

Chapter 95

Current Concepts in the Management of Organophosphorus Compound Poisoning

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INTRODUCTION

Organophosphorous (OP) compounds have been employed as pesticides, petroleum additives and chemical warfare nerve agents. The organophosphates have been used as pesticides for more than 50 years and are still used in most developing countries. It is believed that between 750,000 and 3,000,000 OP poisoning occur globally every year. Organophosphorus pesticides poisoning can result from occupational, accidental or intentional exposure. Mortality is higher in the developing countries where OP pesticides are readily available and may be used for suicide. They are estimated to cause 300,000 fatalities annually. For the first time, organophosphates were synthesized by von Hoffman. In 1873, he synthesized methyl phosphorus chloride, which led to the synthesis of a number of insecticides. The OP warfare nerve agents, (commonly called “nerve agents”) are much more toxic than pesticides. The commonly used OP insecticides are acephate, anilophos, chlorpyrifos, dichlorvos, diazinon, dimethoate, fenitrothion, methyl parathion, monocrotophos, phenthoate, phorate, pirimiphos, quinalphos, temephos, etc. The replacement of an oxygen atom in the organophosphorus structure by sulfur leads to the formation of organothiophosphorus compounds such as malathion and parathion, which have a lower lethal potential but *in vivo* metabolization to the oxon metabolite enhances their toxicity (Table 1). Most organophosphates can be divided into two types: diethyl (e.g. chlorpyrifos, diazinon, parathion, phorate and dichlofenthion) and dimethyl (e.g. dimethoate, dichlorvos, fenitrothion, malathion and fenthion).

GOALS OF TREATMENT

- Reduce absorption of the toxin (xenobiotic)
- Enhance elimination
- Neutralize toxin.

Reduce Absorption

- Removal from surface of skin, eyes and hair
- Emesis induction
- Gastric lavage
- Activated charcoal administration and cathartics
- Dilution—milk/other drinks for corrosives
- Whole bowel irrigation
- Endoscopic or surgical removal of ingested chemical
- Skin decontamination—important aspect—not to be neglected:
 - Remove contaminated clothing
 - Wash with soap and water (soaps containing 30% ethanol advocated).

TABLE 1 | The grading of clinical severity of organophosphate poisoning

Grade	Symptoms	Signs
Mild	Dizziness, anxiety, headache, tightness of breath	Rhinorrhea, sweating, salivation, nausea, weakness, coughing, lacrimation, mild bradycardia and hypotension
Moderate	Restlessness, confusion, dyspnea, disorientation, abdominal pain, vomiting, diarrhea, drowsiness	Pallor, miosis/mydriasis, bradycardia/tachycardia, hypotension/hypertension, muscle twitching, fasciculation, respiratory depression, bronchorrhea, bronchospasm, loss of consciousness
Severe		Convulsions, respiratory failure, pulmonary edema, flaccid paralysis, involuntary micturation/defecation cyanosis, deep coma
Fatal		Coma, convulsions, hypersecretions and apnea within a few minute after exposure

Decontamination

Gastric Decontamination

- Gastric lavage
- Activated charcoal 25 g 2 hourly
- Sorbitol as cathartic.

Gastric Lavage

- Gastric lavage decreases absorption by 42% if done at 20 minutes and by 16% if performed at 60 minutes
- Performed by first aspirating the stomach and then repetitively instilling and aspirating fluid
- Left lateral position delays spontaneous absorption
- No evidence that a larger tube is better
- Simplest, quickest and least expensive way—funnel
- *Choice of fluid is tap water: 5–10 mL/kg*
- Preferably done on awake patients
- Presence of an ET tube does not preclude aspiration, though preferred if Glasgow coma scale is low
- No human studies in OP poisoning showing benefit of gastric lavage.

Treatment: Atropine*Anticholinergic Agents*

- *Atropine or glycopyrrolate*: Animal studies
- Atropine toxicity occurs at therapeutic doses
- Atropine has beneficial effects on central nervous system (CNS)
- Atropine (n = 22) versus glycopyrrolate (n = 17) lesser respiratory complications with glycopyrrolate, other outcomes similar.

Atropinization: Targets

- Adequacy of atropinization
- *Mandatory targets*:
 - SBP greater than 90 mm Hg
 - Heart rate about 110/minute
 - Clear lung fields.
- *Other targets*:
 - Pupils mid position
 - Bowel sounds just present
- *Targets on subsequent days*:
 - Day 2: HR greater than 100/minute
 - Day 3: HR greater than 90/minute
 - Subsequent days: At least 80/minute.

Atropinization: Dose

What dose to use?

- Several recommendations > 20 mg atropine
- 0.02–0.08 mg/kg over 1 hour would take 4 hours to give 20 mg atropine to a 70 kg male.

Study from Sri Lanka

- Twenty-two patients with severe poisoning who survived to hospital discharge
- Mean dose 23.4 mg for atropinization
- Extrapolate to treatment regimens: 8–1,340 minutes
- In a very sick patient who needs 75 mg: Take 25–4,440 minutes.

Anticholinergic Dose

- 1–2 mg initial bolus dose
- Double dose every 5 minutes if targets not met
- In 20 minutes can achieve atropinization for a dose of 25 mg.

WHAT IS THE COMPARATIVE EFFECT OF ATROPINE AND/OR GLYCOPYRROLATE IN THE TREATMENT OF ORGANOPHOSPHATE POISONING?**Atropine and Glycopyrrolate**

Atropine is an antagonist to muscarinic receptors of acetylcholine and is the mainstay of treatment of acute OP poisoning. It is used to reverse cholinergic effects of organophosphate poisoning like decreased heart rate, increased bronchial secretions, urination, lacrimation, etc. There are two approaches to atropinization: (1) bolus dose administration; (2) incremental dose administration with rapid escalation. The goal of therapy is to prevent bradycardia, maintain blood pressure, clear lungs and dry skin. Atropine is associated with toxic effects like tachycardia, agitation and psychoses. Glycopyrrolate has less CNS penetration and may result in less CNS toxicity.

Discussion

The study by Abedin clearly shows that the incremental dosage regimen of atropine is superior to bolus dose administration. Incremental dose was defined as 1.8–3 mg atropine by intravenous (IV) infusion, repeating the dose every 5 minutes interval doubling the dose each

time to the point atropinization occurs, followed by 10–20% of atropine required for atropinization, every hour by IV infusion. Bolus dose was defined as (2–5 mg of atropine every 10–15 minutes) followed by maintenance using reduced doses or increasing the time duration in between the doses. The incremental dosage was clearly better in relation to the outcomes of death (RR = 95% CI-) and intermediate syndrome. The atropinization endpoints used in the study were: clear chest on auscultation with resolution of bronchorrhea, heart rate of greater than 80 beats per minute, systolic blood pressure greater than 80 mmHg, dry axillae and pupils greater than 2 mm in diameter. The study had low risk of bias and had high quality evidence for the outcome of death. This supports the recommendations of Blain PG¹ regarding rapid atropinization and endpoints for therapy.

Inference

We recommend incremental dose administration of atropine as the standard of care. The role of glycopyrrolate alone or in combination with atropine is not clear.

DOES ADMINISTRATION OF OXIMES IN ORGANOPHOSPHATE POISONING IMPROVE HEALTH OUTCOMES?**Oximes**

- Nucleophilic agents
- Reactivate bound acetylcholinesterase
- Earliest compound pralidoxime (1950s)
- Now obidoxime and trimedoxime available.

Oxime Therapy and Mortality

Association between oxime therapy and mortality has been shown in **Figure 1**.

Individual Randomized Controlled Trials

- Cherian et al. JAPI 1997. No bolus. 12 g of pralidoxime chloride over 3 days
- Pawar et al. Lancet 2006. 2 g loading, then 2 g/hour pralidoxime iodide over 48 hours (50 gm total dose)
- Eddleston M, et al. 2009. 2 g loading dose then 0.5 g/hour pralidoxime chloride for maximum 7 days (maximum possible dose 86 g) (**Figure 2**).

Largest Oxime Trial

- 235 patients, pralidoxime = 121, saline = 114
- 2 g loading dose over 20 minutes
- Then 0.5 g/hour for maximum 7 days
- Continued till atropine not required for 12–24 hours or death (**Figure 3**).

Conclusion

Despite clear reactivation of red cell acetylcholinesterase in diethyl organophosphorus pesticide poisoned patients, we found no evidence that this regimen improves survival or reduces need for intubation in patients with organophosphorus insecticide poisoning. The reason for this failure to benefit patients was not apparent. Further studies of different dose regimens or different oximes are required.

Summary of Oxime Trials

- Overall null effect or potential harm with oximes on meta-analysis of trials
- The largest oxime study tend to harm
- Only one study showed a reduction in mortality

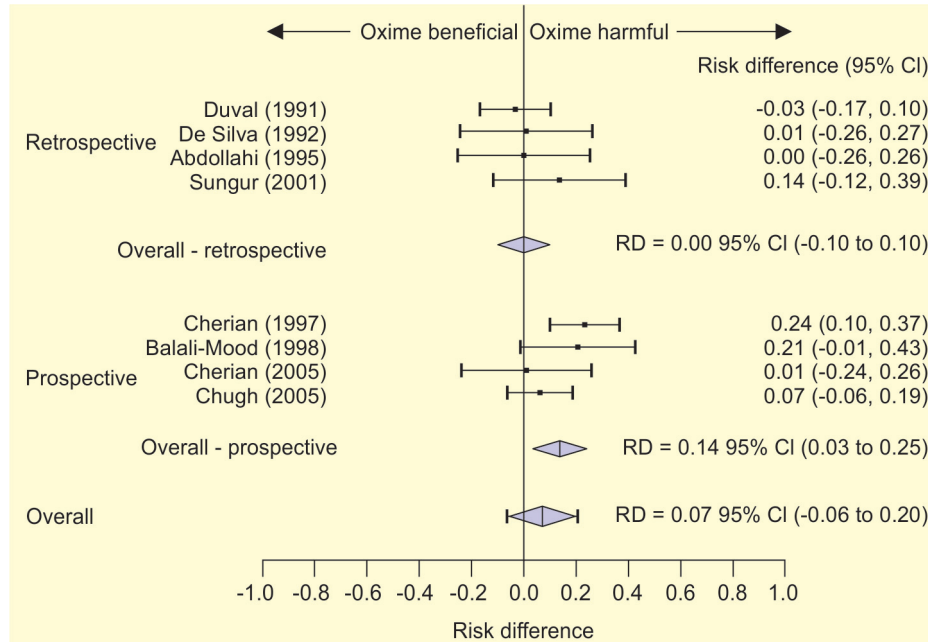


Figure 1: Association between oxime therapy and mortality. Forest plot representation using the random effects model depicting association between oxime therapy and mortality. The vertical straight line denotes null effect. The individual points denote the risk difference (RD) of each study, and the lines on either side the 95% confidence intervals (CI). Combined estimates as well as individual estimates for the retrospective group, as well as the prospective study group are represented. Oxime therapy was not associated with a significant increase in mortality.

Source: Reprinted with permission from Crit Care Med. 2006;34:502-10, © 2006, Society of Critical Care Medicine, Lippincott Williams & Wilkins and Crit Care Update (2004) 153-163, © 2005, Vineet Nayyar, Jaypee Brothers.

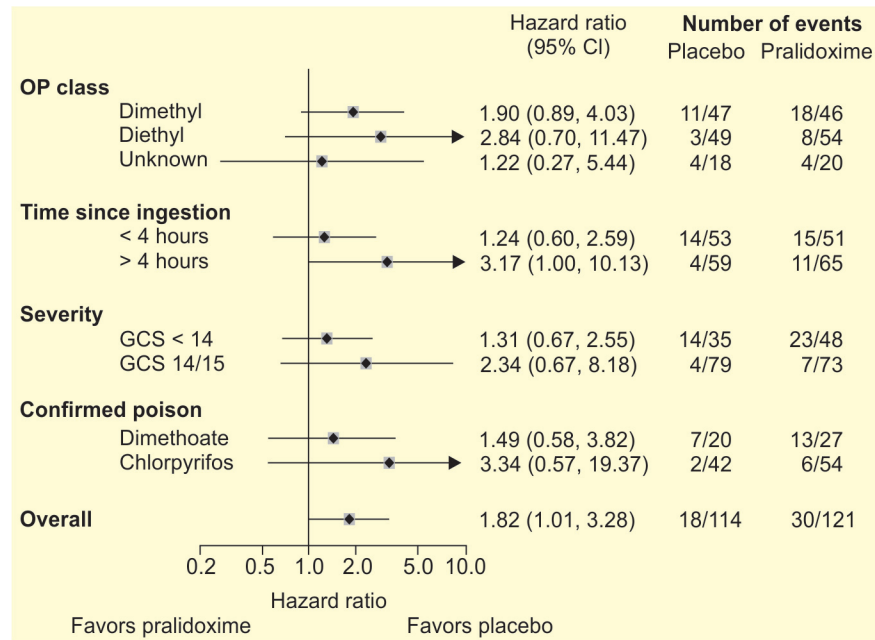


Figure 2: Eddleston M, Eyer P, Worek F, et al. Pralidoxime in acute organophosphorus insecticide poisoning: A randomized controlled trial. PLOS Med 6(6): e1000104.doi:10.1371/journal.pmed.1000104

- Treated only moderate poisoning
- Severe cases referred to government hospitals
- Used very high doses (50 g)
- Patients presented very early (< 2.5 hours).

Why is there No Benefit?

Reasons for oxime failure:

- Study design
- Timing

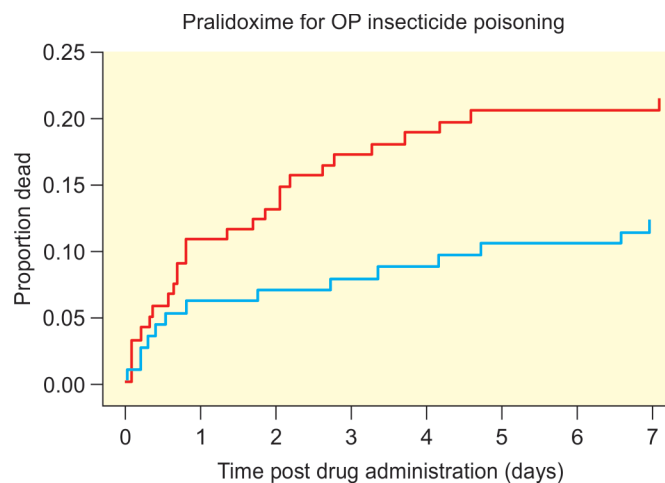


Figure 3: Timing of deaths during the first 6 days. For the purposes of survival analysis, the clock has been started at randomization and stops either at death or discharge (assumed to be 40 days if discharged alive sooner than 40 days)

- Dose of oximes
- Type of compounds
- Toxicity of antidotes.

Study Design

- Some retrospective and prospective studies
- Only four randomized controlled trials (RCTs) (**Table 2**)
- Some methodological flaws in design
- More RCTs—stratified?

Oxime Dose

- Initial study by Cherian: 12 g over 3 days: considered too little
- Pawar study used 50 g: Showed benefit

- Sri Lankan study: relatively high dose 12 g/day: no benefit
- Cost of oximes.

Type of Compound

- Human poisoning by OP bearing two methoxy groups (Dimethyl OP compounds), e.g. Malathion, paraoxon-methyl, dimethoate and oxydemeton-methyl is rather resistant to oxime therapy
- Eddleston study
 - Reactivation happens with diethyl but not dimethyl
 - No difference in mortality
 - Median pseudocholinesterase levels were lower in survivors who received placebo than those who died with pralidoxime.

Toxicity of Antidote

- Oximes by themselves can cause muscle weakness
- Rapid infusion causes dizziness, flushing, numbness
- Formation of stable phosphoryl oximes with high anti-cholinesterase activity.

Cochrane Systematic Review

The results and conclusions are extracted from a recent Cochrane systematic review (Buckley NA, Eddleston M, Li Y, Bevan M, Robertson J. (2012). Oximes for acute organ-ophosphate pesticide poisoning. [online] Available from www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005085.pub2/abstract [cited 2012 Feb 27] did not reveal any additional to RCTs.

Main Results

Seven pralidoxime RCTs were found. Three RCTs including 366 patients studied pralidoxime versus placebo and four RCTs including 479 patients compared two or more different doses. These trials found quite disparate results with treatment effects ranging from benefit to harm. However, many studies did not take into account several issues important for outcomes. In particular, baseline characteristics were not balanced, oxime doses varied widely, there were substantial

Parameter	Study 1			Study 2		
	High dose	Low dose	p value	High dose	Low dose	p value
Number of patients	36	36		100	100	
Dose of oxime	12 g	1 g		48 g	12 g	
Age	24.9 (7.5)\$	25.3 (10.8)	0.89	28 (22–23)	29 (22–35)	NA
Time from ingestion to antidote administration	17.3 (11.6)	16.8 (10.8)	0.85	2 (1.5–2.4)	1.9 (1.0–2.5)	NA
Type of organophosphate compound						
Dimethyl organophosphate	22 (61)	20 (56)		77 (77)	59 (58)	
Diethyl organophosphate	8 (22)	9 (25)		23 (23)	41 (41)	
Unknown compound	6 (17)	7 (19)		0	0	
Pseudocholinesterase levels, mean (SD)	441 (450)	339 (261)	0.24	NA	NA	NA
Median: (IQR) Butyryl cholinesterase levels	NA	NA	NA	866 (752–939)	808 (535–911)	NA
Outcomes						
Duration of ICU stay (Days)	6.8 (5)	5.9 (4)	0.55	NA	NA	NA
Number ventilated	24	17	0.09	64	88	0.0001
Number of ventilation (days)	7.7 (5.2)	6.8 (4.8)	0.70	5 (4–5)	10 (10–12)	< 0.0001
Intermediate syndrome (n)	20	13	0.08	NA	NA	NA
Deaths (n)	8	5	0.35	1	8	0.04

delays to treatment, and the type of organophosphate was not taken into account. Only one RCT compared the World Health Organization (WHO) recommended doses with placebo. This trial showed no clinical benefits and a trend toward harm in all subgroups, despite clear evidence that these doses reactivated acetylcholinesterase in the blood.

Inference

Current evidence is insufficient to indicate whether oximes are harmful or beneficial. The WHO recommended regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/hour infusion) is not supported. Further RCTs are required to examine other strategies and regimens. There are many theoretical and practical reasons why oximes may not be useful, particularly for late presentations of dimethyl OP and those with a large excess of OP that simply re-inhibits reactivated enzymes. Future studies should screen for patient subgroups that may benefit and may need flexible dosing strategies as clinical effectiveness and doses may depend on the type of OP.

DOES ADMINISTRATION OF FRESH FROZEN PLASMA LEADS TO IMPROVEMENT IN HEALTH OUTCOMES IN ORGANOPHOSPHATE POISONING?

Fresh frozen plasma (FFP) is a blood fraction prepared by removing the cellular components by a process called apheresis. Fresh frozen plasma contains important components like clotting factors, proteins, enzymes, etc. It is used in conditions where these components are deficient or lost in blood.

In OP poisoning it is hypothesized that the enzyme butyrylcholinesterase present in FFP will sequester free poison present in blood and remove them from circulation.

Discussion

Two trials:

1. One trial compared the effect of FFP versus no intervention¹
2. One trial compared the effect of FFP versus albumin and saline²

The meta-analysis of the results indicated that the administration of FFP to patients with OP poisoning may be harmful with respect to the outcome of death (RR = 1.67, 95% CI: 0.43–6.44) and duration of hospital stay (greater by 0.48 days in FFP arm), but with low confidence in the estimates. Only one study reported the outcomes of intermediate syndrome (RR = 2.95% CI: 0.84–4.75) and duration of ventilation (greater by 1.5 days in the FFP arm) and both appeared to be unfavorable to the FFP intervention. All the effect estimates have low or very low quality of evidence, majorly because of the high degree of imprecision in the results.

Discussions with the authors of Pichamuthu 2010¹ revealed that the study was terminated before the estimated sample size was achieved because outcomes from the recruited participants showed that FFP appeared to be more harmful than beneficial. They suggested that the negative outcomes in the study may be attributed to butyrylcholinesterase releasing the sequestered organophosphate. The trial had also compared albumin as a bioscavenger but it was not analyzed as a part of this review.

Inference

The currently available research evidence is not strong enough to make any clear conclusion regarding the role of bioscavenger therapy.

DOES EARLY ENTERAL FEEDING IMPROVE HEALTH OUTCOMES IN ORGANOPHOSPHATE POISONING?

Early Enteral Feeding

Early institution of enteral feeds may be associated with improved outcomes in the critically ill because it prevents enterohepatic circulation. Early nutritional supplementation in OP poisoning assumes importance given that these patients may require prolonged ventilatory support because of the development of respiratory failure as a result of the intermediate syndrome.

DOES CLONIDINE IMPROVE HEALTH OUTCOME IN ORGANOPHOSPHATE POISONING?

Clonidine is a centrally acting alpha-2 receptor agonist. It is used as centrally acting antihypertensive drug. It inhibits presynaptic release of acetylcholine, thereby decreasing the cholinergic symptoms caused by organophosphate poisoning.^{3,4} It is expected to have a synergistic action with atropine. Sedation, hypotension, bradycardia, and rebound hypertension (with prolonged use) are the known adverse effects of clonidine in OP poisoning.

Inference

We did not find any good quality evidence for the use of clonidine as an intervention for organophosphorus poisoning. A controlled clinical trial aimed at finding an optimum dose for clonidine regimen of clonidine bolus injection (0.15–0.30 mg) followed by an infusion at the rate of 0.5 mg/24 hours appears to be clinically acceptable.

DOES CHARCOAL-BASED GASTRIC DECONTAMINATION IMPROVE HEALTH OUTCOMES IN ORGANOPHOSPHATE POISONING?

Charcoal

Activated charcoal has been widely used for absorbing poisons including pesticides, plant poisons, and drugs. Evidence for benefit of activated charcoal has been demonstrated for yellow oleander poisoning and oral drugs such as theophyllines, carbamazepine and phenobarbital. The two methods of charcoal administration are: (1) single dose activated charcoal; (2) multiple dose activated charcoal. *In vitro* studies show that charcoal adsorbs organophosphates and therefore may have a potential role in the treatment. However, no formal RCT has addressed this question specifically in the case of OP poisoning.⁵

Inference

While the results from the high quality RCT do not support the benefit of activated charcoal use in acute organophosphate poisoning, there is also no evidence of harm.

DOES GASTRIC LAVAGE IMPROVE HEALTH OUTCOMES IN ORGANOPHOSPHATE POISONING?

Gastric Lavage

Gastric lavage is widely used decontamination procedure across Asia. However, its efficacy has not been proven in any poisoning. The theoretical rationale of the procedure is obvious.

Organophosphates are compounds that are easily absorbed through mucous membranes and gastric lavage may play a role in the early stage after poisoning. However, the duration for which

the organophosphates remain in the stomach after ingestion is still unknown. There are also concerns that this procedure may increase gastric emptying time and also lead to complications of aspiration and respiratory distress. Hence the relative benefit and risks of gastric lavage in OP poisoning is yet to be evaluated.

Inference

We found no RCTs that evaluate the benefit or harm of gastric lavage in OP poisoning. However, this being an easily performed and cheap intervention it could be used as an adjunct measure in the treatment of OP poisoning.

DOES ALKALINIZATION IMPROVE HEALTH OUTCOMES IN ORGANOPHOSPHORUS POISONING?

It has been suggested that IV infusion of sodium bicarbonate produces moderate alkalization (blood pH between 7.45 and 7.55) in OP pesticide poisoning.^{6,7} Sodium bicarbonate was first used to correct the metabolic acidosis. Regarding its enhanced therapeutic effects, the infusion of higher doses of sodium bicarbonate (5 mEq/kg in 60 minutes followed by 5–6 mEq/kg/day) was shown to be useful. The alkalization products of nerve agents such as soman are shown to be less toxic and hence, the IV infusion of sodium bicarbonate may even be more beneficial in nerve agents poisoning.

External Decontamination

Disrobing and washing with soap and water: There are no studies evaluating this particular intervention; however, this seems to be an obvious method by which we can reduce further absorption of the poison into the system. Since there are minimal costs involved and easy to perform it is recommended that the practice is continued by removing contaminated clothes and washing with soap and water. An RCT would be considered unethical to demonstrate the effectiveness of this intervention.

Magnesium Sulfate

Intravenous MgSO₄ (4 g) given in the first day after admission have been shown to decrease hospitalization period and improve outcomes in patients with OP poisoning. Magnesium sulfate blocks calcium channels and thus reduces acetylcholine release. It also reduces CNS overstimulation resulting from N-methyl D-aspartate receptor (NMDAR) activation and reversed for the neuroelectrophysiological defects.

Source: Data from Blain PG 2011.

Forced Emesis

The systematic review considered that by consensus forced emesis (Ipecac) should not be performed on patients with OP poisoning because they may delay specific life-saving treatment and administration of activated charcoal. They found no RCTs which addressed forced emesis as an intervention for OP poisoning or for any other type of poisoning. Adverse effects of ipecac may include aspiration, diarrhea, ileus, dysrhythmias during vomiting, dystonia from treatment of vomiting, and hematemesis from vomiting.

Benzodiazepines

In animal studies with OP there is evidence of increased CNS activity, seizures of respiratory center, and increased phrenic nerve activity with sudden cessation of activity. Pretreatment with diazepam in animal models of OP poisoning reduced respiratory depression and improves outcomes.¹

Benzodiazepines are widely used in human OP poisonings to control agitation, provide sedation in ventilated patients and control of seizures. However, there are no trials evaluating the efficacy of

benzodiazepines as a primary treatment for OP poisoning. Further human studies are required for evaluating the role of benzodiazepines in OP poisoning.⁸

Advanced Neuroprotective Drugs

Ketamine, a noncompetitive NMDAR antagonist, can be used until 1 hour following nerve agent-induced seizures specially, when administered in combination with midazolam or diazepam. In a recent study, Tezampanel, another glutamate receptor antagonist, which is specific for kainate subtype receptors, was reported to be useful against soman-induced seizures and neuropathy in patients exposed to nerve agents.

For intermediate syndrome, which is resistant to the standard treatment, supportive therapy and consideration of artificial respiration are recommended. For organophosphate-induced delayed neuropathy, standard therapy should be accompanied with neuroprotective drugs like corticosteroids. Protease inhibitors have been useful in protecting the neuropathy target esterase and preventing the establishment of delayed neuropathy. However, further studies are required both experimentally and clinically to find out effective treatments for severe OP poisonings.

Cathartics

These are cathartics used to treat organophosphorus poisoning because they are believed to speed the passage of poisons in general out of the gastrointestinal tract. Reduced transit time reduces the absorption of poison. Blain PG 2011¹ did not find any RCTs addressing the effect of cathartics in organophosphate poisonings. Cathartics-induced diarrhea and electrolyte imbalance should be managed accordingly.

Gacyclidine

Gacyclidine is an antiglutamatergic compound that was proved to be beneficial in conjunction with atropine, pralidoxime, and diazepam in nerve agents poisoning. Electroencephalogram findings demonstrated gacyclidine-inhibited seizures that were induced by soman. It also markedly enhanced clinical recovery of soman-challenged primates. Gacyclidine inhibited the neuropathology that occurred 3 weeks following soman exposure in animals. In the presence of severe nerve agent poisoning, gacyclidine can be a useful adjuvant therapy along with the present available polymedications of OP nerve agent poisonings.

Antioxidants

Induction of reactive oxygen radicals and their contributors such as decreased total antioxidant capacity, and increased thiobarbituric reactive substances and lipid peroxidation occur in OP poisoning either as acute, subchronic or chronic exposure. Thus, antioxidants treatment may be beneficial in these patients. In a study on rats, vitamin E was reported to have therapeutic effects in dimethoate and malathion-induced oxidative stress in rat erythrocytes.

New Treatments

Removal of organophosphates from blood by using hemodialysis, hemoperfusion or hemofiltration is not clear. In a recent report, it was claimed that hemofiltration after dichlorvos poisoning had revealed beneficial therapeutic effects.

CARRY HOME MESSAGES

- We recommend incremental dose administration of atropine as the standard of care. The role of glycopyrrolate alone or in combination with atropine is not clear

- Overall null effect or potential harm with oximes was found on meta-analysis of trials. The largest oxime study tends to harm
- Fresh frozen plasma appeared to be more harmful than beneficial
- Early institution of enteral feeds may be associated with improved outcomes in the critically ill as it prevents enterohepatic circulation
- An optimum dose of clonidine with clonidine bolus injection (0.15–0.30 mg) followed by an infusion at the rate of 0.5 mg/24 hours appears to be clinically acceptable in OP poisoning
- *Activated charcoal use in acute OP poisoning*: No evidence of harm or benefit
- Gastric lavage in OP poisoning shows no evidence of harm or benefit. However, this being an easily performed and cheap intervention could be used as an adjunct measure
- Blood alkalinization with high dose NaHCO_3 in OP poisoning was shown to be useful
- *External decontamination*: Disrobing and washing with soap and water can reduce further absorption of the poison into the system
- Intravenous MgSO_4 (4 g) given in the first day after admission has been shown to decrease hospitalization period and improve outcomes in patients with OP poisoning
- Forced emesis (Ipecac) should not be performed on patients with OP poisoning
- Benzodiazepines are widely used in OP poisoning to control agitation, provide sedation in ventilated patients and control of seizures. However, there are no trials evaluating the efficacy of benzodiazepines as a primary treatment for OP poisoning
- Cathartics can reduce the transit time and reduces the absorption of poison
- *Gacyclidine*: Antioxidants are useful adjuvant therapies in OP poisoning.

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