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MODULE 16

Organophosphate & Carbamate (Cholinesterase-Inhibiting) Insecticides Toxicity

Presenter:

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DISCLOSURE: LCDR Rabb does not have any financial arrangements or affiliations with any corporate organizations, which might constitute a conflict of interest with regard to this continuing education activity.

Lecture 15 - Objectives:

- Describe the etiologies of organophosphate and carbamate pesticide toxicity.
- Understand the clinical presentation of patients with organophosphate or carbamate pesticide exposure.
- Understand the laboratory findings of patients with acute or chronic organophosphate or carbamates pesticide exposure.
- Identify the common organophosphate and carbamate pesticides used today.

Required Readings:

COMDTINST M6000.1B, CH-16, pages 12-40 – 12-42 and 12-57
Cholinesterase-Inhibiting Pesticide Toxicity – Case Studies in Environmental Medicine

NOTES:

1. The case study required reading is part of the series of environmental case studies presented by the Agency for Toxic Substances and Disease Registry (ATSDR). This case study is provided as a supplementary material, but is considered essential in order for the reader to acquire a full comprehension of pesticides that affect cholinesterase activity. Additional case studies are available online at www.atsdr.cdc.gov/HEC/CSEM/. The evaluations and post-tests included as part of the ATSDR case study cannot be credited as part of this lecture series. However, the reader may obtain credit by accessing the material and submitting directly to ATSDR.
2. In order to obtain proper accreditation for this lecture series, the reader must successfully complete the post-test included at the end of this presentation (score 70% or better).

INTRODUCTION

Background:

As defined by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the federal law that regulates the manufacture, sale and use of pesticides in the United States, a pesticide is “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any insects, rodents, nematodes, fungi, weeds, or any other form of life declared to be pests - any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant.” Substances are called insecticides when the declared pest is an insect.

Organophosphates:

Organophosphates are esters of phosphoric or phosphorothioic acid that exist in two forms: -thion (sulfur-containing) and -oxon (oxygen-containing). They were developed following WWII as a result of the synthesis of organophosphate nerve gases. The insecticides used today are several generations of development away from those highly toxic chemicals. Organophosphates have largely replaced inorganic pesticides and organochlorines as the principal insecticide used in agriculture. Unlike organochlorines, they are generally not persistent in the environment. However, they can persist longer in hot and dry environments. Groundwater contamination of organophosphates has not been documented as a problem. Some organophosphates are highly toxic and are restricted. Others, such as malathion and diazinon, are of relatively low toxicity and are commonly used in homes and gardens. Some are water-soluble and are taken up into plants and used as systemic insecticides. Dichlorvos is impregnated into pet collars and pest strips. Chlorpyrifos is frequently used against cockroaches and other structural pests. Common organophosphates in use today are found in table 1.

Carbamates:

Carbamates are esters of carbamic acid. All are insecticides and are widely used in homes, gardens, and agriculture. Carbaryl is the most popular due to its low toxicity and a wide spectrum of activity. Water-soluble carbamates are used as systemic insecticides. Propoxur is used against cockroaches. Carbamates are generally thought to rapidly degrade in the environment, however, alicarb, one of the more toxic carbamates has been found in groundwater. Alicarb is water soluble and has been also linked to intoxication of consumers when it was illegally used on fruit and added to the water of hydroponically grown tomatoes and cucumbers. Common carbamates in use today are found in table 1.

Exposure:

Because of their popularity and wide use, the vast majority of acute pesticide poisonings are due to organophosphate and carbamates. Exposure routes are skin absorption (dermal), inhalation, and ingestion. The highest exposures and incidents of poisonings occur in individuals involved in agricultural pest control operations: mixing, loading, applying, and flagging. Mixers and loaders are often exposed to concentrated pesticides and large volumes. Aerosols generated during the application are a significant exposure source for both dermal and inhalation routes. Granular and bait formulations greatly reduce all types of exposure.

A high percentage of pesticides are absorbed across intact skin. Although not the quickest route into the body, skin absorption is the most common occupational exposure route of pesticides. Most have a low molecular weight and high lipid solubility, resulting in this absorptivity. A low ratio of dermal LD50 to oral LD50 indicates a probable high degree of dermal absorption. For example, the organophosphate insecticide mevinphos has a reported oral LD50 ranging from 3.7 to 6.8 and dermal LD50 ranging from 4.2 to 7.0. Common organophosphate and carbamate insecticides in use today and their oral and dermal LD50s are found in table 1.

Toxicology:

Organophosphates:

Organophosphates exert effects on insects and mammals, including humans, in the same manner by phosphorylation of the acetylcholinesterase (AChE) enzyme. The function of AChE is the hydrolysis and inactivation of the neurotransmitter acetylcholine (ACh). A build-up of ACh in the neuronal synapses results in continued, repeated synaptic transmissions. As neurotoxins, organophosphates involve most organs, including the gastrointestinal tract (nausea, vomiting), the respiratory system (excessive bronchial secretions), the cardiovascular system (decrease/increase in heart rate or blood pressure), skeletal muscles (weakness, paralysis), and the CNS (mental confusion, fatigue). The inactivation of AChE by organophosphates is irreversible and normal enzyme activity can only be restored by the synthesis of new AChE. This process can take up to 60 days to complete.

A number of organophosphates are known to cause primary irritant dermatitis. A few, including malathion, methyl-parathion, dichlorovos, and naled are known to cause allergic contact dermatitis.

Carbamates:

Like organophosphates, carbamates inhibit the enzymatic actions of AChE, resulting in accumulation of ACh and similar neurological effects. Unlike organophosphates, biotransformation reactions quickly break up the carbamate-AChE molecule and AChE is reactivated. This results in a shorter duration of acute toxicity and no chronic effects. The only other health effect of carbamates is primary irritant dermatitis.

Signs and Symptoms:

Acute:

Cholinesterase inhibitors produce a relatively stereotypical clinical presentation that, in conjunction with determining cholinesterase levels, makes diagnosis more accurate than with other pesticides.

The mnemonic MUDDLES (miosis, urination, diarrhea, defecation, lacrimation, excitation, salivation) represents the common acute symptoms of AChE-inhibiting insecticides. The neuro-physiological basis of these signs and symptoms is summarized in table 2. The number of systems involved increases with the severity of intoxication. The onset of illness after acute overexposure is unpredictable, but is related to dose and route of exposure. Absorption through the skin is prolonged and onset and progression of symptoms is slower. Mild symptoms generally precede more severe ones, often for periods of 6-8 hours, but following extreme overexposure, severe symptoms and death can occur within minutes. There is some variability in parasympathetic nervous system manifestations because they are opposed by the sympathetic nervous system. For example, the heart rate may be slow, normal, or fast and the pupils may be small, normal, or large, depending on which system predominates.

The degree and duration of acute illness produced by organophosphate and carbamate pesticides are directly related to the degree and rate of AChE inhibition and subsequent accumulation of ACh. Chronic inhibition of AChE appears to result in tolerance to some of the acute effects. Cumulative inhibition of AChE is unlikely to occur from carbamates due to the reversible nature of the AChE inhibition. The clinical expression of acute organophosphate or carbamate poisoning depends upon the organs where ACh is the transmitter of nerve impulses, as found in table 2.

The cause of death in acute organophosphate poisoning is usually respiratory failure. Cardiac arrhythmias, such as heart block and cardiac arrest, are less common causes of death. Seizures are not uncommon, but rarely persist long enough to require treatment.

Severe poisoning from occupational exposure to carbamates is uncommon. Due to the rapid reactivation of AChE, workers who become ill on the job are often better in time they are seen at a medical facility

Chronic:

CNS dysfunction, including irritability, anxiety, mood changes, fatigue, impaired short-term memory, and impaired concentration may persist for weeks or months after acute exposure to organophosphate pesticides.

The only known systemic health effect of organophosphate pesticides that is entirely unrelated to cholinesterase inhibition is organophosphate-induced delayed neuropathy. A small number of organophosphate pesticides also cause this delayed neuropathy that is correlated with inhibition of the enzyme neurotoxic esterase. The mechanism of action is unknown. Following typical cholinesterase-inhibiting symptoms and an asymptomatic period of about 7-21 days (depends on exposure), the neuropathy occurs. Symptoms are cramp-like pains in calves, numbness and tingling in the feet, followed by increasing and ascending weakness. More information can be found in the required reading case study. Carbamates do not cause delayed neuropathy.

A few organophosphates and carbamates are mutagenic, but most have not been found to be carcinogenic in animals and based on animal studies, none have been found to pose a significant carcinogenic risk to humans. Although some are fetotoxic at doses near or at cholinesterase-inhibiting levels in maternal animals, none have been found, in animal studies, to pose a significant teratogenic risk to humans. Because of the fetotoxic properties, there is concern for women handling pesticides. Carbaryl (a carbamate) is teratogenic to beagle dogs, but not to a number of other animal species. It is spermatotoxic in animals, but showed no evidence of that effect in one study of manufacturing workers exposed to relatively low doses.

Treatment:

Please see additional reading material and references for information on treatment of organophosphate and carbamate pesticide exposure.

Laboratory Findings:

Changes in cholinesterase activity, along with the typical signs and symptoms, provide sufficient information for the diagnosis and management of most cases. A number of nonspecific laboratory findings, including leukocytosis, proteinuria, glucosuria, and hemoconcentration, may also be present in an individual with acute poisoning. Red cell cholinesterase (RBC cholinesterase or true cholinesterase) is the same enzyme present in nerve endings and its activity more closely parallels that in the nervous system than does plasma cholinesterase (pseudocholinesterase). However, RBC cholinesterase is more difficult to measure and is more susceptible to analytical error than plasma cholinesterase. Also, some organophosphates, such as the chlorpyrifos (Dursban, Lorsban) preferentially depress plasma cholinesterase, causing illness without significant depression of RBC cholinesterase. Different methods are used to measure RBS and plasma cholinesterase, with results usually reported in different units. There is considerable variability in cholinesterase activity in unexposed persons, so that reports of results relative to "normal" are unimportant.

Individuals with a genetic trait for atypical plasma cholinesterase have lowered plasma, but not RBC, cholinesterase. They are not more susceptible to cholinesterase-inhibiting pesticides, but plasma cholinesterase will not be a reliable indicator of exposure. RBC cholinesterase will be reliable. Plasma cholinesterase production may also be lowered as a result of liver disease. The only medical condition known to influence RBC cholinesterase activity are those associated with reticulocytosis.

When cholinesterase determination is made for biological monitoring of exposure to organophosphate pesticide, it is essential to compare the current level to a pre-exposure baseline level. Biological monitoring of exposure consists of determination of pre-exposure baseline levels followed by periodic determination in intervals based upon the frequency and nature of exposure. If only one test is performed, RBC cholinesterase should be monitored since it is more specific for organophosphate pesticides and is an indicator of cumulative absorption of organophosphate over a relatively long period of time. Plasma cholinesterase is more immediately responsive to inhibition by acute doses and may be preferentially inhibited by some organophosphates, such as chlorpyrifos. Cholinesterase levels are of limited value in assessing exposure to carbamates because of the rapid reversal of inhibition, even in a test tube.

The appearance of symptoms is more dependent upon the rate of inactivation of cholinesterase than the absolute level of activity reached. For example, workers may reach a cholinesterase level of 40% of baseline over the course of a number of weeks without experiencing symptoms, but a previously unexposed person may develop symptoms at a level of 70% of baseline activity following an acute exposure.

An individual's baseline RBC cholinesterase activity may vary up to 22% from day-to-day when measured by the same method by the same laboratory. A 25-30% inhibition during periodic monitoring can be taken as a warning level of a biological response to chronic exposure to organophosphate pesticides.

Table 1. Organophosphate and carbamate pesticides in common use in the United States (**bold italicized** names are on the list of pesticides authorized for use by DoD and other Federal agencies – see references page)

Common Name	Trade name	Oral LD50 (mg/kg)	Dermal LD50 (mg/kg)
Organophosphates: Category I			
Parathion		1-5	1-10
Mevinphos	Phosdrin	1-5	1-10
Methyl parathion		5-10	50-100
Carbophenothion	Trithion	5-10	20
EPN		5-10	20
Methamidophos	Monitor	10-20	100
Azinphos-methyl	Guthion	10-20	200
Methidathion	Supracide	20-30	400
Dichlorvos (DDVP)	Vapona	20-30	50-100
Organophosphates: Category II			
Chlorpyrifos	Dursban, Lorsban	50-150	2000
Diazinon	Spectracide	50-150	400
Phosmet	Imidan	50-150	3000
Dimethoate	Cygon	150-500	150
Fenthion	Baytex	150-500	
Naled	Dibrom	150-500	1000
Trichlorion	Diptarex	150-500	2000
Organophosphates: Category III & IV			
Acephate	Orthene	500-1000	2000
Malathion		500-1000	4000
Stirofos (tetrachlorvinphos)	Gardona Rabon	1000-5000	5000
Carbamates			
Aldicarb	Temik	1-5	1-10
Carbofuran	Furadan	5-10	10,000
Methomyl	Lannate	15-25	1000
Propoxur	Baygon	100	1000
Bendiocarb	Ficam	100-200	
Carbaryl	Sevin	300-600	2000

Table from: LaDou, J., (1997). *Occupational & Environmental Medicine*, 2nd Edition, McGraw-Hill, New York.

Table 2. Signs and symptoms of acute organophosphate poisoning by site of acetylcholine neurotransmitter activity

System	Receptor Type	Organ	Action	Sign or Symptom
Parasympathetic	Muscarinic	Eye, iris muscle, ciliary muscle	Contraction	Miosis
Sympathetic			Contraction	Blurred vision
		Glands: Lacrimal, salivary, respiratory, gastrointestinal, urinary, sweat	Secretion	Tearing, salivation, bronchorrhea, pulmonary edema, nausea, vomiting, diarrhea, urination, perspiration
		Heart: sinus node, atrioventricular node	Slowing: refractory period increased	Bradycardia, arrhythmias, Heart block
		Smooth muscle: bronchial, gastrointestinal	Contraction	Bronchoconstriction
		Wall, sphincter	Contraction Relaxation	Vomiting, cramps, diarrhea
		Bladder, fundus, sphincter	Contraction, relaxation	Urination, incontinence
Neuromuscular	Nicotinic	Skeletal	Excitation	Fasciculations, cramps, followed by weakness, loss of reflexes, paralysis
Central nervous		Brain	Excitation (early)	Headache, dizziness, malaise, apprehension, confusion, hallucinations, manic or bizarre behavior, convulsions
			Depression (late)	Depression of, then loss of, consciousness; respiratory depression

Table from: LaDou, J., (1997). *Occupational & Environmental Medicine*, 2nd Edition, McGraw-Hill, New York.

References
(and Additional Sources of Information)

Reigart, J., and Roberts, J., (1999). *Recognition and Management of Pesticide Poisonings*, 5th Edition, Environmental Protection Agency, Washington, DC. Available online at: <http://www.epa.gov/oppfead1/safety/healthcare/handbook/handbook-ldh.pdf>

Hughes, W.. (1996). *Essentials of Environmental Toxicology*. Taylor & Francis, Washington, DC.

Amdur, M., Doull, J., and Klaassen, C., Eds. (1991). *Cassarett & Doull's Toxicology, The Basic Science of Poisons*, 4th Edition. Pergamon Press, New York.

LaDou, J., (1997). *Occupational & Environmental Medicine*, 2nd Edition, McGraw-Hill, New York.

Standard pesticides available to DoD components and all Federal agencies:
<http://www.afpmb.org/pubs/misc/dodpest1212001.htm>

Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA):
<http://www.epa.gov/pesticides/fifra.htm>

Environmental Protection Agency Office of Pesticide Programs:
<http://www.epa.gov/pesticides/>