Available online at www.elixirpublishers.com (Elixir International Journal)

Pharmacy

Elixir Pharmacy 96 (2016) 41727-41730

ISSN: 2229-712X

Organophosphorus Poisoning

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ARTICLE INFO

Article history:

Received: 9 June 2015;

Received in revised form:

17 July 2016;

Accepted: 22 July 2016;

Keywords

Organophosphorus compounds, organophosphates and carbamate.

ABSTRACT

Acute poisoning by Organophosphorus compounds is one of the important cause of morbidity and mortality in the world, especially in developing countries. Accidental and intentional pesticides poisoning occurs worldwide with a significant mortality. Recent studies have shown an increase in numbers with three hundred thousand deaths occurring in Asia alone. The most common pesticide in India are due to anti-cholinesterase's which includes organophosphates and carbamate, followed by aluminum phosphide. The effective number of cases of pesticide poisoning occurring in India is very high, and the calculated number of intentional cases as reported by NCRB (National Crime Records Bureau) is again very high. A retrospective analysis covering last 15 years showed the most common agents causing acute poisoning was anti-cholinesterase's followed by aluminum phosphide. The with a mean age of 27.8 years(range 13 to 82 years) Organophosphates share structural similarity with acetylcholine and bind covalently with cholinesterase molecule. This results in accumulation of acetylcholine at synapses causing over stimulation at post-synaptic receptors in central and peripheral nervous system. The clinical features of acute OPC poisoning are secondary to stimulation of muscarinic and nicotinic acetylcholine receptors in the parasympathetic system, sympathetic ganglia; neuromuscular junctions. Disrruption of transmission will also occur at the acetylcholine receptor sites within the central nervous system. The muscarinic receptors,M1 and M2 have different regional distribution in brain. The M1 receptors are the main type found in the human cerebral cortex, caudate nucleus, hippocampus, nucleus accumbens, and globus pallidus, while the M2 type dominates in the thalamus, brain stem, pons, and the cerebellum. Different subtypes of nicotinic receptors have been described in human brain using ligands with different affinities. Diagnosis of OPC poisoning is based on history of exposure to known OP compounds, characteristic clinical features. Estimation of acetyl cholinesterase activity is useful for confirmation of poisoning. But the degree of decrease in cholinesterase levels does not show linear relationship with severity of clinical features and prognosis. Detection of the offending agent in gastric lavage sample is one of the methods to determine the involved agent. OPC poisoning has several toxicological effects on the body, namely on respiratory system, cardiovascular system, neurological system & endocrinal system. The patient is managed on a protocol based management. The outcome depends on the severity of toxic sign and symptoms, and the time lag between poisoning and hospitalization.

Introduction

Organophosphate poisoning OP Poisoning results from exposure to organophosphates (OPs), which cause the inhibition of acetyl cholinesterase (AChE), leading to the accumulation of acetylcholine (ACh) in the body. Organophosphate poisoning most commonly results from exposure to insecticides or nerve agents. OPs are one of the most common causes of poisoning worldwide, and are frequently intentionally used in suicides in agrarian areas. There are around 1 million OP poisonings per year with several hundred thousand resulting in fatalities annually.

OP pesticide exposure occurs through inhalation, ingestion and dermal contact.[Because OP pesticides disintegrate quickly in air and light, they have been considered relatively safe to consumers. However, OP residues linger on fruits and vegetables. Certain OP pesticides have been banned for use on some crops, for example methyl parathion is banned from use on some crops while permitted on others. The Environmental Working Group has developed lists for concerned consumers, identifying crops with the highest pesticide residue quantities and the lowest. The "Dirty Dozen" crops are updated yearly and in 2012 included apples, celery, sweet bell, peppers, peaches, strawberries, imported nectarines, grapes, spinach, lettuce, cucumbers, domestic blueberries and potatoes. Forty-five fruits and vegetables are listed by the Environmental Working Group as being regularly found with pesticide residue associated with OPs.

Example:

- Insecticides including malathion, parathion, diazinon, fenthion , dichlorvos, chlorpyrifos, ethion, trichlorfon.
- Nerve gases including soman, sarin, tabun, VX
- Herbicides including tribufos [DEF], merphos are tricresyl phosphate–containing industrial chemicals.

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Exposure to any one of the above-listed organophosphates occurs on a daily basis through inhalation, absorption, and ingestion, most commonly of food that has been treated with an organophosphate herbicide or insecticide. Exposure to these chemicals can occur at public buildings, schools, residential areas, and in agricultural areas. The chemicals chlorpyrifos and mellathion have been linked to reproductive effects, neurotoxicity, kidney/liver damage, and birth defects. Dichlorvos has also been linked to reproductive effects, neurotoxicity, and kidney/liver damage, as well as being a possible carcinogen.

Organophosphates inhibit AChE, causing OP poisoning by phosphorylating the serine hydroxyl residue on AChE, which inactivates AChE. AChE is critical for nerve function, so the irreversible blockage of this enzyme, which causes acetylcholine accumulation, results in muscle overstimulation. This causes disturbances across the cholinergic synapses and can only be reactivated very slowly, if at all. Paraoxonase (PON1) is a key enzyme involved in OP pesticides and has been found to be critical in determining an organism's sensitivity to OP exposure.

Diagnosis

A number of measurements exist to assess exposure and early biological effects for organophosphate poisoning. Measurements of OP metabolites in both the blood and urine can be used to determine if a person has been exposed to organophosphates. Specifically in the blood, metabolites of cholinesterase, such as butyrylcholinesterase (BuChE) activity in plasma, neuropathy target esterase (NTE) in lymphocytes, and of acetyl cholinesterase (AChE) activity in red blood cells Due to both AChE and BuChE being the main targets of organophosphates, their measurement is widely used as an indication of an exposure to an OP. The main restriction on this type of diagnosis is that depending on the OP the degree to which either AChE or BuChE are inhibited differs; therefore, measure of metabolites in blood and urine do not specify for a certain OP.However, for fast initial screening, determining AChE and BuChE activity in the blood are the most widely used procedures for confirming a diagnosis of OP poisoning The most widely used portable testing device is the Test-mate ChE field test, which can be used to determine levels of Red Blood Cells (RBC), AChE and plasma (pseudo) cholinesterase (PChE) in the blood in about four minutes. This test has been shown to be just as effective as a regular laboratory test and because of this, the portable ChE field test is frequently used by people who work with pesticides on a daily basis

Death from acute severe organophosphorus poisoning occurs because of respiratory compromise. Multiple factors impair ventilation and oxygenation in these cases, but the primary cause acutely relates to muscarinic effects of OP agents. The most clinically significant muscarinic effects are bronchorrhoea and bronchospasm and brain dysfunction, respiratory depression (the killer 3 B's).

The airways fill up with secretions and the involuntary muscles of respiratory passage clamp down. The principles of therapy in OP poisoning include resuscitation of the patient (patent airway, effective breathing, and adequate circulation).Therefore atropine remains the mainstay of therapy as it dries up the respiratory secretions and getting the bronchial muscles to relax. It blocks muscarinic receptors limiting neuro effectors transmission by excessive acetylcholine. It also blocks muscarinic effects in brain which is responsible for CNS toxicity leading to CNS depression. Different text books may feature differently for requirement of atropine. E.g. SLUDGE syndrome-salivation, lacrimation, urination, defecation, gastric cramps, emesis.

Others look for meiosis, excessive sweating, poor air entry into the lungs due to bronchorrhoea and bronchospasm, bradycardia and hypotension. Severely OP or carbamate poisoned patients are typically covered with sweats, have a pin point pupil, and labored breathing (often with bronchorrhoea and wheeze).The presence of pinpoint pupil and excessive sweats suggests that the patient has taken an OP or carbamate and requires atropine. The heart rate may be slowed, but normal even faster heart rates are common.

Reproductive effects

Certain reproductive effects in fertility, growth, and development for males and females have been linked specifically to OP pesticide exposure. Most of the research on reproductive effects has been conducted on farmers working with pesticides and insecticides in rural areas. For those males exposed to OP pesticides, poor semen and sperm quality have been seen, including reduced seminal volume and percentage motility, as well as a decrease in sperm count per ejaculate. In females menstrual cycle disturbances, longer pregnancies, spontaneous abortions, stillbirths, and some developmental effects in offspring have been linked to OP pesticide exposure. Prenatal exposure has been linked to impaired fetal growth and development. The effects of OP exposure on infants and children are at this time currently being researched to come to a conclusive finding. Evidence of OP exposure in pregnant mothers are linked to several health effects in the fetus. Some of these effects include delayed mental development, Pervasive developmental disorder (PDD), morphological abnormalities in the cerebral surface.

Neurotoxic effects

Neurotoxic effects have also been linked to poisoning with OP pesticides causing four Neurotoxic effects in humans: cholinergic syndrome, intermediate syndrome, organophosphate induced delayed polyneuropathy (OPIDP), and chronic organophosphate-induced neuropsychiatric disorder (COPIND). These syndromes result after acute and chronic exposure to OP pesticides.

Poisoning

Goals of treatment remains-

1. Reduce absorption of toxins
2. Enhance elimination
3. Neutralize the toxins already present in the body

For reducing absorption, we practice thorough and effective gastric lavage, whole bowel irrigation, endoscopic and surgical removal of toxic material, effective skin decontamination, use of activated charcoal and cathartics, dilution with milk or fluid.

Decontamination

Remove all clothing from and gently cleanse patients suspected of organophosphate exposure with soap and water because organophosphates are hydrolyzed readily in aqueous solutions with a high pH. Consider clothing as hazardous waste and discard accordingly.

Health care providers must avoid contaminating themselves while handling patients. Use personal protective equipment, such as neoprene gloves and gowns, when decontaminating patients because hydrocarbons can penetrate nonpolar substances such as latex and vinyl. Use charcoal cartridge masks for respiratory protection when decontaminating patients who are significantly contaminated.

Irrigate the eyes of patients who have had ocular exposure using isotonic sodium chloride solution or lactated Ringer's solution. Morgan lenses can be used for eye irrigation.

The signs and symptoms for the sake of academic purpose are divided as mild, moderate and severe. Mild-symptoms are shortness of breath and limitation of activity. Signs are coughing and lacrimation, mild bradycardia, runny nose and sweating. Moderate-Symptoms are colic pain, diarrhea, restlessness, vomiting, and weakness. Signs are bronchorrhoea, altered consciousness, muscle twitching, pallor, meiosis. In severe and fatal cases observed signs are convulsions, respiratory failure, pulmonary edema, paralysis, cyanosis and deep coma.

Assess if the patient requires atropine. The aim of atropine therapy is to reverse the cholinergic features and to improve cardiac and respiratory functions as quickly as possible. Severely poisoned patients may require hundreds of milligram of atropine. An initial bolus of 2 mg of atropine is given intravenously after ensuring airway and breathing. Atropine takes a few minutes to act and blood level peaks within three minutes of intravenous administration. Waiting just for five minutes for a response before deciding whether to give another dose is probably sufficient. Therefore, if a consistent improvement in cholinergic feature does not occur within 3-5 minutes after the initial loading dose, the recommendation is to double the dose, and to continue to double the dose till atropinisation occurs. There should be a uniform improvement in most of the cholinergic signs are required, not improvement in just one. However the most important parameters are air entry on chest auscultation, heart rate and the blood presser. Targets end points for atropine therapy are clear chest on auscultation with no wheeze, dry axilla, systolic BP>90mmHg, HR>100/ mnt, mid-position of pupil and normal bowel sounds. There is no need to target for higher heart rates like 120-140beats/min. as these higher heart rates will cause severe complications in elderly patients with pre-existing heart disease and sometimes myocardial infarction may occur.

Once atropinised (with clear lungs, adequate heart rates and blood presser with good urine output),dry skin,mid position of pupil(no longer pin point),as in infusion of atropine is started to maintain blood atropine concentration in a therapeutic level, keeping in mind that this infusion rate is to be indidualised for all patients. The maintenance dose is to be titrated against symptoms and signs. However, excess of atropine (toxicity), cause agitation, confusion, urinary retention, hyperthermia, bowel ileus and tachycardia. If the patient develops toxicity then stop infusion of atropine. Check after 30 minutes if the features of toxicity have been settled. If not, continue to review every 30 minutes. When they settle, restart the infusion at 60-70% of previous dose. The patient should be under close watch to ensure that the new infusion rate has reduced the sign of atropine toxicity without permitting the reappearance of cholinergic signs.

There is no alternative therapy to atropine. Though use of glycopyruvate,a, a quaternary ammonium antimuscarinic agent has been documented as a supplement to atropine. It has peripheral effects similar to atropine, at the same time it is a longer acting agent. As it doesn't cross the blood brain barrier so does not counteract the central nervous system effects of the poison.However,it is more effective antisialagogue than atropine. It is less likely to cause much tachycardia and blocks the bradyarrythmias effectively. Usually, if the lungs are not clear and axilla are not, although other symptoms of poisoning are improved than glycopyrrolate can be used in combination. Alone glycopyruvate, is not used because of limitation of peripheral effects only (does not have any central nervous system effect),and early death in OPC poisoning is a centrally mediated process. So, if at all to be used start with atropine and slowly change to glycopyruvate. Oxime (pralidoxime) therapy has been of great controversy in management of OP poisoning and it's use was not associated with significant increase in mortality. Absolute criteria for intubation are unconsciousness (low GC scoring), shock, arrhythmias, altered ABG, bulbar dysfunction, aspiration and ARDS.

Death due to cardiac reasons in OP poisoning is because of multiple causes including MI, vascular congestion, cardiac arrest- brady-or tachycardia, hyper- or hypotension. Intermediate syndrome occurs after 72 hours of poisoning onset. Mechanism though unknown may be due to reaborption of toxins from the organ and fat cells. Hence a golden rule for not discharging patient before 96 hours is to be followed. It usually recovers completely if treated early when there is no hypoxic encephalopathy. Early institution of enteral feed may be associated with improved outcomes in the critically ill as it prevents enterohepatic circulation.

An optimal dose of clonidine appears to be clinically acceptable in OP poisoning. Similarly blood alkalization with high doses of NaHCO3 is found useful. Intravenous magsulf given on first day after admission has been shown to decrease hospitalization period and improves outcome in OP poisoning. Forced emesis SHOULD NOT BE performed in patients of OP poisoning. Benzodiazepines are widely used to control agitation, provide sedation and control seizures in ventilated patients.
Antioxidants are useful adjuncts of therapy in OP poisoning.

Newer therapies

Obidoxime –used as intramuscular injections with plasma concentration from 5 minutes to 3 hours. Adverse effects described as pallor, nausea, burning sensation, headache, generalized weakness, sore throat, and parasthesias of face. Following, high doses of obidoxime (several grams per day) in severe OP poisoned patients; hepatotoxic effects were occasionally observed including serum transaminases, jaundice and cholastasis.

Asoxime (HI-6)-These are administered 6 hourly intramuscular injections in conjunction with atropine and benzodiazepine (diazepam) treatment.

It is important to note that oximes are not effective for outcome if the patient develops serious complications such as aspiration pneumonia or hypoxic brain injury before treatment. Such complications take place with fast acting pesticides such as parathione and dichlorvos.

Drugs for Future

HuperzineA, and ZT-1 has been proven to be a powerful, highly specific and reversible inhibitor of acetyl cholinesterase (AChE). HupA was developed as a new drug for symptomatic treatment of Alzeimer's disease in China. It is marketed as dietary supplement in USA.HupA has a better penetration through blood brain barrier, higher oral bioavailability and longer duration of AChE inhibitory action.

Multiple Choice Questions

1. The drug of choice in OP poisoning is:
A. Atropine
B. Oximes
C. Ventilatory support
D. Glycopyrrate
2. Death in acute OP poisoning occurs due to
A. Respiratory compromises
B. Cardiac arrest
C. Multi-organ failure
d. Acute kidney injury
3. Once recovered patient of acute OP poisoning
A. Shows a steady recovery

B. May worsen because of intermediate syndrome
C. May die of acute myocardial infarction
D. Needs dialysis due to acute kidney injury
4. OP poisoning occurs because of
A. Accidental ingestion
B. Suicidal ingestion
C. While spraying insecticides when working in fields
D. All of above
5. Slow exposure to OP substances may result in
A. Reproductive side effects
B. Neonal growth retardation (birth defects)
C. Neuropsychiatric disturbances
D. All of above
6. OP substances causes harm to body by
A. Muscarinic effects
B. Nicotinic effects
C. Both of above
D. None of the above
7. Atrone effects are:-
A. Miosis
B. Bradycardia
C. Excessive salivation
D. All of the above
E. None of the above

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