

Toxicology is arguably the oldest scientific discipline, as the earliest humans had to recognize which plants were safe to eat.
Toxins

are produced by plants, animals, or bacteria.

Phytotoxins
Zootoxins
Bacteriotoxins
Toxicants

• Heavy Metals
• Solvents and Vapors
• Radiation and Radioactive Materials
• Dioxin/Furans
• Pesticides
Historical

- 2700 B.C. - Chinese journals: plant and fish poisons

- 1900-1200 B.C. - Egyptian documents directions for collection, preparation, and administration of more than 800 medicinal and poisonous recipes.

- 800 B.C. - India - Hindu medicine includes notes on poisons and antidotes.

- 50-100 A.D. - Greek physicians classified over 600 plant, animal, and mineral poisons.
Historical

50- 400 A.D. - Romans used poisons for executions
The philosopher, Socrates, was executed
using hemlock

Avicenna (A.D. 980-1036) Islamic authority on poisons and antidotes.

1200 A.D. - Spanish rabbi Maimonides writes first-aid book for poisonings,
Poisons and Their Antidotes
The Father of modern Toxicology

Swiss physician Paracelsus (1493-1541) credited with being

“the father of modern toxicology”

“All substances are poisons: there is none which is not a poison. The right dose differentiates a poison from a remedy.”
Milestones of Toxicology

The Dose Makes the Poison!

- An apparently non-toxic chemical can be toxic at high doses. (Too much of a good thing can be bad!).

- Highly toxic chemicals can be life saving when given in appropriate doses. (Poisons are not harmful at a sufficiently low dose)
Toxicology Terms

- The term “toxicant” refers to toxic substances that are produced by or are a byproduct of human-made activities.

- The term “toxin” refers to toxic substances that are produced naturally.

- A toxic symptom is any feeling or sign indicating the presence of a poison in the system.

- Toxic effects refers to the health effects that occur due to exposure to a toxic substance.

- LD$_{50}$: The amount (dose) of a chemical which produces death in 50% of a population of test animals to which it is administered by any of a variety of methods. Normally expressed as milligrams of substance per kilogram of animal body weight (mg/kg)
**LD\textsubscript{50} Comparison**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>LD\textsubscript{50} (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Alcohol</td>
<td>10,000</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>4,000</td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>1,500</td>
</tr>
<tr>
<td>Morphine Sulfate</td>
<td>900</td>
</tr>
<tr>
<td>Strychnine Sulfate</td>
<td>150</td>
</tr>
<tr>
<td>Nicotine</td>
<td>1</td>
</tr>
<tr>
<td>Black Widow</td>
<td>0.55</td>
</tr>
<tr>
<td>Curare</td>
<td>0.50</td>
</tr>
<tr>
<td>Rattle Snake</td>
<td>0.24</td>
</tr>
<tr>
<td>Dioxin (TCDD)</td>
<td>0.001</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Toxicology Terms

**Toxicity** - The adverse effects that a chemical may produce.

**Dose** - The amount of a chemical that gains access to the body (mg/kg)

**Adverse effects**
- any change from an organism’s normal state
- dependent upon the concentration of active compound at the target site for a sufficient time.

**Hazard** – is a chemical substance, physical agent, or biological agent that can harm the health of people

**Exposure** – Exposure means Contact with a hazard
- Exposure Frequency – how often
- Exposure Duration – how long
- Exposure Concentration – how much

**Risk = Hazard X Exposure**
Exposure

Duration and frequency are important components of exposure and contribute to dose.

• Single exposure: Acute exposure - less than 24 hours

• Repeated exposures are classified as:
  • Subacute - repeated for up to 30 days
  • Subchronic - repeated for 30-90 days
  • Chronic - repeated for over 90 days
Mechanisms of Toxicity

1. Interfere with $O_2$ transport or tissue utilization of oxygen
   • (example cyanide, CO)
2. Affect CNS
   • (example cocaine, sedatives)
3. Affect ANS
   • (example organophosphates)
4. Affect lungs
   • (example paraquat)
5. Affect cardiovascular system
   • (example TCA, Ca$^{++}$ channel blockers)
6. Direct local damage
   • (example acids, bases)
7. Delayed effects on liver or kidneys
   • (example acetaminophen, metals)
What is Toxicology?

- Old definition: the basic science of poisons
- New Definition: the study of the adverse effects of chemical agents on biological systems

- The ultimate goal is to increase our understanding of how chemicals affect human health.
Dose - Response Curve

Dose-Response Relationship: As the dose of a toxicant increases, so does the response.

0-1 NOAEL
2-3 Linear Range
4 Maximum Response

NOAL No Observable Adverse Effect Level
Dose-response curve for alcohol

- No effect
- Giddy
- Sleep
- Deep sleep
- Unconscious
- Labored breathing
- Death
Glasses of Wine - Dose Response

% Difficulty Walking

Glasses of Wine

All Effected

Amount half are affected

NO Effect
What is a Response?

- The degree and spectra of responses depend upon the dose and the organism
- Change from normal state
  - molecular, cellular, organ, or organism level
  - Local or Systemic
  - Reversible or Irreversible
  - Immediate or Delayed
  - Graded or Quantal
    - degrees of the same damage vs. all or none
Route of Exposure

- Ingestions account for 79% of exposures
  - 7% dermal
  - 6% ophthalmologic
  - 5% inhalations
  - 3% stings and bites
  - 0.3% injection

Typical Effectiveness of Route of Exposure:

iv > inhale > ip > im > ingest > topical
What toxicologists do?

Most toxicologists work to develop a mechanistic understanding of how chemicals affect living systems:

- Develop safer chemical products
- Develop safer drugs
- Determine risks for chemical exposures
- Develop treatments for chemical exposures
- Teach (e.g. other toxicologists, graduate students)

**Risk**: the probability that harm will occur under specified conditions

**Safety**: the probability that harm will not occur under specified conditions
Areas of toxicology (fields of specialty)

Mechanistic toxicologists study how a chemical causes toxic effects by investigating its absorption, distribution, and excretion. They often work in academic settings or private industries and develop antidotes.

Descriptive toxicologists evaluate the toxicity of drugs, foods, and other products. They often perform experiments in a pharmaceutical or academic setting.

Clinical toxicologists usually are physicians or veterinarians interested in the prevention, diagnosis, and treatment of poisoning cases. They have specialized training in emergency medicine and poison management.
Areas of toxicology (fields of specialty)

**Forensic toxicologists** study the application of toxicology to the law. They use chemical analysis to determine the cause and circumstances of death in a postmortem investigation.

**Environmental toxicologists** study the effects of pollutants on organisms, populations, ecosystems, and the biosphere.

**Regulatory toxicologists** use scientific data to decide how to protect humans and animals from excessive risk.
Are you interested to be a toxicologist??

A career in toxicology

• involves evaluating the harmful effects and mechanisms of action of chemicals in people, other animals, and all other living things in the environment.

• This work may be carried out in government, private industry and consulting firms, or universities and other research settings.

Toxicologists

routinely use many sophisticated tools to determine how chemicals are harmful (e.g.) computer simulations, computer chips, molecular biology, cultured cells, and genetically-engineered laboratory animals.
Types of toxic effect

A wide variety of effects:

• Allergic agents: itching, rashes, sneezing, watery eyes.

• Asphyxiants: cause displacement of oxygen and thus suffocation.

• Irritants: cause pulmonary edema (fluid in the lungs) when inhaled at high concentrations and rashes when spilled onto the skin.

• Necrotic agents – cause cell death.

• Carcinogens, mutagens and teratogens: Cancer, mutations, and deformed embryos result from chronic exposure to low levels

• Systemic poisons – can have an adverse effect on the whole body when taken internally.
Adverse Effect

Not all organs are affected equally

- greater susceptibility of the target organ
- higher concentration of active compound

Liver: high blood flow, oxidative reactions
Kidney: high blood flow, concentrates chemicals
Lung: high blood flow, site of exposure
Neurons: oxygen dependent, irreversible damage
Myocardium: oxygen dependent
Bone marrow, intestinal mucosa: rapid divide
Types of Toxic Effects

Death - arsenic, cyanide

Organ Damage - ozone, lead

Mutagenesis - UV light

Carcinogenesis - benzene, asbestos

Teratogenesis - thalidomide
Mechanisms of Toxic Effects

Adverse effects can occur at the level of the molecule, cell, organ, or organism

**Molecular level:** chemical can interact with: Proteins / Lipids / DNA

**Cellular level:** chemical can

- interfere with receptor-ligand binding
- interfere with membrane function
- interfere with cellular energy production
- bind to biomolecules
- Agitate homeostasis
Types of Interactions

Additive effects: (1+1 = 2)

Synergism: one contaminant enhances the effect of another (1+1 = 3)

Antagonism: one contaminant reduces the effect of another

Tolerance

state of decreased responsiveness to a toxic effect of a chemical, resulting from previous exposure

- dispositional tolerance; a decreased amount of drug reaching the site
- cellular; reduced responsiveness of a tissue
Toxicokinetics

Storage in Tissues (fat, bone, plasma proteins)

Site of Action

Mechanism of Action

METABOLISM

Excretion

Plasma

DOSE

Xenobiotic Exposure
Metabolism

1) Decrease biological activity
2) Increase excretability

Lipophilic (parent compound) → Metabolism

Phase I (oxidative) → Metabolites
Bioactivation
Detoxification

polarity
functionality

Phase II (synthetic) → Metabolites
Detoxification

Hydrophilic (metabolite)

size
ionization
water solubility

Increase excretability
ADME

- Once a living organism has been exposed to a toxicant, the compound must get into the body and to its target site in an active form in order to cause an adverse effect.

- The body has defenses:
  - Membrane barriers
    - passive and facilitated diffusion, active
  - Biotransformation enzymes, antioxidants
  - Elimination mechanisms
Absorption (ability of a chemical to enter the blood; blood is in equilibrium with tissues)

- **Inhalation**
  - readily absorb gases into the blood stream via the alveoli. (Large alveolar surface, high blood flow, and proximity of blood to alveolar air)

- **Ingestion**
  - absorption through GI tract stomach (acids), small intestine (long contact time, large surface area--villi; bases and transporters for others)
    - First Pass Effect (liver can modify)

- **Dermal**
  - absorption through epidermis (stratum corneum), then dermis; site and condition of skin
Distribution: Storage and Binding

• Storage in Adipose Tissue
  • Very lipophylic compounds (DDT) will store in fat.
  • Rapid mobilization of the fat (starvation) can rapidly increase blood concentration

• Storage in Bone
  • Chemicals analogous to Calcium: Fluoride, Lead, Strontium

• Binding to Plasma Proteins
  • can displace endogenous compounds. Only free is available for adverse effects or excretion

\[ \text{dichlorodiphenyltrichloroethane} \]
To make chemical agents more water soluble and easier to excrete:

- decrease lipid solubility --> decrease amount at target
- increase ionization --> increase excretion rate
- Can drastically effect the rate of clearance of compounds
- Can occur at any point during the compound’s journey from absorption to excretion

<table>
<thead>
<tr>
<th>Compound</th>
<th>Without Metabolism</th>
<th>With Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>4 weeks</td>
<td>10mL/hr</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>5 months</td>
<td>8hrs</td>
</tr>
</tbody>
</table>
Metabolism or Biotransformation

Key organs in biotransformation:

- LIVER (high)
- Lung, Kidney, Intestine (medium)
- Others (low)

Biotransformation Pathways

Phase I--make the toxicant more water soluble
Phase II--Links with a soluble endogenous agent (conjugation)
Excretion

Toxicants are eliminated from the body by several routes:

- **Urinary excretion**
  - water soluble products are filtered out of the blood by the kidney and excreted into the urine
- **Exhalation**
  - Volatile compounds are exhaled by breathing
- **Biliary Excretion via Fecal Excretion**
  - Compounds can be extracted by the liver and excreted into the bile. The bile drains into the small intestine and is eliminated in the feces.
- **Milk**
- **Sweat**
- **Saliva**
Scale of Toxicities

- Classifications are arbitrary!
- A typical scale of toxicities:
  
<table>
<thead>
<tr>
<th>Category</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely toxic</td>
<td>50 mg/kg or less</td>
</tr>
<tr>
<td>Moderately toxic</td>
<td>50 – 500 mg/kg</td>
</tr>
<tr>
<td>Slightly toxic</td>
<td>0.5 – 5 g/kg</td>
</tr>
<tr>
<td>Relatively harmless</td>
<td>5 g/kg or more</td>
</tr>
</tbody>
</table>
Individual Susceptibility

There can be 10-30 fold difference in response to a toxicant in a population!

**Genetics** species, strain variation, interindivudual variations

**Gender** (gasoline nephrotox in male mice only)

**Age**
- underdeveloped excretory mechanisms
- underdeveloped biotransformation enzymes
- underdeveloped blood-brain barrier
- body fat

**Nutritional status**

**Health conditions**

**Previous or Concurrent Exposures**
Toxicology helps create a safer world ...

- Toxicology is a fascinating science that makes biology and chemistry interesting and relevant.
- Understanding HOW (i.e. mechanism) something produces a toxic effect can lead to new ways of preventing or treating chemically-related diseases.
- Many diseases are the result of an interaction between our genetics (individual variability) and chemicals in our environment.
- Toxicology provides an interesting and exciting way to apply science to important problems of social, environmental, and public health significance.
A couple of references ...
Study hours ...

Familiarize yourself with the signs and symbols of toxic agents

Together we will explore poisoning on the 5th of Nov...