



Chapter 163 – Pesticides

Episode overview:

Core questions:

1. Describe the cholinergic toxidrome from organophosphates
2. Describe the clinical presentation of organophosphate toxicity
3. How is organophosphate toxicity managed?
4. What are the complications of organophosphate toxicity?
5. What is the difference between organophosphates and carbamates?
6. What are the unique features of chlorinated hydrocarbon toxicity? What is an example of a chlorinated hydrocarbon? How are they managed?
7. How do Substituted Phenols (Dinitrophenol) cause toxicity? How are they managed?
8. How is toxicity from chlorophenoxy Compounds (Agent Orange) managed?
9. What is expected in paraquat toxicity? How is this managed?
10. What are the toxic effects of pyrethrins and pyrethroids?

Wisecracks:

- 1) What is aging – in relation to organophosphate toxicity?
- 2) What is the maximum formulation of DEET in pediatrics? When should you not use DEET?

Key concepts:

- Organophosphates and carbamates cause symptoms by accumulation of acetylcholine.
 - Treat cholinergic symptoms with atropine.
 - Reverse the inhibition of acetylcholinesterase with oximes (for ops only).
- Aging, which results in prolonged toxicity, occurs with organophosphate poisoning, but not with carbamates.
- Chlorinated hydrocarbons can present with seizures and cardiac toxicity
- Substituted phenols are found in weight loss products and exert their toxicity by uncoupling oxidative phosphorylation.
 - They can cause cardiac, liver, and renal injury.
- Chlorophenoxy compounds cause muscular injury.
 - Measure creatinine kinase; assess for acute rhabdomyolysis, kidney injury, and liver injury.
- Bipyridyl compounds cause pulmonary and renal injury.
 - Paraquat concentrates in lungs; limit supplemental oxygen therapy, because this will exacerbate pulmonary toxicity.
 - Diquat causes renal injury.
- Pyrethrins and pyrethroids cause local dermatologic symptoms. With some systemic effect in large overdose (salivation and movement disorders)
- Glyphosate Acute toxicity is likely related to the surfactant included in the product.



- DEET should not be used in infants younger than 2 months old.
- DEET in concentrations of more than 30% should not be used in children and may result in neurotoxicity and self-limited seizure activity if used in excessive amounts.
- Most rodenticide exposures will be superwarfarin compounds.
 - For large exposures, INR should be checked at a minimum of 2 days after ingestion.
 - Vitamin K should be used for reversal; blood products should be used for active bleeding.

Rosen's In Perspective

Pesticide is a general term that refers to all pest-killing agents, and so it includes insecticides, herbicides, rodenticides, and fungicides.

Here are some of the classes and examples

Refer to Table 157.1 in Rosen's 9th edition for a list of pesticide classes and examples

Pesticide Class	Example(s)
Organophosphates	Parathion, malathion
Carbamates	Aldicarb, carbaryl
Chlorinated hydrocarbons	DDT, lindane
Substituted phenols	2,4-dinitrophenol (DNP)
Chlorophenoxy pesticides	2,4,5-T, 2,4-D
Bypyridyl pesticides	Paraquat, diquat
Pyrethrins/pyrethroids	Permethrin
Glyphosate	N-(phosphonomethyl) glycine
Insect repellent	DEET

[1] Describe the cholinergic toxidrome from organophosphates

Organophosphates are a class of insecticide pesticides that work by inhibiting cholinesterases, including acetylcholinesterase and pseudocholinesterase.

Inhibition of cholinesterases results in accumulation of acetylcholine at multiple receptors within the body. (Autonomic nervous system, the sympathetic and parasympathetic ganglionic nicotinic sites, postganglionic cholinergic sympathetic and parasympathetic muscarinic sites, skeletal muscle nicotinic sites, and central nervous system sites).

Refer to Figure 157.1 in Rosen's 9th edition for the cholinergic effects on the nervous system

- **A great figure: check it out in Rosen's and listen to the show for an explanation!**

Notice that ACh can stimulate ALL PARTS of the nervous system:

- Central (seizures, coma)



- PNS
 - Somatic at the NMJ = PARALYSIS!!
 - Parasympathetic (SLUDGE and KILLER B's)
 - Sympathetic
 - HTN, Tachycardia, mydriasis

So to review, the **SLUDGE** and killer **B's** are...

Cholinergic Toxidrome = SLUDGE or DUMBELS

Refer to Box 157.1 in Rosen's 9th edition for the cholinergic toxidrome acronym
SLUDGE DUMBELS

S = Salivation

L = Lacrimation

U = Urinary incontinence

D = Diarrhea

G = Gastrointestinal cramps

E = Emesis

D = Diarrhea/diaphoresis

U = Urination

M = Miosis

(Killer) Bs: Bradycardia/bronchorrhea/bronchospasm

E: Emesis

L: Lacrimation

S: Salivation

[2] Describe the clinical presentation of organophosphate toxicity.

Organophosphates are lipid soluble and are absorbed through dermal, gastrointestinal, and respiratory routes. This can lead to deposition in fat tissues allowing for possible toxicity from acute and chronic, low-level exposures. Some organophosphates have active metabolites that can result in delayed toxicity.

Organophosphate toxicity is represented by the "SLUDGE" or "DUMBBELLS" syndrome (these are mnemonics, which are explained in Box 157.1) manifested by accumulation of acetylcholine at receptor sites. The clinical features in any given case are attributable to the location of the receptors affected, the properties of the specific organophosphate product (predominance of nicotinic (TTM) versus muscarinic effects), and the dose of the exposure.

Can also develop:

- At the neuromuscular junction, excess acetylcholine causes hyperstimulation of the muscles with secondary paralysis, and when the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest.
- Seizures
- Pulmonary edema



However, watch out for chronic toxicity:

Although the classic clinical picture of acute organophosphate poisoning is obvious, toxicity from gradual, cumulative exposure may be subtle.

- These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances; or chronic abdominal cramping, nausea, and diarrhea.

[3] How is organophosphate toxicity managed?

Patients who present with the classic toxidrome should be treated empirically without waiting for laboratory confirmation of decreased cholinesterase activity.

Other laboratory studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance. A measurement of acid-base status should be performed, because patients with acidosis have higher mortality than those without.

Treatment of organophosphate poisoning is directed toward four goals:

(1) Decontamination

- Start this out of hospital!! Protect more people from getting affected!
 - Remove all clothing and flush exposed skin copiously! (if no water available use flour or sand)
 - Caregivers should use universal precautions and PPE!
 - Charcoal is of NO benefit
 - Types of exposure: derm/GI ingestion/volatile gas inhalation
 - Consider NG/OG with massive and recent ingestion

(2) Supportive care with an emphasis on respiratory stabilization

- Death is a result of airway and respiratory failure, supportive care should be directed primarily toward airway management and includes suctioning of secretions and vomitus, oxygenation, and, when necessary, ventilatory support.
- Careful using succinylcholine during intubation (due to a prolonged effect - up to 6 hrs)
- Don't use BB to treat the tachycardia
- Treat agitation and seizures with benzo's
- There is no role for enhanced elimination or hemodialysis in organophosphate poisoning.

(3) Reversal of acetylcholine excess = titrate atropine to respiratory secretions

- **Atropine:** Definitive treatment for organophosphate poisoning is aimed at decreasing the amount and effect of acetylcholine at its various receptor sites.
- Atropine is a competitive inhibitor of acetylcholine at muscarinic receptors. **The atropine dose for the treatment of organophosphate poisoning is 1 to 3 mg (0.05 mg/kg in children) intravenously with doubling of each subsequent dose every 5 minutes until there is control of the muscarinic effects, particularly reduction in airway secretions.**
 - Average reversal dose is typically 20-30mg
 - Some patients need 200-500 mg of atropine in the first hour.
 - Patients often need an atropine infusion (20% reversal dose / hour)



KEY point:

“The endpoint of atropinization is drying of respiratory secretions, easing of respiratory effort, and normalization of respiratory rate. Early and rapid atropinization is associated with better control of seizures and reduced mortality in animal models.” Also, atropine will NOT reverse the respiratory muscle paralysis.

(4) Reversal of toxin binding at receptor sites on the cholinesterase molecule

- The second part of the treatment of organophosphate poisoning is the use of an oxime to regenerate acetylcholinesterase function.
 - Evidence is not great, take with a grain of salt for 2-PAM use and discuss with your toxicologist

Oximes bind to the organophosphate-cholinesterase complex causing a conformational change that allows for the cholinesterase to resume normal function. In other words, it re-activates the cholinesterase.

There are currently five oximes in common use worldwide: pralidoxime (2-PAM) is most commonly used in North America.

Indications for oxime treatment include:

- respiratory depression or failure,
- muscle fasciculations,
- seizures,
- dysrhythmias,
- hemodynamic instability,
- or the use of large amounts or repeated doses of atropine to completely control signs and symptoms of organophosphate intoxication.

We recommend administering pralidoxime as a 1 to 2 g bolus (25 to 50 mg/kg in pediatric patients) over 30 minutes, which can be repeated as needed (up to hourly) based on response (improved mental status, respiratory and heart rate, and decreased secretion).

The severity of the patient’s signs and symptoms guides management.

Refer to Table 157.2 in Rosen’s 9th edition for specific treatment dosing

Agent:	Indication:	Adult dose:	Pediatric dose:	Route:	Comments:
Atropine	Organophosphate toxicity	1-3 mg	0.05 mg/kg	IV, IM	Double dose every 5 minutes until effect
Pralidoxime	Organophosphate toxicity	1-2 g bolus	25-50 mg/kg	IV, IM	Given over 30 minutes, dose can be repeated based on response



[4] What are the complications of organophosphate toxicity?

Acute

- Complications from SLUDGE
- Complications from the killer B's
- Respiratory failure
- Seizures, coma, death

Delayed:

- Psychiatric sequelae
- Rebound toxicity:
 - *Patients may have rebound toxicity several days after apparently satisfactory response to initial treatment. This may occur for many reasons, including persistent release of organophosphates from lipid stores. Poisoning with fenthion is of particular concern, because initial symptoms could be mild and progress to life-threatening intoxication over time.*
 - *Essentially just a prolonged effect of the drug*
- Intermediate syndrome:
 - *The intermediate syndrome (IMS) can occur after the acute intoxication from organophosphates has resolved. IMS is delayed muscle paralysis, including respiratory muscles, which can occur **24 to 96 hours** after the resolution of the cholinergic crisis. The precise cause of IMS is not well documented.*
 - *Likely related to problem at NMJ*
- *Delayed peripheral neuropathy may occur 7 to 21 days after acute organophosphate intoxication. Therefore, close patient follow-up is important after stabilization.*
- *Complications from ICU stay*

Patients who present with significant symptoms (acute respiratory compromise associated with depressed cholinesterase levels) require admission and close monitoring, usually in an intensive care unit (ICU).

[5] What is the difference between organophosphates and carbamates?

Organophosphates	Carbamates (e.g. neostigmine / physostigmine)
	Are acetylcholinesterase inhibitors whose toxicological picture is similar to organophosphates.
<ul style="list-style-type: none">• Long duration of effect<ul style="list-style-type: none">○ At risk for rebound toxicity and intermediate syndrome• Aging can occur (see wisecracks)	Key differences: (1) short duration of effect (minutes to 24 to 48 hours) (2) the process of aging <u>does not</u> occur
	No need for Oxime therapy



Treatment:

- Decontamination, supportive care, and atropinization are usually adequate
 - Severe toxicity, including respiratory depression and seizures, can occur.
 - Don't cross the blood-brain barrier as readily as organophosphates, neurotoxicity is less likely.
 - Dosing for atropine is the same as for organophosphates, but the duration of treatment is usually less.
 - There is controversy regarding the use of oximes in carbamate poisoning. We recommend the use of oximes only when the poisoning is severe (as defined for organophosphates) and the provider cannot differentiate carbamate from organophosphate poisoning

[6] What are the unique features of chlorinated hydrocarbon toxicity? What is an example of a chlorinated hydrocarbon? How are they managed?

Dichlorodiphenyltrichloroethane (DDT) is the best-known example of chlorinated hydrocarbon insecticides. This class is also known as organochlorine insecticides.

Chlorinated hydrocarbon insecticides are highly lipid soluble. They are readily absorbed via dermal, respiratory, and gastrointestinal routes and are stored in fatty tissues.

MOST IMPORTANT ASPECT = refractory seizures from complete GABA blockage. If Benzos are ineffective switch to barbituates, for example

This storage allows for toxicity from repeated, low-level exposure.

Lindane toxicity often occurs from excessive external (dermal) exposure or accidental oral exposure.

Chlorinated hydrocarbon insecticides affect neuronal voltage gated sodium channels. They are also gamma-aminobutyric acid (GABA) antagonists. This results in **hyperexcitability and irritability of both central and peripheral neurons**. Chlorinated hydrocarbons also increase susceptibility to **ventricular tachydysrhythmias** because of increased myocardial sensitivity to circulating catecholamines.

Clinical features: No specific toxidrome

- **Neurologic excitation**
 - Fasciculations, ataxia, tremors, delirium, weakness, paralysis, paresthesias, seizures, death
 - May present with **new onset seizures** without any premonitory symptoms
- Hyperthermia
- Metabolic acidosis, renal failure
- Chronic exposure



- Liver, cardiac, CNS effects

Management:

- Decontamination
 - Remove all clothing and wash the skin and hair with soap and water.
- Stabilization / supportive care
 - Treat seizures
 - Benzo's and Barbs
 - Treat the catecholamine surge induced tachydysrhythmias with metoprolol
 - Treat hyperthermia, metabolic acidosis, rhabdomyolysis, AKI
- No role for enhanced elimination
- No antidote known

[7] How do Substituted Phenols (Dinitrophenol) cause toxicity? How are they managed?

Dinitrophenol (DNP - used as a weight loss medicine over the counter), pentachlorophenol, and dinitrocresol belong to a class of compounds called substituted phenols and have been used as dyes, wood preservatives, photograph developers, and insecticides.

Because these patients can present undifferentiated...think of some other causes.

Refer to Table 157.3 in Rosen's 9th edition for a differential diagnosis for substituted phenol poisoning

Toxicological	Infectious	Environmental
Cocaine	Meningitis	Hyperthermia
Salicylates	Encephalitis	Heat stroke
Amphetamines/MDMA	Sepsis	
Caffeine		
Other sympathomimetics		

Substituted phenols uncouple oxidative phosphorylation. This results in decreased adenosine triphosphate (ATP) formation and increased heat generation, which is the mechanism of action for DNP in weight loss because calories are burned excessively. DNP also stimulates glycolysis, which, along with the uncoupling of oxidative phosphorylation, increases lactic acid production.

[8] How is toxicity from chlorophenoxy Compounds (Agent Orange) managed?

- Chlorophenoxy compounds are effective herbicides for broad-leaved weeds
- Widely used in both commercial and residential settings



- Absorbed through the gastrointestinal tract, skin, and respiratory tract
- Most cases from ingestion
- Skeletal muscle is the primary organ of toxicity

Management

- Decontamination
 - dermal exposure=remove the clothing and wash the skin with soapy water
 - activated charcoal is not indicated
- Stabilization and Supportive Care
 - fluid resuscitation is the mainstay
- Enhanced Elimination
 - critically ill patient = urinary alkalinization or hemodialysis can be used
- Antidote = none
- Disposition
 - Admit = muscular symptoms
 - Asymptomatic > 6 hours= safely discharged home

[9] What is expected in paraquat toxicity? How is this managed?

- The bipyridyl (also called dipyridyl) herbicides = paraquat and diquat
- Paraquat = particularly toxic to humans and is under strict regulation in the United States
- Diquat = less toxic and is subject to less regulation
- Paraquat causes **production of superoxides** created during cyclic oxidation-reduction reactions in tissues
- This causes oxygen radical damage that results in cell death
- Paraquat selectively concentrates in the lungs, **regardless of the route of exposure**
- High concentration of **oxygen** in the lungs **increases the extent** of paraquat-induced oxygen radical injury
- Paraquat poisoning = ARDS, progressive pulmonary fibrosis, and respiratory failure
- Paraquat damages other organ systems by the same oxygen radical injury effect, including the liver, kidneys, heart, and central nervous system
- Diquat = similar mechanism of action **but does not accumulate** in the lungs
 - Diquat is poorly absorbed through the skin

*** Note: Paraquat can be fatal in small amounts ***

Management

- Decontamination
 - Dermal = treated by removing soiled clothing and washing the skin with water
 - In general, no gastrointestinal decontamination
 - Paraquat consider GI decon because of potential lethality



- Use AT LEAST 100 g activated charcoal within 1 hour of ingestion
- Stabilization and Supportive Care
 - Upper airway corrosive injury can lead to an obstructed airway = ETT early
 - Target SPO2 >95% as hyperoxia WORSENS LUNG DAMAGE
- Enhanced Elimination
 - Hemodialysis = controversial. If renal failure, metabolic acidosis, or electrolyte imbalance develops as a result of the poisoning, dialysis is indicated
- Antidote Therapy
 - Currently no specific antidotal therapy
- Disposition = ICU

[10] What are the toxic effects of pyrethrins and pyrethroids?

- Pyrethrins = naturally occurring insecticides derived from the chrysanthemum plant
- Pyrethroids = synthetic derivatives of pyrethrins
- In humans pyrethrins block:
 - Voltage-gated sodium channels
 - Voltage-gated calcium channels
 - Chloride channels on GABA receptors
- Commonly used to treat human infestations of scabies and lice (eg, permethrin)
- Poorly absorbed dermally but are well absorbed via gastrointestinal and respiratory routes

Wisecracks:

1) What is the aging process in organophosphate insecticide ingestions?

*A unique feature of organophosphate insecticides is the process called aging, the **irreversible conformational change that occurs when the organophosphate is bound to the cholinesterase enzyme for a prolonged time.** This causes the clinical effects to persist for periods of days to weeks. The time to aging varies by the specific product involved. Once an enzyme has aged, an oxime antidote cannot regenerate the cholinesterase.*

2) What is the maximum formulation of DEET in pediatrics? When should you not use DEET?

“The American Academy of Pediatrics recommends 30% as the maximum concentration for use in infants and children and does not recommend use of DEET in infants younger than 2 months old. It is available as lotions, aerosols, pump sprays, roll-on applicators, and impregnated towelettes. Concentrated DEET solutions (up to 100%) can cause plastic products, such as sunglasses, to melt on contact.” –Rosen’s