Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/12284
DOI URL: http://dx.doi.org/10.21474/IJAR01/12284

ISSN NO. 2320-5407

RESEARCH ARTICLE

ORGANOPHOSPHATE POISONING

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Manuscript Info

Manuscript History
Received: 05 November 2020
Final Accepted: 10 December 2020
Published: January 2021

Key words:-
Organophosphate, Cholinesterase, Atropine

Abstract

Organophosphorus compounds are very commonly available substance especially in agriculture based countries. Its use as a suicidal agent is rampant. Early management of the patient is critical in the final outcome. Use of atropine forms the mainstay of management after early decontamination. The role of oximes has been a matter of controversy. Use of Fresh Frozen Plasma and monitoring the patient using cholinesterase levels is amongst one of the developments in the management of the patient.

Introduction:-

Use of Organophosphorus (OPC) compounds in agriculture is quite common, especially in agriculture based societies. They arealso used as nerveagentsinchemicalwarfare(e.g.Saringas),and as therapeutic agents for glucoma(ecothiopate).The use of OPCs for attempting suicide is quite common, especially by ingestion. Other modes of poisoning may be accidental absorptionfromskin, conjunctiva, oral mucosa, respiratory tract by direct contact,inhalation and by injection.[1,2] They may be highly toxic organophosphates: (e.g. tetra-ethyl pyrophosphates, parathion)mainly used as agricultural insecticides, Intermediately toxic organophosphates: (e.g.coumaphos, clorpyrifos, trichlorfon), used as animal insecticides or Low toxicity: (e.g. diazinon, malathion, dichlorvos), used for household application and as fieldsprays.[1]

Pharmacodynamics:

Acetylcholine (ACh), a neurotransmitter at all postganglionic parasympathetic nerve endings,the synapses of both sympathetic and parasympathetic ganglia and at the skeletal muscle myoneural junction,ishydrolyzedbyacetylcholinesteraseintotwofragments:acetic acid and choline.[3]

Acetylcholinesterase may be True acetylcholinesterase found primarily in the tissues and erythrocytes, and pseudocholinesterase found in the serum andliver.[1]

OPC compounds inhibit cholinesterase enzyme by firmly (andsometimesirreversibly)phosphorylating the esterase site, leading to accumulation of Acetylcholine at the muscarinic and the nicotinic receptors and in the central nervous system.[1,2]Reactivation of the inhibited enzyme dependsonthespecies,thetissue,and thechemicalgroupattachedtotheenzyme.Oxmies enhance this rate by hydrolysis of the acid-radical-enzyme. However, this response declines with time, a process called “ageing” of the inhibited enzyme.[1]

Pharmacokinetics:

Mostorganophosphates being highlylipidsolubleget rapidly redistributed with highest concentrationsintheliverandkidneys.Theyeasilycrosstheblood/brainbarrierand have significant CNS

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effects.Metabolismoccurs intheliver by oxidation and esterase hydrolysis. Half-liferanges from minutes-hours.The are eliminated mainly via urine, bile and faeces.[1,2]

Intermittent release from the fat stores is incriminated for the sudden deterioration in a stable patient.[2]

Signs and symptoms:
Pungant garlic odour in breath and vomitus is characteristic with miosis, bradycardia, muscle weakness, excessive salivation, lacrimation or respiratory secretions are common findings. Clinical features appear within 30 minutes to 3 hours of exposure dependingon the specific agent, the quantity and the route of entry.[1]Cholinesterase levels usually fall to 30% of its normal activity by the time signs and symptoms appear.[4]

The clinical features may bedue to muscarinic or nicotinic effects or central receptor stimulation.[5]Most fatalities occur within 24 hours and those who recover usually do so within 9days.[1]

Cardiac:
Hypotension (with warm, dilated peripheries), and bradycardia due to muscarinic blockade is common. Occasionally, predominant nicotinic receptor blockade may causetachycardiaandhypertension.ECG changes include prolonged Q-Tc intervals, elevation of the ST segment, inverted T waves, a prolonged PR interval,sinusbradycardia,ventricularextra-systoles,ventricular tachycardia and fibrillation.[1,6]

Occular:
pin point pupilsand weakness of extraoccular muscles

Respiratory:
Muscarinic Blockade: Bronchorrhoea,rhinorrhoea,bronchospasm, laryngeal spasm and cough.1,6Nicotinic Blockade: Weakness and subsequent paralysis of respiratory and oropharyngeal muscles. Patient may need intubation and ventilation due to excessive secretions or paralysis or due to respiratory arrest because ofCentral neurological depression.

Gastrointestinal:
Vomiting,diarrhea, abdominal cramps, increased salivation and faecal incontinence. 1,6

Neurological:
Three different types of paralysis are recognized

Type I paralysis or acute paralysisoccurs ininitial cholinergicphase due to persistentdepolarizationattheneuromuscularjunction causing muscle fasciculation, cramps, twitching and weakness. Weakness of the respiratory muscles may lead respiratory depression and arrest requiring ventilatory support.

Type IIparalysis or intermediate syndromedevelops 24-96 hours after the poisoning,followingrecoveryfromtheacutecholinergiccrisis and lasts for about 4-18 days.There is muscleparalysis withweakness affectingtheproximallimb musclesandneckflexors, sparingthedistal musclegroup.Inabilitytoliftheadfromthepillow is an early manifestation.Cranialnerves,especially thosesupplyingtheextra-ocularmusclesare mostlyinvolved,withalessereffectonVIIandX.

Type IIIparalysis or organophosphate- induced delayed polyneuropathyisasensory-motordistalaxonopathyoccurring after a latent period of 2-4 weeks in patients who consume large doses of OPCs. There is weakness of hands and feet and ataxia, often precededby calf pain, and in some cases, parasthesia of the distal part ofthe limbs. Delayed CNS signs include tremor, anxiety andcoma.[1,7]

Management:
Treatmentisinitiatedimmediatelyonclinicalsuspicion.Bothtrueand pseudocholinesteraselevels may be assessed.A 25-30%orgreaterreductionintruecholinesteraselevelindicates OPCpoisoning, levels correlating withtheseverity ofpoisoningatpresentation.[1,4]

Inj. Atropine 0.6 mg to1.0mgIV maybegiven if the clinical presentation is not clear.Increaseinheartratebymorethan20-25beats/minandflushingwouldsuggestthatthepatientdoesnothavesignificantcholinergicpoisoningandfurtherobservationis required.[2,8]

Resuscitation:
500-1000mlofnormal saline(9-20ml/kg)over9-20mintocompensatefluidlossdue to sweating, diarrhoea and cholinergic hyper-secretion.[2,8]

Decontamination: Remove thepatient from the site of exposure, andwash his body with soap and water to prevent further absorption. Gastric lavage is initiated within one hour of ingestion, with normal saline in lots of 300 ml through a nasogastric tube after aspirating gastric contents, the end point being colourless odourless returning fluid. Avoid larger volumes as this may push the poison into the small bowel.1,2,8

Airway and respiration: Protect the airway and ensure adequate oxygenation to prevent atropine induced ventricular fibrillation in hypoxic patients.

Anticholinergics:
Atropine. 2mg IV bolusevery5-15minutesshouldbeadministered until atropinization is achieved.[1,2][increased heart rate (>100 beats/min.), moderately dilated pupils, a reduction in bowel sounds, a dry mouth/ axilla, a decrease in bronchial secretions and systolic blood pressure above 80 mm Hg.][1,2]Total atropinization (fully dilated pupils, absent bowel sounds, heart rate >150 beats/min) is not recommended due to complications(hyperexcitability,restlessness,hyperpyrexia and cardiac complications). Continuous atropine infusion 0.02-0.08mg/kg/hrmaintainsconstant plasma concentration.[2,9] The rate of infusion required is 9-20% of the total loading dose required for atropinisation.[1,8] Atropine levels should be maintained for 3-5 days and then tapered.[4]

In case pesticide has been splashed into the eyes directly pupils may not dialate with atropine.[8]

Review every 15 min. In case of bronchospasm or bradycardia, give further boluses of atropine and increase the infusion rate. Once settled observe every 2-3 hours.[8]

Atropine toxicity:
In case of Confusion, agitation, hyperthermia, ileus, tachycardia, urinary retention discontinue atropine infusion and restart at 70- 80 % of the previous rate after the signs of toxicity settle.[2,8]

Glycopyrolate:
Glycopyrrolate is equallyeffective,withfewercentralnervoussystemsideeffects and a better control ofsecretions.[10]However, since it does not penetrate the blood brain barrier, CNS symptoms like coma or drowsiness will not respond. Hence it's use is recommended when there is copious secretionasanadjuncttoatropineorwhenfeaturesofatropine toxicity like delirium etc are confused with CNS effects of poison or when atropine is not available[2]. Diphenhydraminecanbeanalternatecentrallyacting anticholinergic agent if atropine is not available[11]

Cholinesterase reactivator:
Pralidoxime has three main actions:

1. A direct reaction converting the organophosphate to aharmless compound.
2. A transient reaction protecting the enzyme from further inhibition.
3. Reactivation of the inhibited alkyl phosphorylated enzyme to free the active unit (if given early enough)

It does not reverse the muscarinic effects of OPCcompounds. The recommended dose is1gram,byintravenousinjection, every 6-11 hour in adults (maximum dose 12g/24 hours) and 25-50mg/kg in children.[1]WHOguidelinesare30mg/kgloading dose of Pralidoxime over 9-20 min followed by a continuous infusion of 8-9 mg/kg/hr until clinical recovery or seven days whichever is later. Alternately obidoxime 250mgloading dosefollowedbyaninfusionof750mgevery 24hrs may be used.[2,8]The effective plasma concentration of pralidoxime is4 µg/ml. Sideeffectsofpralidoxime includedrowsiness,visualdisturbances,nausea,tachycardiaand muscleweakness.[1]

Pralidoxime should be started as early as possible to prevent permanentbindingoftheorganophosphatetoacetylcholinesterase. The half-life of aging seems to be much less than 1 h; thus, oximes are completely ineffective if the patient presents more than an hour or two after ingestion.[4]
Oximes are not recommended for carbamate poisoning[8]

The use of oximes has been a matter of controversy for long. The use depends on the following features:

A: Most of the OPC compounds can be classified as dimethyl phosphoryl or diethyl phosphoryl compounds. Dimethyl compounds respond poorly to oximes. Further, compounds with low lipid solubility have a poorer outcomes as these reach higher blood concentrations. Those with high lipid solubility have a higher chance of causing intermediary syndrome.

B: Inadequate dose of oximes is a major cause of poor response. The minimum threshold of serum level required is 4 µg/ml.

C: The response also depends upon the dose of intoxication. If large quantity of OPC has been taken, the plasma levels of more than 4 µg/ml will be required

D: Dimethyl OPCs age faster than diethyl group. Thus, treatment should be started early in dimethyl group for effective regeneration.

E: Duration of therapy should be as per WHO recommendations.

Ventilator support:

Ventilator support may be required if tidal volume is below 5 mL/kg or vital capacity is below15mL/kg,oriftheyhaveapneicspells,orPaO$_2$is<8kPa (60mmHg)orF$_1$O$_2$is<8kPa(60mmHg)onF$_1$O$_2$ofmorethan 60%.Peradeniyascoreof>7isanindicationforventilation.[4]

Succinylcholineshould beavoided. Non-depolarisingneuromuscular blocking agents require higher doses.

Active cooling and sedation:

Hyperthermia is a serious complication. A febrile patient should receive the minimum amount of atropine needed to control muscarinic signs and sedation for excessive agitation as well as active cooling.[8]

Diazepam 9 mg IV slowly, repeated as necessary may be used. Tying a non-sedated agitated patient to the bed is associated with complications. Such patients struggle against their bonds and generate excess body heat, which may result in hyperthermic cardiac arrest.[4,8]

Diazepam is preferred over haloperidol because large doses of haloperidol may be required. Haloperidol is also non-sedating, associated with disturbances of central thermoregulation and prolongation of the QT interval, and is a pro-convulsant.[4,8]

Magnesium:

Magnesium sulfate ($MgSO_4$) 16g over 24 hours as an infusion reduces Ach release from presynaptic terminal by blocing ligand gated calcium channels and may thus improve neuromuscular junction function and reduce N-methyl-D-aspartate receptor mediated centralnervoussystemoverstimulation.[2,4,6]

Clonidine:

An alpha2-adrenergicreceptoragonist, alsoreduces Achsynthesisandreleasefrompresynaptic terminals.Though animal studies have shown benefit but effects on human beings is unknown[4,6]

Hemodialysis and Hemofiltration:

Therole isnotyetclear

ButyrylCholinesterase:

FFP therapy for 3 consecutive days (4units1st day,3units2nd day,and2units3rd day)may increaseserumcholinesterase levels in blood thereby reducing the total dose of atropine as well as the ICU stay.[4,6]

FFP acts by neutralizing toxins released into circulation by redistribution from adipose tissue.[13]

The causes of death includes large dose ofOPC,toolate arrival to casualty, coma/convulsions/ pulmonary edema at the time of presentation, omittinggastric decontamination at presentationand inadequateatropine dose.[4]

Antibiotics:
Broad spectrum antibiotics as per antibiotics policy of the institution

Drugs to be avoided

1. Methyl Xanthines – AntagonisesPAM
2. Aminoglycosides – may aggravate muscleweakness
3. Drugs metabolized by plasmacholinesterase like opioids, succinylcholine, Mivacurium, esmolol.
4. Phenytoin may suppress cardiac activity due to effect on Na channels
5. Haloperidol is non-sedating, associated with disturbance of central thermoregulation, prolongation of QT interval and is proconvulsant.

Cholinesterase Levels:
Though synaptic inhibition can be better assessed by RBC Cholinesterase but plasma cholinesterase is easier to assay. Sr. Cholinesterase levels should be monitored daily. Mild poisoning is defined as a cholinesterase activity of 20 – 50%, moderate 9 – 20% and severe <9%. Raising cholinesterase levels favors good prognosis. Cholinesterase levels should be followed daily even after pralidoxime is discontinued, with a rising trend for 3 consecutive days before the patientsdischarge.

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