Organophosphorous Poisoning : an Evidence Based Approach

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Acute organophosphorous poisoning (OPP) occurs following dermal, respiratory or oral exposure [1]. Organophosphorous compounds (OPCs) can be classified into low volatile compounds eg. chlopyrifos, dimethoate, dichlorvos, methyl parathion etc. used for agricultural purposes as pesticides or highly volatile nerve gases eg. sarin, tabun etc., mainly used in chemical warfare [1]. Most cases occur in developing countries and are generally following suicidal ingestion [2,3]. World Health Organization (WHO) has estimated that nearly 200,000 people worldwide die from pesticide poisoning mainly in developing countries following intentional poisoning [4]. This is because of their wide and easy availability and occupational exposure because of inadequate or inappropriate protective equipment [2,4]. Military and terrorist attacks with nerve gases always remain possible eg. Iran-Iraq war [5], Tokyo underground attack.

In India, it is the commonest poisoning [6]. OPCs inhibit acetylcholinesterase at neuromuscular junction, in autonomic and central nervous system resulting in accumulation of acetylcholine (ACh) and over stimulation of ACh receptors resulting in acute cholinergic crisis which is characterized by bradycardia, bronchorrhoea, miosis, sweating, salivation, lacrimation, defecation, urination and hypotension [1]. In addition, there occurs muscle weakness and fasciculations. The CNS involvement results in alteration in sensorium and seizures [1]. Following resolution of cholinergic crisis, some patients may develop intermediate syndrome i.e. cranial nerve palsies, proximal muscle weakness, respiratory muscle weakness [1]. Some may develop peripheral neuropathy (OPIP) at a later stage [1].

The diagnosis can be made from history of ingestion or exposure e.g. following spray, clinical features and plasma cholinesterase (PChE) and red cell acetylcholinesterase (Red Cell AChE) inhibition [1]. However, between inhibition of these enzymes and severity of poisoning there is no correlation [7]. The management

of these patients involves washing of skin and induction of vomiting or gastric lavage to remove OPCs from skin and stomach, administration of activated charcoal, atropine, glycopyrrolate, oximes and some newer compounds in addition to ventilatory support which they may require.

Washing of skin and removal of contaminated clothes

No randomized controlled trials (RCTs) are available in literature. However, it seems to be the most obvious way of reducing further dermal and mucosal absorption. However, care should be taken by health workers to protect themselves by using gloves, aprons, eye protection etc. as they run the risk of getting poisoned [8]. Moreover, this should not be priority if patient requires resuscitation first.

Induction of vomiting with ipecac

No RCTs are available in literature. However, complications have been reported following its use. These are aspiration, diarrhoea, ileus etc [9]. One systematic review suggests that the use of ipecac in any poisoning does not improve the outcome [9]. Moreover, administration of it is likely to result in delay in administration of activated charcoal.

Gastric lavage

The complications include aspiration, laryngeal spasm, oesophageal perforation, hypoxia [10]. These are especially common when it is being performed in a struggling, non-consenting patient. Although anecdotal reports suggest that OPCs may remain in gut for prolonged duration and it may help in their removal, there is no obvious evidence at present that it helps in outcome [11]. In India, as suicide is still an offence and gastric lavage is being done routinely, for medico-legal reasons to collect gastric sample and for therapeutic reasons, it will be better to carry out RCTs to see whether it benefits the patients.

Activated charcoal

The complications include aspiration pneumonia, vomiting, diarrhoea, constipation, ileus and reduction in absorption of oral medications [12]. There are few trials which suggest that incidence of complications is low with multiple dose regimen [13]. One non-systemic review of single dose of activated charcoal in all forms of poisoning has found that it does not improve the outcome [11]. There is a need to carry out RCTs to find benefit of single or multiple dose regimen in patients with OPP.

Atropine

Atropine remains the main stay of treatment [14,19]. Although it has not been compared with placebo, several case series have found that it reverses the early muscarinic effects of OPP. Atropine competes with excess ACh at muscarinic receptors. The first doses are generally given as boluses followed by infusion if dose requirement is large. The rate of infusion should be kept to maintain pupils at midpoint, heart rate greater than 100 beats per min, normal bowel sounds and clear lungs [16].

Glycopyrrolate

Glycopyrronium bromide has been used in place of atropine. In a small RCT comparing it with atropine (total 39 patients), it was found that there was no significant difference in the outcome in two groups except that fewer respiratory infections were observed in patients who were given glycopyrrolate and were ventilated [20]. The mortality rate and duration of ventilation did not differ. However, a major limiting factor is the cost. Glycopyrrolate is about 10 times more costly and it may be worthwhile to carry out more RCTs to know whether it has any benefit over atropine.

Oximes

Oximes reactivate the acetylcholinesterase inhibited by OPCs [1], reactivation is limited by ageing and by high concentration of pesticide [21]. With diethyl compounds ageing takes longer than with dimethyl compounds [11]. Complications of oximes include hypertension, cardiac dysrhythmias, headache, blurred vision, dizziness etc. [22]. Obidoxime can lead to hepatic failure [22]. Two RCTs are available from Vellore (India) [17-19], suggesting that oximes do not benefit and with 12 gm over 3 days increase the risk of death, intermediate syndrome and requirement of ventilation. However, the studies have been criticized for randomization bias and inadequate dose. It is suggested that 2-PAM infusion should be given till patient recovers [22,23]. WHO currently recommends 30 mg/kg bolus followed by 8 mg/kg/hr as IV infusion [11]. RCTs

involving large number of patients are required to prove its benefit.

Newer compounds

Organophosphorus hydrolases [24] such as mammalian paraoxonase can hydrolyze the OPCs thus reducing their concentration rapidly. However, no human studies are available.

Sodium bicarbonate : Animal studies suggest that increasing pH with sodium bicarbonate may reduce mortality rate and this effect is independent of acidosis [25,26]. At present, a few uncontrolled studies are available [5] to show its benefit but no RCTs are available.

Clonidine : It inhibits the release of ACh from cholinergic neurons and has adrenergic agonist effects. In animal studies, pre-treatment with it improves survival [27]. However, no human studies are available.

N-methyl-D-aspartate receptor antagonists (NMDA receptor antagonists) : Primate studies have found that pre-treating with NMDA receptor antagonists such as gacyclidine improves recovery [28]. However, no human studies are available.

Benzodiazepines : Diazepam is the standard treatment for organophosphorous induced seizures. No RCTs are available but several studies support that diazepam controls seizures [29].

Conclusion

Washing the patients and removing the contaminated clothing, administering atropine to control muscarinic manifestations and diazepam to control seizures are undoubtedly of use in management of acute organophosphorous poisoning. Induction of vomiting with ipecac may prove more harmful. Gastric lavage, at present, seems to lead to more harm than benefit especially in a struggling, non consenting patient. Oximes need to be studied in larger RCTs to find the benefit, using the recommended doses. There is no evidence at present that organophosphate hydrolases, sodium bicarbonate, clonidine, NMDA receptor antagonists help in outcome.

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