Medical Aspects of Pesticide and Herbicide Exposures (selected)

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Objectives/Disclaimers

• Review selected pesticides and herbicides
  • Not a whirlwind list you won’t remember, but will discuss a few high yield products that the Poison Center hears about a lot
• Structures are presented for perspective
  • If you don’t like chemistry, then look away.....
Carolinas Poison Center

• We are the state poison center
• Take calls from the public, law enforcement and from health care providers
  – Function as entity for reporting occupational pesticide exposures
• The CPC reports all severe pesticide poisonings (not just occupational) to Public health
• Medical Toxicologists are available 24/7/365 for consultation by other health care providers
• Education efforts to the public
Ideal Product

• Lethal against target organism (plant or insect)
  – Limited toxicity against similar organisms
  – No toxicity in humans
• No resistance can develop vs. agent
• Agent degrades in environment in favorable time frame
• No product is perfect
  – Especially when you consider the human tendency to use things in ways never imagined
Herbicides

• Designed for killing undesirable plants
• Several different categories
• In general, humans do not usually experience toxicity from herbicides.
  – But...
Recent Case Example

- A 61 year old man drank “a few tablespoons”/one mouthful of unknown weed killer he got from a friend in a water bottle
  - Was thirsty after the gym and just grabbed bottle by accident.
  - Bluish green color
- Throat pain, vomiting—brought up blue colored vomitus
- Started on antibiotics, steroids and discharged after 23 hr observation; felt embarrassed about whole event.
- Returns 4 days later with continued problems swallowing, mouth sores and breathing issues; labs revealed renal failure
- Bilateral chest x-ray infiltrates which progressed; pneumonia
- Vasopressors, steroids, cyclophosphamide, nitric oxide, N-acetyl cysteine, antibiotics, ventilator, and dialysis
- Died 21 days after the ingestion. (Black Friday)
Bipyridyliums

- Consists of two compounds
  - Paraquat
  - Diquat
- Non-selective herbicides
- Diverts electrons in the plant during photosynthesis (Photosystem – I – electron diversion)
  - Meaning the electrons don’t go to plant energy but to generate toxic oxygen species
- Rapidly deactivated with soil contact
- Fast acting herbicide
- Significant Human toxicity
Paraquat

- Used extensively around the world
  - Popular suicide method
- In US, it is available but is restricted to licensed applicators.
  - Multiple cases of toxicity from “shared” products
- For safety, dyed dark blue
- Concentrate quite deadly
- Respect even for dilute
Paraquat

- Once absorbed, unfortunately selectively taken up by specialized lung cells (alveolar cells)
  - Undergoes redox cycling with oxygen within human lungs
    - Sort-of a controlled “burn”
    - Oxygen becomes toxic (more than the usual)
    - Similar killing mechanism as with plants
  - Results in toxic oxygen species (hydrogen peroxide)
    - Giving oxygen as therapy is the wrong answer.
  - Paraquat is removed from those cells very slowly
  - Unavoidable, progressive, irreversible lung injury over several days
- Sometimes more rapid death with larger doses (acidosis, renal failure, coma)
Paraquat

- Not a risk most circumstances when dilute sprayed
  - Occasional dermal injury
- Weak link with chronic applicators and Parkinson's disease
  - But not consistent in all studies.
  - Given mechanism of action, lack of toxicity with the dilute product and inability to cross the blood brain barrier, somewhat suspect finding.
Paraquat

- Renal elimination
  - “pumped out”; not metabolized
  - Paraquat also poisons kidneys
- Horrible corrosive mucosal injuries
- Can find in urine via spot test
  - Paraquat is also known as Methyl Viologen – indicator used for redox reactions
Diquat

• Less dangerous of the two “quats”
• Often found combined with Glyphosate, another broad spectrum herbicide
  – Increases effectiveness
  – Rapid onset
  – Reduced resistance
• When diquat is diluted, not usually problematic
Diquat

- Shape of molecule doesn’t “Fit” the uptake pump in the lung cells
  - So no pulmonary injury
- But it does fit in uptake pump in renal cells
- Renal failure
- Brain stem infarction
- But less likely to be lethal even with unintentional concentrated ingestions (still kills)
- Much milder dermal irritation
- Can also perform the dithionite urine test
Glyphosate

• Broad spectrum herbicide
  – One brand is Roundup®
• Inhibits a pathway (shikimic acid) that animals do not have.
• Organic phosphorus containing compound
  – But not an organophosphate.
• Genetically engineered crops with resistance to glyphosate now used
  – Spray the field, kill everything green that is not your engineered crop.
  – Benefits to this technique
• Doesn’t kill plants as fast as other herbicides
Glyphosate

- Is not metabolized and does not accumulate
- Is (almost) completely non-toxic in humans
- Requires formulation with surfactant ("soap") to get into solution and into a plant.
- The *surfactant* is what is concerning when there is ingestion exposure to the concentrate
Glyphosate

• One of the most common agricultural product exposures to poison centers
• Only really problems when there is ingestion of the concentrate (i.e. surfactant)
  – These cases are nearly always intentional
  – Gastrointestinal injury
  – Hypotension
  – Acidosis
• Dilute exposures are a non-issue in humans, even chronic exposures
Selected Insecticides

• Organophosphates
• Carbamates
• Pyrethroids
Organophosphates

- Group of very important pesticides
- Used extensively around the world in huge quantities
- Some organophosphates in use (WHO classification)
  - Acephate
  - Chlorpyrifos*
  - Diazinon*
  - Dimethoate*
  - Malathion (&medicinal)
  - Parathion***
  - Phosmet*
  - Phorate***

- CPC gets plenty of calls that start with “I was cleaning out an old barn/shed when I found/spilled...X”
Organophosphates

• Term used to describe a class of compound with cholinergic effects
  – “Organic phosphorus” compounds would include things like ATP and DNA

• Careful choosing side groups has resulted in compounds with selectivity against insects.

• “Nerve gases” are basically human insecticide
  – VX (not a gas), Sarin, Soman are nerve agents
  – Incredibly high lethality
  – Very similar process of causing injury
  – Similar therapies

![Sarin](image)
Organophosphates

• Inhibit several enzymes in the human body
• Two important enzymes are
  – Acetylcholinesterase
  – Neuropathy Target Esterase
Organophosphates

• The organophosphate compound binds to the active site of acetylcholinesterase
• Part of the organophosphate breaks away.
• The enzyme now is inactivated and remains inactivated. Two possibilities now for the enzyme:
  – The part can leave/undergo hydrolysis and the enzyme can become active again (therapy)
  – The part can “age” and now be permanently bound to the enzyme
Organophosphates

• **Acetylcholinesterase** enzyme responsible for breaking down acetylcholine and “ending” certain neuronal transmission
  – Acetylcholine used in muscle cells (nicotinic)
  – Acetylcholine used in certain secretion cells (muscarinic)
  – Sympathetic/parasympathetic systems

• By preventing the acetylcholinesterase enzyme from working, victims have persistent acetylcholine at synapses
Organophosphates

• Elevated levels of acetylcholine causes a combination of toxicological syndromes -- Cholinergic toxicity
• DUMBBBELL$S$ [Muscarinic contribution]
  – Diarrhea
  – Urination
  – Miosis (not always*)-vision changes
  – Bronchorrhea
  – Bronchospasm
  – Bradycardia (not always)
  – Excitation of CNS-headache, seizures
  – Lacrimation
  – Lots of vomiting
  – Salivation
• Weakness, Fasciculations, Tachycardia [Nicotinic contribution]
Autonomic Nervous System

Parasympathetic

- Autonomic Ganglia
  - ACh
  - M
  - Glands
  - Bladder
  - Gut
  - Heart

Sympathetic

- ACh
- M
- A
- Epinephrine
- Norepinephrine
- Heart
- Blood Pressure

Somatic

- ACh
- Brain

Central

- ACh

Thanks to Z. Kazzi, MD
Organophosphates

- Due to lipophilicity and conversion to active metabolite, recurrence of symptoms reported days after acute exposure to some agricultural OPs
  - Extending therapy for sufficient time
- Intermediate syndrome can develop several days after acute exposure
  - Sometimes some degree of recovery from cholinergic sx before it develops
  - Marked by weakness, cranial neuropathies
  - May take weeks to resolve
  - Not the same as insufficient therapy although there is possibly a link
Organophosphates

- Chronic symptoms
  - Because of longer biological half life, repeated low level exposures can result in cholinergic illness
  - Neuropsychiatric changes reported in some populations (acute & chronic exposures)
    - Anxiety, sleep changes, changes in mentation
    - It is known that these changes can occur with acute exposure episodes, especially with war agents
    - Neuropsychiatric changes with chronic low level exposures are harder to define as these populations are not studied as well
  - Concerns for chronic exposures resulting in neurocognitive developmental delays in children.
Organophosphates

• Neuropathy target esterase (NTE) inhibition
• Compounds used in North America all have much greater affinity for Acetylcholinesterase than for the NTE
• This is good because inhibition of NTE causes neuronal death
  – Loss of sensation and motor function
  – Degree of permanence to the injury
• Organophosphate induced delayed polyneuropathy (OPIDP)
Organophosphates
NTE

• Mass poisoning episode of Ginger Jake Leg Paralysis from TOCP
  – TOCP is an Organophosphate compound
  – Contaminated ginger extract
  – 1000s affected; records poor
  – Woke up unable to walk; never had cholinergic sx.

• The cholinergic symptoms serve as a “warning”

• Will not generally occur without episode of significant systemic poisoning with agricultural organophosphates.
Organophosphates

- Diagnosis of exposure
  - History and exam
    - Concentrate/Dilute
    - Acute/Chronic
    - Route(s) of exposure
  - Serum cholinesterase (plasma cholinesterase) and Red Blood Cell cholinesterase can be done for acute diagnosis and chronic surveillance
  - Peripheral cholinesterases are similar to what is happening in the nerves---but not the same.
Organophosphates

• Treatment
  – Remove from exposure;
    • Concentrated product will require decontamination and disposal of leather due to permeation
    • Solvent used for concentrated product is volatile; the OP has much less volatility
    • Protect your staff- limit dermal exposure (vomitus, dermal contamination, clothing)
    • Cases of ED staff developing “illness” following treating a patient with pesticide ingestion vomiting
  – Decontamination
    • Activated charcoal would work for the GI tract, but usually they are vomiting so much the value is questionable
  – ABCs; Most patients die an airway death
    • Intubation
    • Secretions
    • Ventilation becomes impossible- you can’t squeeze in enough air past the secretions.
Organophosphates

- Treatment
  - Muscarinic antagonist/blocker; anticholinergic
    - Atropine (IV probably best route, but inhaled/IM used)
    - Dose much above published doses
    - 100’s of mg (50x+ usual doses) used*
    - Dosed to dry secretions to ventilate- tachycardia is not a reason to stop
  - Diazepam (Valium ®) for seizure prophylaxis
• Restore the acetylcholinesterase enzyme
  – Oxime therapy using pralidoxime / 2-PAM
  – Bolus followed by infusion
  – Removes the OP from not-aged enzyme

Mark I and Antidote Treatment nerve Agent Auto injector (ATNAA) are designed for military use and have atropine and 2-PAM
Carbamates

• Insecticides similar to organophosphates
  – Medicinal ones include neostigmine and physostigmine
  – More toxic members include aldicarb, methomyl and propoxur

• Similar mechanism of toxicity to organophosphate

• Some have good water solubility (better than OP)
  – Can result in episodes of toxicity where it is incorrectly used on vegetables with high water content
  – Aldicarb
Carbamates

- Inhibition of acetylcholinesterase by binding to the enzyme and rendering it inactive (same as OP)
- However, it does not “age” and carbamates will hydrolyze off the acetylcholinesterase without specific treatment
- No bio-accumulation in humans; enzyme recovery is fast
  - Less concern for chronic exposures
- Rare chronic neuropsychiatric effects with acute toxicity event as well as chronic exposure, but less severe than organophosphates
  - Sleep changes, anxiety, lethargy, vertigo, changes in decision making
  - Not well studied
Carbamates

- Treatment is similar to organophosphates
- The role of 2-PAM is controversial, but is probably not needed
- I think of Carbamates as weak Organophosphates
- But intentional large ingestions of the concentrate are still rapidly lethal
Pyrethroids

- Pyrethrins found in Chrysanthemum are natural insecticides
- Limitations in their stability and selectivity
- Synthetic derivatives are pyrethroids
Pyrethroids

• First generation are sensitive to light and temperature changes
  – This is a good thing
  – Used for indoor pest control
  – Make up the majority of insecticide calls to CPC

• Second generation are more stable and are used outdoors in agriculture
Pyrethroids

• Cause neuroexcitation by interaction with sodium channels
  – These channels are what allow for nerve conduction
  – Channels rapidly open then have “second” gate which slams closed
  – Pyrethroids slow activation and slow the inactivation
  – Also effect at chloride channels which cause additional excitation by the Type II Pyrethroids

• Rapidly paralyzes insects whose channels are more sensitive to these effects

• Some of this selectivity in the pyrethroids comes from control of chiral centers
  – Variability of toxicity with product mixtures based on quality control during synthesis

Cyhalothrin
Pyrethroids

• Rapidly metabolized in humans (hours-days)
  – No bio-accumulation
• Human toxicity can occur with high doses absorbed over a reasonably short period of time
• Greater peripheral nerve sensitivity in humans than central nervous system
• Differences in the rate which the pyrethroid “falls off” the sodium channel differentiate Type I vs. Type II Pyrethroids
Pyrethroids

- Two types of pyrethroids
  - Type I (shorter binding, less toxic)
    - Permethrin (&medicinal), bioallethrin, cismethrin
  - Type II-(have cyano group, longer binding)
    - Cyhalothrin, cypermethrin, deltamethrin, fenvalerate
- Some with mixed properties (I and II)
- Division based on effect on sodium channel
- Differences in symptoms
- Compounded with solvents which can add additional toxicity (aspiration, dermal irritation)
Pyrethroids

• Type I (not seen much)
  – Fine tremor, reflex hyperexcitability, hyperthermia and sympathetic activation.
  – “T-syndrome" (Tremors).
• Type II [worse]
  – Salivation, coarse tremor, sympathetic activation, increased extensor tone, hyperexcitability, seizures, choreoathetosis, pulmonary edema, and coma.
  – "CS-syndrome" (choreoathetosis, seizures, salivation).
• Useful in helping differentiate from other pesticide toxidromes such as cholinergic toxicity
• Therapy will be mostly supportive following whatever decontamination can be performed.
Pyrethroids

• Inhalational exposure can result in “localized” symptoms of sodium channel effects; runny nose, sneezing, occasional hypersensitivity reactions (cough, dyspnea, wheezing) as well as headache and dizziness.

• Ingestion is usually intentional and results in irritant symptoms, GI distress as well as the systemic effects. The solvent often contributes to toxicity in these situations.
Pyrethroids

- Dermal absorption is poor, but localized symptoms (itching, paraesthesias/ sensory changes) common with Type I and II
  - Very common call to the CPC
- Treatment for dermal effects
  - Complete decontamination with soap and water
  - Vitamin E cream (probably either its lipophilicity or the cream itself).
Questions

- Thank you for your attention
- Please do not hesitate to contact the Carolinas Poison Center for all your poisoning needs
- Not just for pesticides!