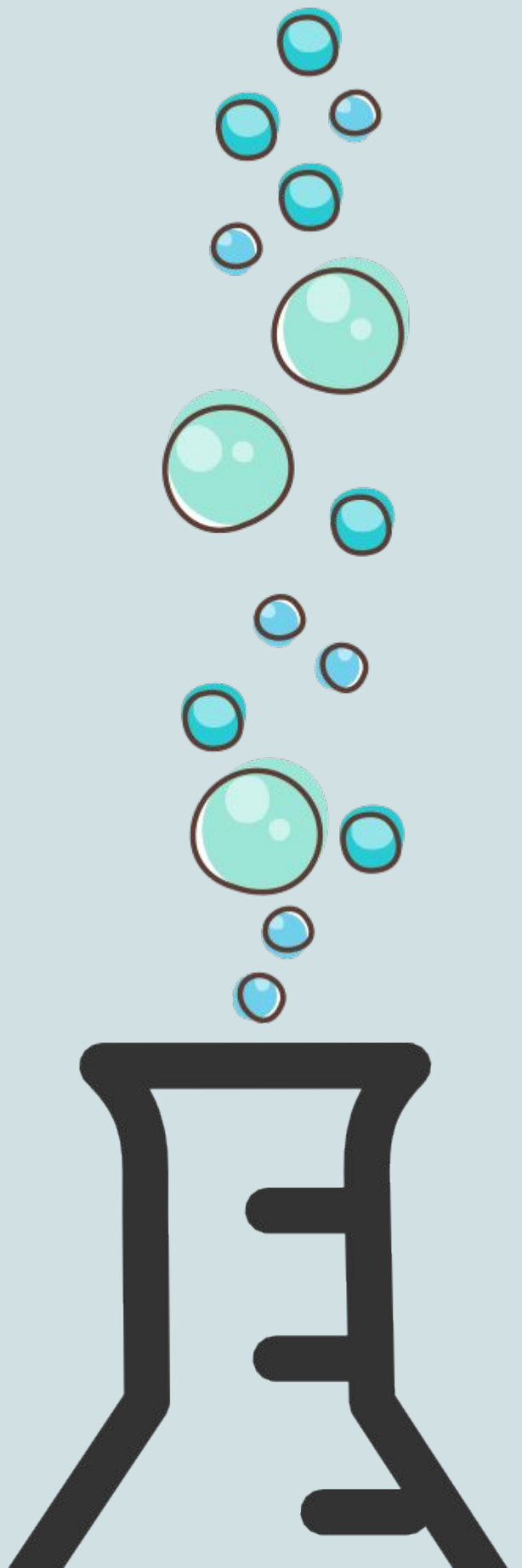
TOXICOLOGY TEAM · CSI KSU · 435

Organophosphate



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Objectives

? Not given)':

NOTES EXTRA BOOK IMPORTANT GOLDEN NOTES

Pesticides

Perspective:

Pesticides, a generic term used to refer to all pest-killing agents and include:

Insecticides
Chemical substances used to kill insects like mosquito, most commonly used pesticides, most are organophosphates

Herbicides

Rodenticides used to kill rats. it is commonly used warfarin like product "vitamin k antagonist" causing bleeding of these rodents and they will die

Fungicides

Fumigants

Many are general protoplasmic poisons affecting a wide range of organisms, including humans.

Organophosphate & Carbamate Insecticides.....

- Some of the most common pesticides for home and industrial use
- Organophosphorus insecticides are highly lipid soluble and are readily absorbed via dermal, GI, and respiratory routes distribute to all tissue very fast and cross the BBB
- This lipid solubility results in the storage of organophosphorus compounds in body fat, making toxic systemic levels possible from gradual or rapid accumulation from repeated low-level exposures
- The parent compound and its metabolites are acetylcholinesterase inhibitors the enzymatic deactivator of acetylcholine toxicity in farmers and misuse of animal products, so people who works with camels they give them a body wash to get rid of lice .Also, frequently we have seen with anti-lice shampoo mostly in children usually at the end of summer before school
- Many parent organophosphorus compounds are less potent than their metabolites (e.g., parathion to paraoxon), which may result in delayed onset of clinical toxicity.

Organophosphate

Principles of Disease:

- They work by persistently inhibiting the enzyme acetylcholinesterase, the enzymatic deactivator of the neurotransmitter acetylcholine. the function of the enzyme is breaking down the Ach that released at the nerve ending mainly in autonomic nervous system. when AchE block, Ach release and keeps accumulating and cause poisoning 'cholinergic toxicity'

- Because of the global penetration of organophosphorus compounds, inhibition occurs at tissue sites (true acetylcholinesterase represented by erythrocyte cholinesterase) and in plasma (circulating pseudocholinesterase).

- Inhibition of cholinesterase results in the accumulation and subsequent prolonged effect of Acetylcholine at neurotransmitter receptors: the level of toxicity relates to amount of inhibition of AchE

Sympathetic & parasympathetic Ganglion (Nicotinic sites)

Postganglionic Cholinergic sympathetic and parasympathetic (Muscarinic sites)

Skeletal muscle (Nicotinic sites)
(motor nerves)

Central nervous system sites
Mainly NMDA[1] receptors, can cause seizures and coma

1- N-methyl-d-aspartate receptor, it will be mentioned later in the lecture and it is very important to remember this type of receptors (:

Next slide will be illustrating ANS and all the good things we know from Basic Science, so don't panic, we know you'll remember it (:

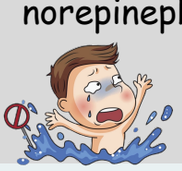
{ Organophosphate }

Principles of Disease:

- The ANS is divided further into the: (Muscarinic and Nicotinic receptors)
- Atropine can block Muscarinic receptors but not Nicotinic receptors.(that's why we use oximes for nicotinic receptors)
- Neuromuscular junction uses ACh as effector neurotransmitter.
- In the brain, ACh is just one of several active neurotransmitters.

Sympathetic

Sympathetic nervous system (thoracolumbar outflow):
-The neurotransmitter in ganglia is acetylcholine (ACh).
-The neurotransmitter in the target organ is norepinephrine (NE).



Parasympathetic

Parasympathetic nervous system (craniosacral outflow):
-Use ACh as the neurotransmitter in preganglionic and postganglionic target organ

Signs and Symptoms:

mostly muscarinic

- The accumulation of acetylcholine results in **a classic cholinergic syndrome**, manifested by hyperactivity of cholinergic responses at the receptor sites indicated previously.
- The clinical syndrome of muscarinic acetylcholinesterase inhibition is commonly called the **SLUDGE** syndrome or **DUMBELS**. Fluid loss and secretion from every orifice

Clinical Features

Signs and Symptoms:
mostly muscarinic

Bradycardia

It is a classic sign of the cholinergic syndrome, but the increased release of norepinephrine from postganglionic sympathetic neurons precipitated by excess cholinergic activity at sympathetic ganglia may result in normal or even tachycardic heart rates (nicotinic effect). the major system involvement is parasympathetic activation, classically bradycardia happen, but through ganglion receptor activation they can also have tachycardia. Another reason for tachycardia is hypovolemia

CNS

A combination of sympathetic stimulation, involvement of the N-methyl-d-aspartate receptor, and enhanced acetylcholine concentrations can lead to seizures. increase Ach level, ultimately going fatigue so they will stop responding and initially can be twitching followed by paralysis

NMJ[1]
1-Neuromuscular Junction

-At the neuromuscular junction, excess acetylcholine causes hyper stimulation of the muscles with secondary paralysis.at the NMJ the Ach is received by a nicotinic cholinergic receptors
-Because the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest

Acute Organophosphate poisoning

The clinical picture of acute organophosphorus poisoning is impressive, toxicity from gradual, cumulative exposure may be much more subtle.
These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances;or chronic abdominal cramping, nausea, and diarrhea.
The scenario that might hint of organophosphate poisoning is a family called an insecticide company to fumigate their house and a container of organophosphate (insecticide) were left and nobody noticed it and the patient will say he will have the symptoms at home but if he left he feels comfortable again.

SLUDGE symptoms or DUMBELS

Very imp must have a question in the exam

Salivation
Lacrimation
Urinary incontinence
Defecation
Gastrointestinal cramps
Emesis

They call me Sludge (it is true, search it), and once you touch me, your body will turn into liquid (hypersecretion) and we will both vomit all the night!

Diarrhea/Diaphoresis
Urination
Miosis
Bradycardia/Bronchorrhea/Bronchospasm
Emesis
Lacrimation
Salivation

My name is DUMBELdore and all these issues will be resolved by one spell, we call it "ATROPINEsus!" But we have to cast it asap!!

Harry Potter fans if you ever forget this, I will hex you (;

Clinical Features

Complications:

- ➔ Seizure, bronchorrhea and bronchoconstriction are prominent mechanisms of early morbidity
- ➔ Obstruction of upper and lower airways produce hypoxia
- ➔ Muscle hyperactivity eventually gives way to muscle paralysis (including respiratory muscles and diaphragm)
- ➔ Respiratory insufficiency results in death if not anticipated and corrected

Enzyme Complex Aging:

Unique effect of organophosphorus insecticides results from "aging," the irreversible structural change that occurs in cholinesterase enzyme when the organophosphorus agent is bound to it for a prolonged time.
Attachment with organophosphate component to Ach ,this is reversible. you can somehow remove this attachment, then the enzyme will become active again

On average, for commercial organophosphorus agents aging will occur by 48 hours "window period", but may take longer.

> Once the enzyme has aged, **an oxime antidote cannot** regenerate the cholinesterase.

Assessment & Management

Diagnostic Strategies:

Known or suspected exposure to cholinesterase inhibitors should be confirmed by ordering: Which one is reflex toxicity better? RBC cholinesterase

Plasma

Plasma cholinesterase levels may recover in 4 to 6 weeks.

Erythrocyte (RBC) cholinesterase levels.

RBC cholinesterase levels recover at a rate of 1% per day in untreated patients and take approximately 6 to 12 weeks to normalize.

EXPOSURE....!

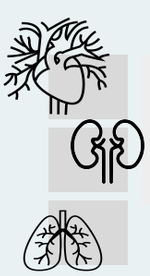
Acute Exposure VS **Chronic Exposure**

In acute exposures:
-The plasma cholinesterase levels decrease first
-Followed by decreases in RBC cholinesterase levels.

The RBC cholinesterase level is more indicative of what is occurring at the nerve terminal (tissue level).

Patients with chronic exposures may show:

Only reduced RBC cholinesterase activity, with a normal plasma cholinesterase level.



Other studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance.

(Patients presenting with no acidosis, or only a metabolic acidosis on the arterial blood gas, have lower mortality than those presenting with a respiratory or mixed acidosis) Respiratory acidosis is a late manifestation and has bad prognosis

Assessment & Management

Management:

We usually start with resuscitation then decontamination but in cases of Organophosphate toxicity, we don't; we start with decontamination first then ABC! Why? Because it is highly absorbable and it will just keep causing toxicity for the patient and also medical staff and who is around! So be smart and get rid of it then do your ABC (;

Treatment is directed toward four goals:

1. Decontamination
2. Supportive care (DABC) with continuous suction of the secretions
3. Reversal of acetylcholine excess at muscarinic sites (Atropin)
4. Reversal of toxin binding at active sites on the cholinesterase molecule. (Pralidoxime)

1-Decontamination

- Decontamination should start in the out-of-hospital phase
- Decontamination is particularly important in cases of dermal exposure; removal and destruction of clothing and thorough flushing of exposed skin may limit absorption

- Dermal decontamination can be done with dry agents, such as military resins, flour, sand, or bentonite.
- Caregivers are at risk from splashes or handling of contaminated clothing.

- In the case of ingestion, GI decontamination procedures are of questionable benefit because of the rapid absorption of these compounds.
- Profuse vomiting and diarrhea are seen early in ingestion and may limit or negate any beneficial effect of additional GI decontamination.

- Should use universal precautions. stop the exposure so if it is applied to hair, wash it with shampoo and water ,remove the clothes and put them in a plastic bag so it is not kept exposed to the air and the people around be exposed to
- Equipment, but not tissues, may be washed with a 5% hypochlorite solution to inactivate the cholinesterase inhibitor.

Assessment & Management

Management:

2-Supportive care

Supportive care should be directed primarily toward:

(Airway management, Breathing and Circulation)

- Airway management includes suctioning of secretions and vomitus, oxygenation, and when necessary, intubation and ventilatory support
- Intravenous access and fluid boluses as needed for circulatory collapse
- Seizure/Convulsions can be controlled by Benzodiazepine

3-Reversal of acetylcholine excess at muscarinic sites

-The definitive treatment of acetylcholinesterase inhibition starts with Atropine. atropine can reverse muscarinic side effect
-A competitive inhibitor of acetylcholine at muscarinic receptor sites, atropine reverses the clinical effects of cholinergic excess at parasympathetic end organs and sweat glands.
-Atropine is not active at nicotinic sites and does not reverse the skeletal muscle effects (e.g., muscle fatigue and respiratory failure).

-Large doses of atropine may be required.
-Data suggest that the more rapid the atropinization, the faster control is obtained

-Suggested dosing is 1 or 2mg of atropine (0.02–0.05 mg/kg) IV, with doubling of each subsequent dose every 5 minutes until there is control of mucous membrane hypersecretion and the airway clears. one dose can't corrected so he might need 4-5 dose before the sign and symptoms reverse
-If IV access is not immediately available, atropine may be administered IM

-Tachycardia and mydriasis may occur at these doses, but they are not indications to stop atropine administration as the half life of atropine is shorter than the half life of organophosphates, initial improvement doesn't necessarily indicate resolution of toxicity until secretions dry.
-The endpoint of atropinization is drying of respiratory secretions, easing of respiration, and a mean arterial pressure greater than 60 mmHg

Assessment & Management

Management:

4-Reversal of toxin binding at active sites on the cholinesterase molecule.
(Pralidoxime)

The second part of acetylcholinesterase inhibition treatment is the use of an **Oxime**: Oxime reversing the nicotinic side effects, what will happen is AchE will be reactive before aging happen by removing the organophosphate. oxime will start decreasing the Ach by breaking down so the nicotinic effect will disappear, not because the oxime acts on nicotinic receptor but because it decreases Ach level

someone have very severe muscarinic symptoms, someone needing large dose of atropine, someone with nicotinic symptoms and already has respiratory failure -> give pralidoxime

Pralidoxime,the mechanism of action of pralidoxime,it degrades the bond between poison and acetylcholinesterase (2-PAM, Protopam)

Obidoxime (Toxogonin)

- These degrade the organophosphate-acetylcholinesterase complex and restore the active cholinesterase form
- Work at muscarinic and nicotinic sites

In the past, pralidoxime was only used within the first 24 hours because of aging of the organophosphate-acetylcholinesterase complex, but not all organophosphates behave in a similar manner

- The medication may be given as repeated boluses or continuous infusion
- The infusion may need to be continued for several days for complete reversal of cholinesterase activity

Indications for oxime therapy include:

- Respiratory depression/apnea
- Fasciculations
- Seizures
- Arrhythmias, cardiovascular instability
- Patients who need large amounts of atropine (2-4 mg) to completely reverse the signs and symptoms of intoxication
- Patient who requires repeated doses of atropine

{ Disposition & more }

Disposition:

Most patients with significant exposures require hospital admission including intensive care settings

ICU

OR

A person with chronic exposure, and mild visual or GI symptoms may be followed as outpatient

OUTPATIENT

OR

Asymptomatic or mildly symptomatic patients with near normal cholinesterase levels may be discharged after 4 to 6 hours

DISCHARGED

After discharge...

Intermediate Syndrome (IMS)	Organophosphorus-Delayed Neuropathy
-A secondary syndrome, the intermediate syndrome (IMS), **occurs 24 to 96 hours after exposure** and consists of proximal muscular weakness specifically of the respiratory muscles. -It is believed to be an abnormality at the neuromuscular junction. -Patients with IMS present with respiratory failure **several days after the acute cholinergic symptoms have resolved** and may require several weeks of ventilatory support.	Organophosphorus-delayed neuropathy has been reported as a different entity and affects an axonal enzyme, neurotoxic esterase, and leads to a peripheral sensorimotor neuropathy **7 to 21 days after exposure**. it is self-limiting

Carbamate Insecticides

What are they:

In brief, both toxicities -Organophosphate and carbamate- are similar but with less severity of signs and symptoms and shorter duration seen in carbamate and no role of oxime in the latter.

Carbamate insecticides are another class of acetylcholinesterase inhibitors and are differentiated from the organophosphorus compounds by their relatively short duration of toxic effects.

Carbamates inhibit acetylcholinesterase for minutes to 48 hours, and the carbamate-cholinesterase binding is **reversible**. Although the clinical picture of acute carbamate poisoning may be identical to that of organophosphate poisoning. there is not much role of nicotinic receptors by using oxime

The toxic effects are limited in duration and patients may require only decontamination, supportive care, and treatment with adequate doses of atropine. Although the duration is limited in scope, patients may become just as sick and require assisted ventilation and seizure therapy.

The use of pralidoxime is controversial in carbamate poisoning

organophosphate and carbamate insecticides They both respond to atropine

Summary

Pesticides: ORGANOPHOSPHATES and CARBAMATE INSECTICIDES -Both inhibit AChE, but Carbamate Insecticides have shorter duration and they are reversible (No "Aging" process on the enzyme)

Carbamate Insecticides: -Decontamination and Atropine are usually enough, Ventilator and seizure therapy is only used in severe cases.

Organophosphates: -Lipid soluble compounds that block the AChE leading to an increase of ACh levels at tissue and plasma sites, (Muscarinic sites) and (Nicotinic sites)

Symptoms(SLUDGE and DUMBELS)

Salivation **L**acrimation **U**rinary incontinence **D**efecation **G**astrointestinal **E**mesis	**D**iarrhea/**D**iaphoresis **U**rination **M**iosis **B**radycardia/**B**ronchorrhea/**B**ronchospasm **E**mesis **L**acrimation **S**alivation

Signs; Bradycardia or tachycardia, Seizures, Hyperstimulated muscles

Diagnosis; mainly plasma and RBC cholinesterase levels

Management:
-Decontamination with military resins, flour, sand or bentonite for dermal decontamination -ABCs -Atropine for the reversal of ACh excess at muscarinic sites -Oxime for the reversal of toxin binding at active sites on the ch

Complications: Seizures, Hypoxia, Paralysis, Respiratory insufficiency.

How toxic is your knowledge

1-Neuro terminal activities in organophosphate toxicity will be identified through?
A. Acetylcholine levels in the blood.
B. Acetylcholinesterase levels in the blood
C. Dopamine levels in CSF
D. Adrenaline levels in the blood

2-Which of the following neuro-receptors is responsible in organophosphate positioning?
A.Adrenergic receptor
B.Muscarinic receptor
C.Dopaminergic receptor
D.Nicotinic receptor

3-Inhibition of Acetylcholinesterase leads to which one of the following signs & symptoms?
A. Cholinergic
B. Anticholinergic
C. Sympathomimetics
D. Sympatholytic

4-A 40 year old farmer called an ambulance, as he was unwell having diarrhea and vomiting. He finished spraying his crops with pesticide same day. As he arrives in hospital you notice that patient has excessive salivation, lacrimation and miosis. Which toxidrome this patient has?
A. Organophosphorus
B. Sympathomimetic
C. Opioid
D. Sedative

5-In which way is the mechanism of organophosphate and carbamate insecticides similar?
A. They activated acetylcholinesterase
B. They produce anticholinergic syndrome
C. They both respond to atropine
D. They both respond to Oximes

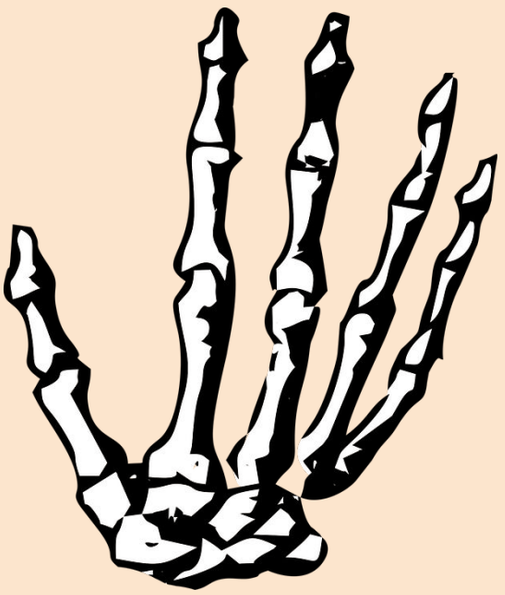
6-What is the Mechanism of the action of pralidoxime?
A.It degrades the bond between the poison and acetylcholinesterase
B.It provides new acetylcholinesterase
C.It increase the concentration of acetylcholine by 50%
D.It increase the concentration of acetylcholinesterase by 50%

7-Which one of the following is the characteristic of "aging" in organophosphorus poisoning?
A- There is no bond between the poison and acetylcholinesterase
B-All the acetylcholinesterase is consumed by the poison
C-The body cannot synthesize any more acetylcholinesterase
d. The bond between the poison and acetylcholinesterase is irreversible

8-Which one of the following is the antidote for organophosphorus poisoning?
A- Atropine
B-Calcium gluconate
C-Potassium chloride
D- Hyoscine

1-B
2-B
3-A
4-A
5-C
6-A
7-D
8-A

Thank you and good luck!



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A+ is yours (:

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