Introduction to Clinical Pharmacology & Toxicology

K. Scott Whitlow, DO, FAAEM
Assoc. Medical Director – VA Poison Center
Asst. Prof. Emergency Medicine – VCU-SOM
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Objectives

- Review the principles of Toxicology
  - LD50, dose-response, branches
- Review basic metabolism of toxins
  - Phase one / phase two rxns, CYP450
- Review mechanisms of toxicity
  - Acute/Chronic toxicity
  - carcinogenesis, mutagenesis, teratogenesis
  - Organ toxicity
  - hypersensitivity
- Discuss approach to the poisoned patient
  - Initial evaluation
- Discuss toxidromes
Definitions

1. Toxicology:
   The study of the adverse effects of chemical agents on biologic systems.

2. Xenobiotic:
   A chemical that interacts with an organism that is not found in the normal metabolic pathway of that organism.

LD50

- It is a dose that kills 50% of the exposed animals.
- Can vary among chemicals
- Examples:

<table>
<thead>
<tr>
<th>LD50 (mg/kg body weight)</th>
<th></th>
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<tbody>
<tr>
<td>Ethyl alcohol</td>
<td>10,000</td>
</tr>
<tr>
<td>Morphine</td>
<td>900</td>
</tr>
<tr>
<td>Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin:TCDD)</td>
<td>0.001</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>0.00001</td>
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Toxicity

Exposure:
- **Acute**: Usually a single dose within 24 hours
- **Sub acute**: repeated exposure to a chemical for < 4 weeks
- **Sub chronic**: 1-3 months
- **Chronic**: > 3 months

Dose response relationship

No observed effect level (NOEL) → Used to detect safety levels

mg/kg

Chemical
Branches of Toxicology

- Biochemical Toxicology
  - PhD’s
- Forensic Toxicology
  - PhD’s
- Clinical Toxicology
  - PharmD’s, PhD’s, MSN’s
- Medical Toxicology
  - MD/DO’s
- Immunotoxicology
  - PhD’s

Metabolism of Toxins

- Enzymes
  - Convert lyophilic to hydrophilic.
- Phase-one reactions → a polar reactive group is introduced into the xenobiotic molecule.
  - cytochrome P450s.
  - CYP 2E1 plays a critical role in the metabolism of Acetaminophen.
    - Creates toxic free radical (NAPQI)
- Phase-two reactions → enzymes conjugate the xenobiotic
  - to sugars, aminoacids, etc
  - forming water-soluble products that are readily excreted.
- metabolites ? are more toxic
  - APAP, alcohols, carbamazepine, meperidine, propoxyphene
Chemical Hypersensitivity

- Two types:
  - Type I hypersensitivity (allergy): IgE Abs, Neutrophils
  - Type IV hypersensitivity (contact dermatitis): T cells, macrophages

Contact Dermatitis (Nickel)
Carcinogenesis

- Carcinogenesis:
  - Process by which chemicals cause cancer.
- Many environmental chemicals/agents are known carcinogens
  - Tobacco, heavy metals, coal tar, UV light, radiation, etc
  - Chemicals classified as carcinogens based on ability to induce tumors in animal models.
- Chemicals can induce tumors
  - directly
    - damaging or modifying DNA (genotoxic)
  - Indirectly
    - suppressing the immune system, changing hormone balance

Mutagenesis

- Mutagenesis
  - Toxicity on genetic material and its inheritance.
- Mutagens include:
  - ionizing radiation
  - alkylating agents
  - most carcinogens
Teratogenesis

- Teratogenesis:
  - Deleterious effects on developmental process.
- Thalidomide:
  - known human teratogen (3-7 weeks gestation)
  - Phocomelia
    - shortening or complete absence of limbs.
- Methyl mercury
  - Neurotoxic to fetus/developing brains
- Alcohol
  - Fetal Alcohol Syndrome
- Diethyl stilbestrol (DES)
  - a synthetic estrogen
    - Reproductive CA in female children of exposed pts

Reproductive toxicity

- Many chemicals are toxic to the reproductive system.
  - decreased sperm count.
  - “environmental estrogens” (DDT, DDE)
    - cause hermaphroditic fish
    - sex reversal in alligators.
Immunotoxicology

- Late 1970-early 1980s
  - Chemicals alter the immune system
    - immunotoxicity
- Several are environmental pollutants
  - metals, halogenated hydrocarbons, carbamates, organophosphates.
- Alter immune functions at very low concentrations
  - doses that do not produce organ toxicity.

Immunotoxic Compounds

- Environmental Contaminants:
  - Insecticides, pesticides, herbicides, hydrocarbons and heavy metals.
- Dusts:
  - Silica, carbon.
- Heavy metals:
  - Lead, mercury, arsenic, thallium, etc
    - Metals have both acute and chronic toxicities
      - Acute: N, V, D, AMS, MSOF
      - Chronic: neuropathies, alopecia, skin changes
- Addictive substances:
  - Alcohol, heroin, tobacco
- Food additives:
  - pyrogallol, carrageenan, etc
## Dioxin (TCDD) Toxicity in Humans

### Agent Orange
- Dioxin was the primary toxic component of Agent Orange.
- Was a byproduct of production.

### Conditions recognized as service-connected for Vietnam veterans based on exposure to Agent Orange or other herbicides:
- Chloracne
- Non-Hodgkin's Lymphoma
- Soft Tissue Sarcoma
- Hodgkin's Disease
- Porphyria Cutanea Tarda
- Multiple Myeloma
- Respiratory Cancers (lung, larynx, trachea and bronchus)
- Prostate Cancer
- Peripheral Neuropathy (acute or subacute)

### Conditions recognized in the children of Vietnam Veterans:
- Spina bifida
- High levels of dioxin found at ground zero of WTC
- Suspected toxicity and links to disease have NOT been PROVEN.
Neurotoxicity

- Pesticides:
  - Organophosphorus (OP) insecticides
    - inhibit acetyl choline esterase
  - SLUDGE- BBB
    - Seizures
    - Intermediate syndrome
- Nerve gas
  - Soman, vx, sarin, etc
    - seizures
- MPTP (1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine)
  - contaminant of “synthetic heroin”
    - irreversible Parkinson’s-like symptoms.

Mercury

Mercury (Hg)
  - elemental, inorganic and organic forms.
    - immune, sensory, neurological, motor, and behavioral dysfunctions.

Mercury compounds (thimerosal) are used as preservatives in nasal solutions, opthalmic drugs, Vaccines.

- NO plausible link to autism
- NO epidemiologic link
Nephrotoxicity

- Kidneys
  - Heavy metals are potent nephrotoxins
    - Cadmium, mercury, lead etc
  - Ethylene Glycol
    - metabolites
- Effects:
  - Glucosuria, proteinuria, renal necrosis and death.

Pulmonary Toxicity

- Inhalation of silica (mining and quarrying area)
  - causes fibrosis or formation of collagenous tissue.
  - can impair respiration.
- Asbestosis
  - may cause lung cancer
    - mesothelioma
- Cigarette smoke
  - polycyclic aromatic hydrocarbons
    - benzo(a)pyrene
      - metabolized by cytochrome P450. This metabolites may trigger cancer
ALI (Acute Lung Injury):

- hypoxia, aspiration, barotraumas, cardiac stunning
  - Assoc with opiates, hydrocarbons, caustics, irritant gases, etc
- Opiate induced
  - Onset > 24h after use
  - Described in 48% pts admitted with heroin OD
  - 90% of pts who die pre-hospital
Hepatotoxicity

- Liver is highly susceptible
  - First organ to encounter xenobiotic when ingested.
- Carbon tetrachloride is the most widely studied.
  - Cytochrome P450 converts it to a free radical
- > 1100 pharmaceuticals assoc with FHF in US
  - APAP = 50%
    - Causes centrolobular necrosis
    - Prophylaxis and treatment with N-Acetyl-Cystiene

History

- Often unreliable
- Rely on EMS, bystanders, family members and other physicians
- Psychiatric/PMHx
- Where are the bottles?
- What was the environmental setting
  - Factory, Gas space heater in winter – think CO!!
  - Dorm Room, obtunded – think GHB, MDMA
- Check pockets, bags, belongings
Physical exam: Vital signs

- Vital signs are very important:
  - Hyperthermia (ASA, cocaine, anticholinergics)
  - Hypothermia (opiates, barbiturates and sedatives)
  - HTN (cocaine, amphetamines, sympathomimetics)
  - Hypotension (calcium channel and beta blockers)
  - Tachycardia
  - bradycardia (Clonidine, Organophosphates)
  - Hypoxemia
  - Blood glucose (hypoglycemia from sulfonylureas, insulin overdose)

Neurologic exam

- Level of consciousness
- ? focal findings.
- Miosis
  - clonidine, opiates, cholinergics
- Mydriasis
  - Sympathomimetics, anticholinergics
- Clonus and rigidity
  - Neuroleptics
  - Serotonin receptor agonists
  - Depolarizing neuromuscular blockers
- Seizures
Skin exam

- Dry: anticholinergic
- Diaphoretic: cholinergic, hypoglycemia or sympathomimetic
- Cyanosis: MetHb
- Blisters: Barbs and CO
- Cherry red: Cyanide
- Track marks for IVDA

Abdominal Exam

- ? Bowel sounds/peristalsis
- ? Palpable bladder
Diagnostics-Radiology

- Chest X-ray for pneumonitis and prior to HBO therapy
- KUB for radioopaque ingestions (CHIPES)
  Chloral Hydrate
  Heavy metals
  Iron
  Packers
  Enteric coated
  Sustained release
- Bezoars: displace the gastric bubble.
EKG

- Look at the rate
- Look at the size of different intervals
- Look at the shape of QRS in aVR
- Remember certain pathognomonic EKG’s
  - bidirectional V-tach = Digoxin
  - widened QRS = TCA
Labs

- Anion gap
  \( \text{Na}-(\text{HCO}_3+\text{Cl}); \text{nl}<14-16 \)

- Osmolal gap: Meas Osm – Cal Osm
  \( \text{Cal Osm}= 2\text{Na}+\text{BUN}/2.8+\text{Gluc}/18+\text{EtOH}/3.7 \)
  A normal gap is –14 to 10
  (Hoffman R. Clin Tox. 1993;31:81-93)

  Co-oximetry MetHB, COHb. Venous pH is acceptable.

- Pregnancy test

Drug levels

- APAP in all intentional OD’s but not ASA:
  - 6-11% of suicidal pts had detectable APAP
  - 0.3% had a negative history of ingestion and APAP level >50mg/dl,
  - .016% had toxic ASA levels but also had AG acidosis
    in another study 1.9% had APAP levels
  (Ann Emerg Med. 18(10):1035-8)
Drug levels

- Specific drug levels:
  - ASA
  - EtOH
  - Phenytoin
  - Iron
  - Tegretol
  - Ethylene glycol
  - Valproic Acid
  - Methanol
  - Theophylline
  - Lithium
  - Digoxin
  - Others

Urine drug screens

- Urine drug screens are usually not helpful
- Cocaine stays positive for 3 days
- False positives
  - Dextromethorphan for PCP
  - Benadryl for TCA
  - Pseudophed for amphetamines
- False negatives
  - Benzo assay does not detect all benzodiazepenes
Disposition

- Intentional overdoses
  - Observation for at least 4 to 6 hrs
  - Mandatory psychiatry evaluation
- Admission
  - Persistent AMS
  - Unstable vital signs
  - Substances with the potential for delayed toxicity

Disposition

- Substances with the potential for delayed toxicity
  - Oral sulfonylureas
  - Sustained-release medications
  - Bodpackers
  - Toxic alcohols
Disposition

- Drug abusers should be offered rehab
- Consult your regional poison center.
  - In VA 3 centers serve commonwealth
- VPC 828-9123
  - National Toll free number 1-800-222-1222

Toxidrome - Sympathomimetic

- Cocaine, Amphetamines, PCP
  - Hypertension
  - Tachycardia
  - Diaphoresis
  - Mydriasis
  - Agitation
Anticholinergic

- TCA, Benadryl, Antihistamine meds
  - Tachycardia
  - Hyperthermia
  - Dry skin
  - Mydriasis (lack of constriction to light)
  - Decreased bowel sounds
  - Urinary retention
  - Delirium, agitation

*Hot as a hare, Dry as a bone, Red as a beet, Mad as a hatter,*
*Blind as a bat.*

Cholinergic

SLUGBAM mnemonic for muscarinic effects

- S- SALIVATION, SEIZURE
- L- LACRIMATION
- U- URINATION
- G- GI DISTRESS (diarrhea & vomiting)
- B- BRONCHORRHEA, Bronchoconstriction, Bradycardia
- A- ABDOMINAL CRAMPS
- M- MIOSIS
Cholinergic

MTWThF (Nicotinic effects)
- M-Mydriasis
- T-Tachycardia
- W-Weakness
- TH-Hyperthermia
- F-Fasciculations

Organophosphates, Carbamates, Nerve agents

Opiates

- Opiates, Clonidine
  - Miosis
  - Hypotension
  - Bradypnea
  - Bradycardia
  - Hypothermia
  - CNS Depression
Sedative-Hypnotic

- Benzodiazepines, GHB
- “Coma with normal vital signs”
  - CNS Depression
  - Normotensive
  - Mild bradypnea or normal respiratory rate

Withdrawal

- ALWAYS consider!!!
- chronic drug administration
  - Physical dependent patient
  - Abrupt cessation
  - Antagonists or lack of access
- S/S (signs and symptoms) tend to be opposite of intended therapeutic effects