

# Organophosphate and Carbamate Poisoning



Andrew M. King, MD<sup>\*</sup>, Cynthia K. Aaron, MD

## KEYWORDS

- Organophosphate • Carbamate • Pesticides • Insecticides • Nerve agents
- Chemical warfare • Atropine • Oxime

## KEY POINTS

- Organophosphates (OPs) and carbamates have a variety of applications, but are primarily used agriculturally as pesticides.
- OPs and carbamates are responsible for the deaths of hundreds of thousands of people every year.
- Acute toxicity results from acetylcholinesterase (AChE) enzyme inhibition and subsequent excessive nicotinic and muscarinic stimulation in the central and autonomic nervous systems and the neuromuscular junction.
- Good supportive care, decontamination, aggressive antimuscarinic therapy, early seizure control, and early antidotal oxime therapy are the keys to good outcomes.

## INTRODUCTION

### *Epidemiology*

Experts believe that acute poisoning from acetylcholinesterase (AChE)-inhibiting insecticides is responsible for more deaths than any other class of drug or chemical.<sup>1</sup> They are a particular problem in the developing world, where highly toxic pesticides are readily available and are used in the suicides of hundreds of thousands of people every year.<sup>2</sup> With an estimated case fatality rate of 10% to 20%, the subsequent health care burden of those who do not die after a suicidal ingestion is an order of magnitude higher.<sup>3,4</sup> The disease burden of OP and carbamate toxicity is much less in developed countries. In contrast with the 25,288 people who committed suicide with pesticides in India in 2010,<sup>5</sup> the American Association of Poison Control Centers in 2012 received a combined 4150 calls for OP and carbamate exposures, resulting in a total of 3 deaths.<sup>6</sup> Although unintentional agricultural poisonings do occur, they are generally less severe.<sup>7,8</sup>

---

Disclosure Statement: The authors of this paper have no disclosures.

Department of Emergency Medicine, Children's Hospital of Michigan Regional Poison Control Center, Detroit Medical Center, Wayne State University School of Medicine, 4707 Street Antoine, Suite 302, Detroit, MI 48201, USA

\* Corresponding author.

E-mail address: [aking@dmc.org](mailto:aking@dmc.org)

Emerg Med Clin N Am 33 (2015) 133–151  
<http://dx.doi.org/10.1016/j.emc.2014.09.010>

[emed.theclinics.com](http://emed.theclinics.com)

0733-8627/15/\$ – see front matter © 2015 Elsevier Inc. All rights reserved.

## Uses

Commercially, organophosphorus chemicals have a number of applications, but are mostly employed as pesticides in a variety of settings (**Box 1** from<sup>9</sup>). They protect commercial and food crops from damaging insect vectors. They also control insect infestations in commercial and residential settings. It should be noted that the Environmental Protection Agency has banned or plans to remove many OPs from the United States and thus OP use for many of these applications has been sharply curtailed. Some medical indications for organophosphates (OPs) include the eradication of corporeal insect infestations in humans and animals. One organic phosphorus chemical is used for glaucoma (diisopropyl phosphorofluorodate).

Militarized OPs (also known as nerve agents) are classified as chemical weapons and weapons of mass destruction. Despite the manufacture of hundreds of thousands of tons of these chemicals by various countries during the 20th century, only small amounts have been deployed in a number of clandestine situations, including the Iran–Iraq war, the Iranian attack on the Kurds, and more recently in the Syrian Civil war in August 2013, resulting in more than 1400 deaths.<sup>10</sup> Before this, the most notable use of nerve agents was the 1995 terrorist attack in Tokyo, Japan, which left 11 dead and more than 5000 victims seeking medical attention.<sup>11</sup> These recent episodes are tragic reminders of the persistent threat posed by nerve agents.

By volume, carbamates are used most frequently as pesticides. However, they do have number of interesting medical indications (**Table 1**).

## History

OPs are of particular historical interest given their development and use as chemical weapons. The early part of the 20th century saw the development of the G-series of nerve agents (tabun, sarin, and soman) by the Germans, the V-series (VE, VG, VM,

### Box 1

#### Sources of organophosphorus pesticides

##### *Domestic*

- Garden sheds—in particular insecticidal preparations but also other products that are marketed as fertilizers but contain some organophosphorus pesticides, available as solid or liquid formulations
- Surface and room sprays
- Baits for cockroaches and other insects (eg, chlorpyrifos)
- Shampoos against head lice (eg, malathion)
- Pet preparations (eg, pet washes, collars)

##### *Industrial or occupational*

- Crop protection and livestock dipping
- Large scale internal control, including fumigation

##### *Terrorism or warfare (nerve agents)*

- Sarin, for example, was used in the Tokyo subway attack, and both tabun and sarin were used during the Iraq–Iran conflict; although nerve agents share a similar mechanism of toxicity with organophosphorus pesticides, their treatment is a specialized topic and not dealt with in this review

From Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. *BMJ* 2007;334(7594):629-34; with permission.

**Table 1**  
Human disease treated with carbamates

Indication	Carbamate
Myasthenia gravis	Edrophonium, pyridostigmine
Antimuscarinic poisoning	Physostigmine
Alzheimer's disease	Rivastigmine, donepezil, galantamine, tacrine
Glaucoma	Physostigmine, ecthiopate
Neuromuscular blockade reversal	Pyridostigmine, neostigmine
Elapid envenomation	Neostigmine
Adynamic ileus	Neostigmine

and VX) by the allies, and, more recently, the ultratoxic group of agents called the Novichok or newcomer agents by the Russians.<sup>12</sup> Many tens of thousands of tons of nerve agents were produced and stockpiled by various countries during World War II. Since then, most countries, in compliance with the Chemical Weapons Convention of 1997, have destroyed or scuttled more than 80% of their declared stockpiles.<sup>13</sup> However, as the incidents in Tokyo and Syria have reminded us, nerve agents continue to be a threat in the hands of terrorists and other militant groups.

The delayed peripheral neuropathy caused by certain OPs (also known as OP-induced delayed peripheral neuropathy [OPIDN]) has led to many well-known, toxin-induced epidemics throughout the world. The Ginger Jake paralysis that affected thousands of Americans during prohibition was caused by an organic phosphorus adulterant (triorthocresyl phosphate, added to Jamaican Ginger ["jake"] extract) to pass US Department of Agriculture inspections. Consumption of this adulterated extract resulted in lower extremity weakness, paraparesis, paralysis, and impotence.<sup>14,15</sup> Similar outbreaks of OPIDN have subsequently been reported in Sri Lanka, Vietnam, and other developing countries.<sup>16,17</sup>

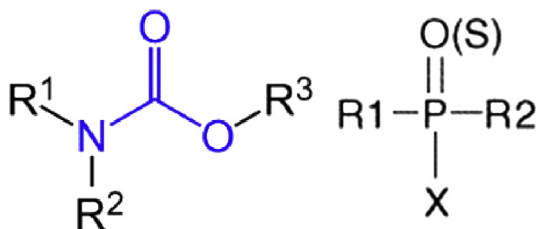
Physostigmine and its carbamate derivatives have an interesting and tragic past as well. Physostigmine is the ordeal bean of Old Calabar (*Physostigma venenosum* *Balfour*), and was the first carbamate isolated by Westerners.<sup>18</sup> Since then, a number of carbamates have been synthesized and employed as fungicides and insecticides. Unfortunately, it was this synthesis that led to the largest industrial accident in history<sup>19</sup> in 1984 during production of the carbamate carbaryl at The Union Carbide Corporation's factory in Bhopal, India. Methyl isocyanate accidentally leaked, immediately killing more than 3800 people and leaving thousands more suffering health effects and premature death.

## AGENTS OF TOXICITY

### Biochemistry

The general structures of carbamates and OPs are shown below (Fig. 1). *N*-Methyl carbamate compounds are the only carbamate derivatives that inhibit AChE. Other derivatives, such as thiocarbamates, do not inhibit AChE and are not discussed in this article. The major carbamates and their relative toxicities are found in Table 2.<sup>20</sup> A number of these are not available commercially in the United States.

The structure–function relationship of organic phosphorus compounds is clinically relevant in that each derivative's chemical properties relates to its toxic potential. The general structure includes a phosphoryl group (O = P) or a thiophosphoryl group (P = S), 2 lipophilic R groups, and the leaving group (X; see Fig. 1). The X group or leaving group serves as a means of classifying the various OPs.<sup>1</sup> These groups tend to



**Fig. 1.** *N*-Methyl carbamates contain a common NCOO structure with various side chains R1-R3 (*left*). The basic structure of an organophosphate (OP) is shown on the *right*. Each OP contains a phosphoryl or thiophosphoryl group, 2 side chains, and a leaving group (X).

share certain physical and pharmacodynamic characteristics, but generally do not affect acute management.

### Pharmacokinetics

A number of pharmacokinetic properties are important with respect to onset and duration of toxicity. These include route of exposure, lipophilicity, and volume of distribution, whether the agent requires metabolism before it can exert its toxic effects, serum paraoxonase activity (an intrinsic enzyme capable of hydrolyzing certain OPs), and elimination. Important pharmacodynamic properties include potency, rate of AChE inhibition, and rate of aging.

### Route

- OPs and carbamates are absorbed through all routes
- Ingestion and inhalation lead to immediate onset of symptoms if vaporized or misted.
- Dermal exposure may have immediate local effects (local diaphoresis and fasciculations) and delayed systemic effects.<sup>21</sup>

**Table 2**

**The main carbamate insecticides in use and their relative toxic potency (estimated human values)**

High Toxicity (LD <sub>50</sub> <50 mg/kg)	Moderate Toxicity (LD <sub>50</sub> = 50–200 mg/kg)	Low Toxicity (LD <sub>50</sub> >200 mg/kg)
Aldicarb (Temik)	Bufencarb (Bux)	BPMC (Fenocarb)
Aldoxycarb (Standak)	Carbosulfan	Carbaryl (Sevin)
Aminocarb (Metacil)	Pirimicarb (Pirimor)	Isoprocarb (Etrofolan)
Bendiocarb (Ficam)	Promecarb	MPMC (Meobal)
Carbofuran (Furadan)	Thiodicarb (Larvin)	MTMC (Metacrate, Tsumacide)
Dimetan (Dimetan)	Trimethacarb (Broot)	XMC (Cosban)
Dimetilan (Snip)		
Dioxacarb (Eleocron, Famid)		
Formetanate (Carzol)		
Methiocarb (Mesuroil)		
Methomyl (Lannate, Nudrin)		
Oxamyl (Vydate)		
Propoxur (Baygon)		

Data from National Crime Records Bureau. Accidental Deaths and Suicides in India - 2010. Available at: <http://ncrb.nic.in/ADSI2010/home.htm>. Accessed June 4, 2014.

### ***Pharmacokinetic Properties***

---

- OPs are lipophilic compounds with some sequestering in fat stores.
- Highly lipophilic agents may have a delay in symptoms development.<sup>22,23</sup>
- Highly lipophilic agents cause protracted toxicity.<sup>24,25</sup>
- Redistribution of lipid soluble OPs from fat stores can “repoison” a patient.
- Carbamates are inactivated more quickly and generally do not cause prolonged toxicity.

### ***Metabolism and Subsequent Activation***

---

- OPs are either “oxons” (which can directly inhibit AChE) or “thions” (which require desulfuration to the oxon form to become maximally active).
- Once “thions” (P = S) are oxidized to “oxons”(P = O), they have enhanced toxicity.
- Carbamates do not require metabolism to become active.

### ***Toxicodynamics***

---

OPs and carbamates both inhibit synaptic AChE. Synaptic AChE normally prevents further downstream neurotransmission by hydrolyzing acetylcholine to acetic acid and choline. Acetic acid feeds into the Krebs cycle, whereas choline is taken back up by the neuron and resynthesized to new acetylcholine. Subsequently, acetylcholine accumulates in the nerve or myoneuronal synapse, which leads to characteristic toxic manifestations (cholinergic toxidrome). True AChE is found not only in nervous tissue, but also on the surface of erythrocytes (erythrocyte or red blood cell cholinesterase). Butyrylcholinesterase (also known as pseudocholinesterase or plasma cholinesterase) is found primarily in the liver and is responsible for xenobiotic metabolism (eg, cocaine, succinylcholine). It is important to note that erythrocyte AChE activity more closely mirrors neuronal AChE activity than does butyrylcholinesterase, and is a better marker for neuronal physiologic status.<sup>26–28</sup>

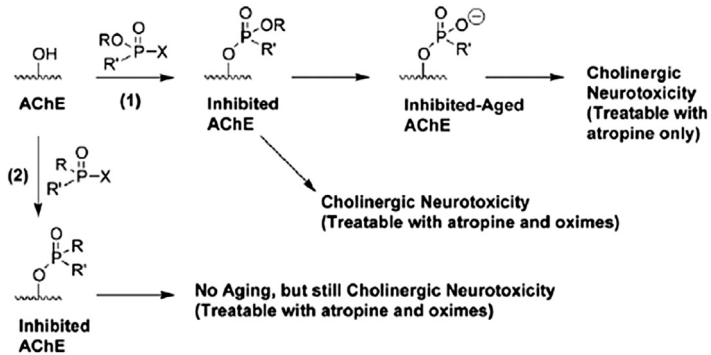
### ***Toxicodynamic Differences Between Organophosphates and Carbamates***

---

The unique pharmacodynamics of organophosphates and carbamates and their differences in interaction with AChE play a role in the clinical toxicity differences as well as implications for antidotal therapy.

Within the anticholinesterase protein catalytic site lays a serine hydroxyl group (–OH). The serine group becomes phosphorylated once the leaving group (X) is released. At this point, the OP–serine bond can spontaneously hydrolyze and the enzyme regains its function, or, an R group leaves (ages), it becomes irreversibly phosphorylated, and the enzyme is permanently inhibited (**Fig. 2**). The relative speeds of these processes have major implications with respect to administration of the antidotal oximes.

Antidotal oximes increase the rate of hydrolysis and reactivation and prevent irreversible aging. Although those OPs with shorter R-group side chains age more quickly, they also reactivate more quickly and are theoretically more responsive to oxime therapy, provided it is administered early. In contrast, although there is more time to administer oximes to patients poisoned with long-R chain OPs, a greater amount of oxime administered over a longer period of time is required.<sup>21</sup> The reverse can be argued as well; administration of oximes to dimethyl phosphoryl–poisoned patients is less likely to benefit precisely because of those OPs propensity to age quickly.<sup>29</sup> In other words, by the time the oxime is available to facilitate hydrolysis and reactivate AChE, the OP has already aged. Unfortunately, once aged, oximes



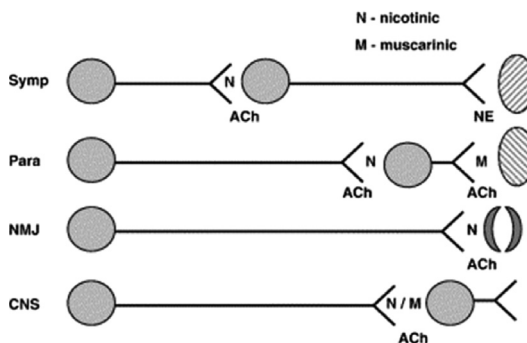
**Fig. 2.** Phosphonyl (1) and phosphinyl (2) organophosphate molecules bind to the acetylcholinesterase enzyme with resultant loss of the leaving group (X). The acetylcholinesterase (AChE) enzyme is now inhibited in both cases and cholinergic toxicity ensues. Before the loss of the R group in (1), both complexes are treatable with atropine and oximes. However, after the loss of the R group (1), the OP has "aged" and the AChE enzyme is irreversibly inhibited.

cannot reactivate the enzyme and any further AChE activity requires the de novo synthesis of additional AChE enzyme<sup>30</sup>

Carbamates also inhibit AChE enzyme in an identical fashion; however, the carbamate–AChE bond is weaker than that formed by OPs. Thus, carbamate–AChE bonds spontaneously hydrolyze more rapidly and AChE function returns typically within 24 to 48 hours. In contrast with OPs, carbamates cannot age and prolonged toxicity is uncommon.

### Pathophysiology

The 2 acetylcholine receptor subtypes found in humans and animals are the muscarinic and nicotinic receptors. These receptors are further subclassified according to their locations in the body and what occurs after acetylcholine binds to the receptor. In general, muscarinic receptors are found in the central nervous system (CNS), exocrine glands, and the hollow end-organs innervated by the parasympathetic system, and nicotinic receptors are located in the postganglionic neurons of both the parasympathetic and sympathetic chains, the adrenal medulla, and the neuromuscular junction (**Fig. 3**).<sup>31</sup> Both are found in the brain.



**Fig. 3.** Graphic representation of the acetylcholine-relevant physiology and anatomy. (From Cannard K. The acute treatment of nerve agent exposure. *J Neurol Sci* 2006;249(1):86–94; with permission.)

Excess acetylcholine at the 2 receptor subtypes results in different end-organ effects. When poisoned by OP and carbamate xenobiotics, toxicity varies and may manifest with primarily nicotinic effects (hypertension, tachycardia, fasciculations, weakness, mydriasis), muscarinic effects (miosis, bradycardia, bronchospasm, bronchorrhoea), or a combination of the two. Acetylcholine excess at the neuromuscular junction results in a type II paralysis in the same way succinylcholine depolarizes and paralyzes skeletal muscle. Additionally, cholinergic neurons interact with other neurotransmitter systems ultimately leading to  $\gamma$ -aminobutyric acid (GABA) inhibition and *N*-methyl-D-aspartate activation, which may in part be responsible for CNS-mediated respiratory depression and seizure activity.<sup>32–35</sup> **Table 3** summarizes the clinical effects of cholinergic toxicity.

### CLINICAL MANIFESTATIONS

Onset and severity of toxicity depend on a variety of factors, including agent, route, formulation, amount, and duration of exposure. For example, death may occur within minutes of inhalational exposure to nerve agents, whereas symptoms from dermal exposures of highly lipophilic agents requiring activation may be delayed by up to 48 hours.<sup>36</sup> Time to onset of symptoms after ingestion tends to be slightly delayed compared with inhalation, with clinical effects expected to begin within 30 to 90 minutes.

Similarly, initial and presenting symptoms depend on the route of exposure. Ingestion often presents with vomiting and other gastrointestinal symptoms, whereas aerosol exposure causes ocular and respiratory symptoms. Dermal exposure may present with localized sweating and fasciculations. Both dermal and inhalational exposures are recognized occupational hazards and exposure can occur during formulation

<b>Table 3</b>	
<b>Clinical effects of organophosphate poisoning (acetylcholine excess)</b>	
<b>Anatomic Site of Action</b>	<b>Signs and Symptoms</b>
<b>Muscarinic effects</b>	
Sweat glands	Sweating
Pupils	Constricted pupils
Lacrimal glands	Lacrimation
Salivary glands	Excessive salivation
Bronchial tree	Wheezing
Gastrointestinal	Cramps, vomiting, diarrhea, tenesmus
Cardiovascular	Bradycardia, decrease in blood pressure
Ciliary body	Blurred vision
Bladder	Urinary incontinence
<b>Nicotinic effects</b>	
Striated muscle	Fasciculations, cramps, weakness, twitching, paralysis, respiratory embarrassment, cyanosis, arrest
Sympathetic ganglia	Tachycardia, elevated blood pressure
<b>Central nervous system effects</b>	Anxiety, restlessness, ataxia, convulsions, insomnia, coma, absent reflexes, Cheyne-Stokes respirations, respiratory and circulatory depression

From Bradberry SM, Vale J. Organophosphorus and carbamate insecticides. In: Wallece K, Brent J, Burkhart KK, editors. Critical care toxicology: diagnosis and management of the critically poisoned patient. Philadelphia: Elsevier Mosby; 2005. p. 940; with permission.

manufacture, mixing, or spraying. Nonsuicidal ingestion can occur when workers do not adhere to appropriate industrial hygiene.

Clinical effects are owing to stimulation of the muscarinic and nicotinic receptors (see [Table 3](#)). Muscarinic stimulation causes defecation, urination, miosis, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation, and salivation (remembered by the mnemonic DUMBBELS). Stimulation of the nicotinic receptors in the sympathetic ganglia and neuromuscular junction will cause *mydriasis*, *tachycardia*, *weakness*, *hypertension*, and *fasciculations* (*Monday–Tuesday–Wednesday–Thursday–Friday*).<sup>37</sup> The “mixed” nicotinic and muscarinic clinical effects can be confusing and lead to misdiagnosis.<sup>38</sup> Clinical effects owing to nicotinic receptor stimulation tend to occur first in more severe poisonings.<sup>39</sup>

CNS effects are varied and can be both nonspecific and severe. These effects include headache, dizziness, restless, anxiety, insomnia, confusion, tremor, dysarthria, ataxia, seizures, coma, and central respiratory depression.<sup>40</sup> Finally, given the balance needed between the dopamine and cholinergic systems, it is not surprising that both acute and delayed extrapyramidal symptoms occur.<sup>41–43</sup>

Muscle weakness and paralysis is of particular importance, which contributes to respiratory arrest and death. Severe OP poisoning results in depolarizing paralysis, preceded by muscle twitching and fasciculations. Mechanical ventilation is often necessary because striated intercostal and diaphragmatic muscles become paralyzed.

Additionally troubling is the “intermediate syndrome,” which develops after acute exposure to certain highly lipophilic OPs.<sup>44</sup> This syndrome, which occurs a few days after a well-defined cholinergic phase, is defined by the development of diffuse weakness, often leading to respiratory failure requiring ventilatory assistance.<sup>45</sup> It is so named because it typically occurs after the initial cholinergic phase and before the delayed-neuropathic phase (see Intermediate syndrome, elsewhere in this article).

Inhibition of neuropathy target esterase by certain OPs leads to a syndrome known as OPIDN. OPIDN typically develops weeks after an acute exposure. A characteristic progression of symptoms occurs, starting with paresthesias in the hands and feet leading to sensory loss, weakness, ataxia, and distal muscle flaccidity. Those who develop OPIDN may recover after a few months; however, in some cases, the effects are permanent (see Organic Phosphorus-Induced Delayed Neuropathy, elsewhere in this article). OPs and carbamates affect a number of additional organ systems. The various cardiac effects are shown in [Box 2](#).

Ventricular dysrhythmias occur a few days after admission and may be related to direct myocardial damage from interstitial inflammation, myocarditis, or patchy pericarditis, which has been described in post mortem histopathology.<sup>46–49</sup> The prognostic utility of the QTc interval with respect to respiratory failure and mortality has been described in at least 3 studies,<sup>50–52</sup> but this is not a consistent finding.<sup>53,54</sup> QT prolongation and Torsades de pointes is reported with relative frequency.<sup>49,55</sup> Pancreatitis and hyperamylasemia have been reported<sup>56</sup> and has a reported incidence of 12% of OP-poisoned patients in 1 case series.<sup>57</sup> Hyperglycemia and hypokalemia are the most common metabolic abnormalities.<sup>58</sup>

Hypotension can occur in up to 17% of OP-poisoned patients based on 1 case series and may have a variety of etiologies.<sup>59</sup> OP- and carbamate-poisoned patients are invariably volume depleted (emesis, diaphoresis, urination, etc), which indicates a need for fluid resuscitation during atropinization. Additionally, OPs may cause additional hypotension by a generalized decrease in the sympathetic outflow from the medulla (“sympatholysis”).<sup>60–62</sup> This has been a particular issue with dimethoate. Hypotension refractory to fluid resuscitation should be managed with direct-acting vasopressors, the choice of agent depending on the physiologic parameters of the



**Box 2****Cardiac manifestations of organophosphorus insecticide poisoning**

Bradycardia, tachycardia

Ventricular arrhythmias

    Torsades de pointes

Ventricular fibrillation

Asystole

ECG changes

    ST-segment changes

    Peaked T waves

    AV block

    QT interval prolongation

Histopathologic changes

    Lysis of myofibrils

    Z-band abnormalities

*Abbreviations:* AV, atrioventricular; ECG, electrocardiogram.

*Adapted from* Bradberry SM, Vale J. Organophosphorus and carbamate insecticides. In: Wallece K, Brent J, Burkhart KK, editors. *Critical care toxicology: diagnosis and management of the critically poisoned patient*. Philadelphia: Elsevier Mosby; 2005. p. 940. Table 91–2; with permission.

individual patient. Other medications or therapies that can be considered for refractory shock include methylene blue or lipid emulsion therapy.<sup>63</sup> Neither of these treatments has been evaluated in the setting of OP or carbamate poisoning and should be considered off-label indications.

## MANAGEMENT

### *Diagnosics*

The diagnosis of OP or carbamate poisoning is typically a clinical diagnosis based on history and physical examination. In the United States, an exposure is usually known and reported by the patient, bystanders, coworkers, or emergency medical services. The simultaneous presence of both muscarinic and nicotinic effects should strongly suggest OP exposure and empiric, immediate treatment is warranted. Similarly, any multicase incident where multiple victims have seizures, became comatose, or suffer cardiac arrest should raise suspicion for nerve agent release. Nevertheless, the diagnosis can be elusive, especially in the case of mild toxicity or atypical presentations; laboratory evaluation and consultation with a medical toxicologist or poison center may help.

Exposure is typically confirmed in 1 of 2 ways. The first method involves detection of organophosphorus metabolites (para-nitrophenol or dialkyl phosphate) in the urine. The second approach involves the assay of AChE and is most useful when the diagnosis is not evident or when mild or chronic toxicity is present. Cholinesterase activity levels are often not readily available within a practical time window for emergency clinicians.<sup>64–66</sup> However, laboratory testing can provide useful parameters to follow while managing an intoxicated patient and can give insight into the disease course and

response to therapy.<sup>22,27,67–69</sup> In general, erythrocyte cholinesterase activity correlates best with neuronal AChE activity at the neuromuscular junction and is the preferred test to evaluate oxime effectiveness.<sup>70</sup> Plasma cholinesterase activity can also be useful, but there are a number of mitigating factors and differences with plasma cholinesterase assays that affect their utility.<sup>22,26,27,67–69</sup>

### ***Clinical Management***

---

Removal from the source and patient decontamination is often performed before health care facility arrival and ideally should be performed by health care providers in appropriate personal protective equipment. Although secondary contamination from exposed individuals is likely minimal, level C personal protective equipment used by properly trained, hospital-based health care providers is recommended.<sup>71</sup> See the article by Holland for further information on personal protective equipment and decontamination.

Further decontamination should be addressed only after initial stabilization and injury assessment. Removal of all clothing and equipment may substantially reduce residual exposure directly to the patient and prevent off-gassing of fumes.<sup>72</sup> The patient should then be washed down with soap and water. Alternative methods of decontamination include dilute alkaline soap, military reactive skin decontamination lotion towelettes, sponges, or lotion. Dry decontamination can be performed with talcum powder, flour, or Fuller's earth (<sup>73</sup>available online at <http://www.bt.cdc.gov/agent/agentlistchem.asp>).<sup>74</sup> Any agent used for decontamination is hazardous waste and should be disposed of appropriately.

Most patients who succumb to OP or carbamate exposure die from loss of airway and respiratory drive or from seizures. Threats to airway patency include salivation, emesis and aspiration, bronchorrhea, bronchospasm, pulmonary edema, seizures, CNS depression, muscular weakness, and overt paralysis. In severely poisoned patients, early control of airway and breathing is often required and may need to be performed concurrently with decontamination. Rapid atropinization should be initiated even before oxygen administration because oxygenation may be impossible until secretions are controlled.<sup>75,76</sup> The need for rapid sequence intubation depends on the clinical situation and response to aggressive and early atropinization. If succinylcholine is used for rapid sequence intubation, there will be prolonged paralysis because succinylcholine is metabolized by plasma cholinesterases.<sup>77,78</sup> Although not contraindicated, the use of succinylcholine for rapid sequence intubation is discouraged and short-acting, nondepolarizing agents are preferred.

Because seizures can be lethal in cholinesterase-inhibiting agent intoxication, aggressive seizure control with benzodiazepines is paramount and may increase survival, prevent CNS injury, and avoid cardiac dysrhythmias.<sup>74</sup> Although any GABAergic agent is likely to be effective, an initial dose of 10 mg of intravenous diazepam is suggested given its rapid onset and ease of titration, although any parenteral benzodiazepine may be used. If intravenous access is not immediately available, intramuscular lorazepam or midazolam can be substituted. Other often-employed anticonvulsants are unlikely to be effective.<sup>79</sup> Specific therapeutic recommendations are discussed elsewhere in this article.

Gastrointestinal decontamination after OP or carbamate ingestion is of unknown benefit; however, emesis is common and further removal via gastric aspiration or lavage is unlikely to have added benefit. OPs are often dissolved in various hydrocarbons and attempted mechanical decontamination may lead to pulmonary aspiration and pneumonitis. It may however, be reasonable to attempt gastric aspiration under appropriate conditions if the patient's airway is intact or protected. Further

decontamination with activated charcoal may be reasonable to limit agent absorption. However, a large, prospective, randomized, clinical trial for all self-poisonings in rural Asia utilizing therapy with multidose activated charcoal did not find improved outcomes with multidose activated charcoal administration.<sup>80</sup> Furthermore, the use of activated charcoal should be balanced against atropine-induced ileus and subsequent risk of aspiration and charcoal pneumonitis.<sup>81</sup>

## PHARMACOLOGY AND TREATMENT OPTIONS

The pharmacologic section is divided into 3 main sections based on their therapeutic mechanisms: Antimuscarinic agents, oxime therapy, and seizure control with benzodiazepines. The options available to most health care facilities include antimuscarinics, oximes, and benzodiazepines.

### *Antimuscarinics*

---

#### **Atropine**

Atropine is a competitive inhibitor of muscarinic receptors both in the CNS and peripheral nervous systems. Atropine has no effect at nicotinic receptors and cannot ameliorate symptoms caused by nicotinic stimulation. It is readily available in most hospitals and easily titrated, given its quick onset of action. Atropine is indicated to reverse any clinical evidence of muscarinic toxicity, especially respiratory embarrassment from bronchorrhea, bronchospasm, and pulmonary edema. Atropine has the added advantage of helping to control seizures as well as cardiac toxicity.<sup>82–84</sup>

Rapid administration of atropine in rapidly escalating doses is recommended. Patient should receive 1 to 2 mg of atropine initially, and the dose should be doubled every 5 minutes until pulmonary secretions are dried and the patient has an adequate heart rate and blood pressure.<sup>76</sup> Once control is achieved with bolus dosing, an atropine infusion should be initiated at 10% to 20% of the total dose required to stabilize the patient per hour.<sup>85</sup> Very large doses may be required and the clinician may quickly exhaust the hospital's supply of atropine. Early discussion with pharmacy regarding the mobilization of hospital and regional stores is suggested. See the article by elsewhere in this issue on resources for information on mobilizing Chempacks.

#### **Glycopyrrolate**

Because atropine is able to cross the blood–brain barrier, CNS anticholinergic toxicity may occur before adequate control of peripheral cholinergic symptoms. Atropine treatment can be replaced with glycopyrrolate, a peripheral antimuscarinic agent without CNS muscarinic receptor activity. Despite limited evidence, glycopyrrolate is not inferior to atropine, and should be considered an appropriate alternative to atropine if atropine supply is limited.<sup>86</sup> Finally, if bronchorrhea and bronchoconstriction are the primary forms of toxicity, ipratropium can be administered by inhalation with direct effects on the target end organ.<sup>87,88</sup> Indications for antimuscarinic pharmacologic therapy are provided in [Table 4](#).

#### **Oxime Therapy**

---

Early initiation of oxime therapy prevents OP aging by reactivating enzymes and improving outcomes. The main goal of oxime therapy is reversal of nicotinic effects and muscular weakness/paralysis. In vitro experiments demonstrate effective reactivation of OP-poisoned AChE.

<b>Sign/Symptom</b>	<b>Agent</b>
Salivation, lacrimation, nausea, vomiting, diarrhea	Atropine, glycopyrrolate
Bronchorrhea, bronchospasm	Atropine, ipratropium, glycopyrrolate
Hypotension	Fluids, atropine, vasopressors, inotropes
Bradycardia	Atropine, glycopyrrolate
Eye pain	Ophthalmic preparations that are mydriatics and cycloplegics
Muscle weakness	Oxime therapy
Respiratory failure	Intubation and ventilation, oxime therapy (muscle weakness)
Seizures	Benzodiazepines (diazepam, midazolam, lorazepam)

Unfortunately, robust demonstration of clinical efficacy remains elusive.<sup>89,90</sup> The most recent Cochrane review evaluated the existing randomized, controlled trials and concluded that the “current evidence was insufficient to indicate whether oximes are harmful or beneficial”; however, study heterogeneity limited the ability to group results.<sup>89</sup> Lower quality evidence suggests efficacy<sup>91–95</sup> and oxime therapy continues to be recommended by many authorities until better evidence emerges that demonstrates a lack of benefit or harm. A recent, retrospective analysis from India found that mortality, in combination with poisoning severity and duration of ventilation, was dependent on delay in oxime administration.<sup>96</sup>

The most commonly utilized oximes include pralidoxime (2-PAM, Protopam), obidoxime (Toxigonin), P2S, and TMB-4. The various oximes are dosed differently and optimal dosing regimens are debated. The suggested US textbook dosing of pralidoxime (1–2 g IV, then 1 g every 6–12 hours or 500 mg/h) may be inadequate.<sup>92,97–99</sup> The World Health Organization recommends a higher dosing regimen (30 mg/kg bolus, then 8 mg/kg/h or 30 mg/kg every 4 hours). The recommended obidoxime dosing regimen is 4 mg/kg, then 0.5 mg/kg/h or 2 mg/kg every 4 hours.<sup>74</sup> In all situations, the dosing should be individualized, depending on patient response.

Administration of oximes to carbamate-poisoned patient is likewise controversial. However, the preponderance of the data suggests that oxime therapy in the setting of carbamate toxicity improves morbidity and mortality<sup>28,67,100</sup>; empiric oxime therapy should be employed in any patient presenting with cholinergic symptoms.<sup>20</sup>

Adverse reactions reported with oxime administration include hypertension, vomiting, and short-lived augmentation of neuromuscular block and may be dosing rate related.<sup>91,101,102</sup>

### ***Benzodiazepines***

In animal models, duration of seizure activity has been correlated with the extent of neuronal damage. Benzodiazepines should be utilized as early as possible to halt seizure activity. There are no head-to-head studies in humans that suggest 1 agent is superior to another. Once an intravenous line is established, a benzodiazepine can be easily titrated. A reasonable initial dose of diazepam is 5 to 10 mg IV repeated every 5 minutes until seizure control is obtained. If an IV is not established, diazepam has erratic intramuscular bioavailability and alternative agents such as midazolam or lorazepam should be considered. Intranasal and buccal

formulations of midazolam are viable alternatives if no intravenous access is available. Midazolam has a relatively short elimination half-life when compared with other benzodiazepines owing to its relatively high water solubility and may require redosing.

## NONPHARMACOLOGIC TREATMENT OPTIONS

Good supportive care is the cornerstone of management of any poisoned patient. Patients poisoned with OPs and carbamates often develop respiratory failure and require intubation and ventilation. Respiratory failure suggests a poor prognosis.<sup>103</sup> The usual care of a ventilated patient should be maintained such as elevation of the head of the bed, deep venous thrombosis prophylaxis, and lung-protective ventilatory settings. There is no strong evidence to suggest that hemodialysis or hemoperfusion improve outcomes in the setting of OP and carbamate toxicity.<sup>104</sup>

## SPECIAL CONSIDERATIONS

### *The Intermediate Syndrome*

---

Upon resolution of the acute cholinergic phase and before the development of delayed neuropathy, the intermediate syndrome may occur. A few days after poisoning and during resolution of the cholinergic crises, some OP-poisoned patients develop severe weakness leading to respiratory failure with the need for (re-)intubation and mechanical ventilation in otherwise seemingly improved, conscious patients.<sup>44</sup> The amount of weakness is variable<sup>23</sup> and demonstrates a spectrum of findings. The first clinical signs of intermediate syndrome are bulbar muscle insufficiency and a simple bedside test is the inability to lift one's head off of the bed. The intermediate syndrome may persist for several weeks. The pathophysiology of the intermediate syndrome remains unclear, but seems to be multifactorial<sup>74</sup> and care remains supportive.

### *Organic Phosphorus-Induced Delayed Neuropathy*

---

Delayed peripheral neurologic dysfunction, occurring weeks after an acute poisoning, is well-documented after acute exposures (ie, OPIDN). OPIDN is a separate entity from the intermediate syndrome with a different pathophysiologic process. OPIDN results from phosphorylation and inhibition of neuropathy target esterase, leading to a "dying back" neuronopathy with preservation of the cell body.<sup>105</sup> Exposure to certain OPs, such as triorthocresyl phosphate, can cause OPIDN in the absence of a cholinergic toxidrome. Historically, contaminated food products and beverages have led to a number of epidemics in the United States, Vietnam, and Sri Lanka. Onset of OPIDN is variable, often within weeks and months of exposure. Recovery is similarly variable and may take months or years.<sup>14,106</sup> Interestingly, delayed neuropathy owing to the carbamates carbaryl, carbofuran, and m-tolyl methyl carbamate has also been described.<sup>107-110</sup>

## SUMMARY

The outcomes of victims of carbamate and OP poisoning are multifactorial. In general, outcome depends on the severity of poisoning (amount, duration, and agent), certain individual factors including one's intrinsic ability to metabolize certain OPs, preexisting disease, time to receipt of medical therapy, access to specialists, and hospital capabilities. Despite good supportive and antidotal care, mortality remains high, especially in the case of OP poisoning. Therapy includes supportive care and aggressive and early administration of antimuscarinic agents and oximes. Patients poisoned by OPs

should be observed closely after the resolution of acute cholinergic toxicity for development of the intermediate syndrome and OPIDN. In general, although acute carbamate toxicity should resolve within 24 to 48 hours, clinicians should be aware of the potential for these patients to develop delayed neuropathy as well.

## REFERENCES

1. Eddleston M, Clark R. Insecticides: organophosphorus compounds and carbamates. In: Nelson LS, editor. Goldfrank's toxicologic emergencies. New York: McGraw Hill Medical; 2011. p. 1450–66.
2. Gunnell D, Eddleston M, Phillips MR, et al. The global distribution of fatal pesticide self-poisoning: systematic review. *BMC Public Health* 2007;7:357.
3. Gunnell D, Eddleston M. Suicide by intentional ingestion of pesticides: a continuing tragedy in developing countries. *Int J Epidemiol* 2003;32(6):902–9.
4. Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. *QJM* 2000;93(11):715–31.
5. National Crime Records Bureau. Accidental deaths and suicides in India - 2010. Available at: <http://ncrb.nic.in/ADSI2010/home.htm>. Accessed June 4, 2014.
6. Mowry JB, Spyker DA, Cantilena LR Jr, et al. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. *Clin Toxicol (Phila)* 2013;51(10):949–1229.
7. Maddy KT, Edmiston S, Richmond D. Illness, injuries, and deaths from pesticide exposures in California 1949–1988. *Rev Environ Contam Toxicol* 1990;114:57–123.
8. Wesseling C, McConnell R, Partanen T, et al. Agricultural pesticide use in developing countries: health effects and research needs. *Int J Health Serv* 1997;27(2):273–308.
9. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. *BMJ* 2007;334(7594):629–34.
10. Government Assessment of the Syrian Government's Use of Chemical Weapons on August 21, 2013. 2013. Available at: <http://www.whitehouse.gov/the-press-office/2013/08/30/government-assessment-syrian-government-s-use-chemical-weapons-august-21>. Accessed June 5, 2014.
11. Okumura T, Takasu N, Ishimatsu S, et al. Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med* 1996;28(2):129–35.
12. Mirzayanov VS. State secrets: an insider's chronicle of the Russian Chemical Weapons Program. Denver (CO): Outskirts Press, Inc; 2009. p. 142–5, 179–80.
13. Organisation for the Prohibition of Chemical Weapons. Demilitarisation. Available at: <http://www.opcw.org/our-work/demilitarisation/>. Accessed June 5, 2014.
14. Morgan JP, Penovich P. Jamaica ginger paralysis. Forty-seven-year follow-up. *Arch Neurol* 1978;35(8):530–2.
15. Morgan JP, Tulloss TC. The jake walk blues. A toxicologic tragedy mirrored in American popular music. *Ann Intern Med* 1976;85(6):804–8.
16. Senanayake N, Jeyaratnam J. Toxic polyneuropathy due to gingili oil contaminated with tri-cresyl phosphate affecting adolescent girls in Sri Lanka. *Lancet* 1981;1(8211):88–9.
17. Dennis DT. Jake walk in Vietnam. *Ann Intern Med* 1977;86(5):665–6.
18. Proudfoot A. The early toxicology of physostigmine: a tale of beans, great men and egos. *Toxicol Rev* 2006;25(2):99–138.
19. Broughton E. The Bhopal disaster and its aftermath: a review. *Environ Health* 2005;4(1):6.

20. Rosman Y, Makarovsky I, Bentur Y, et al. Carbamate poisoning: treatment recommendations in the setting of a mass casualties event. *Am J Emerg Med* 2009;27(9):1117–24.
21. Aaron CK. Organophosphates and carbamates. Chapter 76. In: Haddad Shannon MW, Borron SW, Burns MJ, editors. *Haddad and Winchester's clinical management of poisoning and drug overdose*. Philadelphia: Saunders Elsevier; 2007. p. 1171–84.
22. Eddleston M, Eyer P, Worek F, et al. Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. *Lancet* 2005; 366(9495):1452–9.
23. Eddleston M, Mohamed F, Davies JO, et al. Respiratory failure in acute organophosphorus pesticide self-poisoning. *QJM* 2006;99(8):513–22.
24. Davies JE, Barquet A, Freed VH, et al. Human pesticide poisonings by a fat-soluble organophosphate insecticide. *Arch Environ Health* 1975;30(12):608–13.
25. Soummer A, Megarbane B, Boroli F, et al. Severe and prolonged neurologic toxicity following subcutaneous chlorpyrifos self-administration: a case report. *Clin Toxicol (Phila)* 2011;49(2):124–7.
26. Coye MJ, Barnett PG, Midtling JE, et al. Clinical confirmation of OP poisoning of agricultural workers. *Am J Ind Med* 1986;10(4):399–409.
27. Coye MJ, Barnett PG, Midtling JE, et al. Clinical confirmation of OP poisoning by serial cholinesterase analyses. *Arch Intern Med* 1987;147(3):438–42.
28. Lifshitz M, Rotenberg M, Sofer S, et al. Carbamate poisoning and oxime treatment in children: a clinical and laboratory study. *Pediatrics* 1994;93(4):652–5.
29. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev* 2003;22(3):165–90.
30. Taylor P. Anticholinesterase agents. In: Brunton LL, Lazo JS, Parker KL, editors. *Goodman and Gilman's the pharmacological basis of therapeutics*. New York: McGraw-Hill; 2006. p. 201–16.
31. Katzung BG. Section II: autonomic drugs, introduction to autonomic pharmacology. In: Katzung BG, editor. *Basic and clinical pharmacology*. New York: Lange Medical Books/McGraw-Hill; 2004. p. 75–93.
32. Bird SB, Gaspari R, Dickson EW. Early death due to severe OP poisoning is a centrally mediated process. *Acad Emerg Med* 2003;10(4):295–8.
33. Dickson EW. Diazepam inhibits organophosphate-induced central respiratory depression. *Acad Emerg Med* 2003;10(12):1303–6.
34. Dekundy A, Kaminski RM, Zielinska E, et al. NMDA antagonists exert distinct effects in experimental organophosphate or carbamate poisoning in mice. *Toxicol Appl Pharmacol* 2007;219(2–3):114–21.
35. Kozhemyakin M, Rajasekaran K, Kapur J. Central cholinesterase inhibition enhances glutamatergic synaptic transmission. *J Neurophysiol* 2010;103(4):1748–57.
36. Sakamoto T, Sawada Y, Nishide K, et al. Delayed neurotoxicity produced by an organophosphorus compound (Sumithion). A case report. *Arch Toxicol* 1984; 56(2):136–8.
37. *Advanced Hazmat Life support Provider Manual*, 3rd edition. Walter FG, editor. Arizona Board of Regents for the University of AZ, Tucson. 2003.
38. Zwiener RJ, Ginsburg CM. Organophosphate and carbamate poisoning in infants and children. *Pediatrics* 1988;81(1):121–6.
39. Bradberry SM, Vale J. Organophosphorus and carbamate insecticides. In: Wallece K, Brent J, Burkhart KK, et al, editors. *Critical care toxicology: diagnosis and management of the critically poisoned patient*. Philadelphia: Elsevier Mosby; 2005. p. 937–45.

40. Asari Y, Kamijyo Y, Soma K. Changes in the hemodynamic state of patients with acute lethal organophosphate poisoning. *Vet Hum Toxicol* 2004;46(1):5–9.
41. Joubert J, Joubert PH, van der Spuy M, et al. Acute organophosphate poisoning presenting with choreo-athetosis. *J Toxicol Clin Toxicol* 1984;22(2):187–91.
42. Senanayake N, Sanmuganathan PS. Extrapyrmidal manifestations complicating organophosphorus insecticide poisoning. *Hum Exp Toxicol* 1995;14(7):600–4.
43. Shahar E, Andraws J. Extra-pyramidal parkinsonism complicating organophosphate insecticide poisoning. *Eur J Paediatr Neurol* 2001;5(6):261–4.
44. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Engl J Med* 1987;316(13):761–3.
45. De Bleecker J, Van Den Neucker K, Willems J. The intermediate syndrome in organophosphate poisoning: presentation of a case and review of the literature. *J Toxicol Clin Toxicol* 1992;30(3):321–9 [discussion: 331–2].
46. Kiss Z, Fazekas T. Organophosphates and torsade de pointes ventricular tachycardia. *J R Soc Med* 1983;76(11):984–5.
47. Chacko J, Elangovan A. Late onset, prolonged asystole following organophosphate poisoning: a case report. *J Med Toxicol* 2010;6(3):311–4.
48. Anand S, Singh S, Nahar Saikia U, et al. Cardiac abnormalities in acute organophosphate poisoning. *Clin Toxicol (Phila)* 2009;47(3):230–5.
49. Wang MH, Tseng CD, Bair SY. Q-T interval prolongation and pleomorphic ventricular tachyarrhythmia ('Torsade de pointes') in organophosphate poisoning: report of a case. *Hum Exp Toxicol* 1998;17(10):587–90.
50. Chuang FR, Jang SW, Lin JL, et al. QTc prolongation indicates a poor prognosis in patients with organophosphate poisoning. *Am J Emerg Med* 1996;14(5):451–3.
51. Hrabetz H, Thiermann H, Felgenhauer N, et al. Organophosphate poisoning in the developed world - a single centre experience from here to the millennium. *Chem Biol Interact* 2013;206(3):561–8.
52. Shadnia S, Okazi A, Akhlaghi N, et al. Prognostic value of long QT interval in acute and severe organophosphate poisoning. *J Med Toxicol* 2009;5(4):196–9.
53. Akdur O, Durukan P, Ozkan S, et al. Poisoning severity score, Glasgow coma scale, corrected QT interval in acute organophosphate poisoning. *Hum Exp Toxicol* 2010;29(5):419–25.
54. Yurumez Y, Yavuz Y, Saglam H, et al. Electrocardiographic findings of acute organophosphate poisoning. *J Emerg Med* 2009;36(1):39–42.
55. Bar-Meir E, Schein O, Eisenkraft A, et al. Guidelines for treating cardiac manifestations of organophosphates poisoning with special emphasis on long QT and Torsades De Pointes. *Crit Rev Toxicol* 2007;37(3):279–85.
56. Moore PG, James OF. Acute pancreatitis by acute organophosphate poisoning. *Postgrad Med J* 1981;57(672):660–2.
57. Sahin I, Onbasi K, Sahin H, et al. The prevalence of pancreatitis in organophosphate poisonings. *Hum Exp Toxicol* 2002;21(4):175–7.
58. Saadeh AM. Metabolic complications of OP and carbamate poisoning. *Trop Doct* 2001;31(3):149–52.
59. Saadeh AM, Farsakh NA, al-Ali MK. Cardiac manifestations of acute carbamate and organophosphate poisoning. *Heart* 1997;77(5):461–4.
60. Chang AY, Chan JY, Kao FJ, et al. Engagement of inducible nitric oxide synthase at the rostral ventrolateral medulla during mevinphos intoxication in the rat. *J Biomed Sci* 2001;8(6):475–83.
61. Yen DH, Yen JC, Len WB, et al. Spectral changes in systemic arterial pressure signals during acute mevinphos intoxication in the rat. *Shock* 2001;15(1):35–41.



62. Yeo V, Young K, Tsuen CH. Anticholinesterase-induced hypotension treated with pulmonary artery catheterization-guided vasopressors. *Vet Hum Toxicol* 2002; 44(2):99–100.
63. Jang DH, Nelson LS, Hoffman RS. Methylene blue for distributive shock: a potential new use of an old antidote. *J Med Toxicol* 2013;9(3):242–9.
64. Rehiman S, Lohani SP, Bhattarai MC. Correlation of serum cholinesterase level, clinical score at presentation and severity of organophosphate poisoning. *JNMA J Nepal Med Assoc* 2008;47(170):47–52.
65. Aygun D, Doganay Z, Altintop L, et al. Serum acetylcholinesterase and prognosis of acute organophosphate poisoning. *J Toxicol Clin Toxicol* 2002;40(7):903–10.
66. Rajapakse BN, Thiermann H, Eyer P, et al. Evaluation of the test-mate ChE (cholinesterase) field kit in acute organophosphorus poisoning. *Ann Emerg Med* 2011;58(6):559–64.e6.
67. Lifshitz M, Shahak E, Sofer S. Carbamate and organophosphate poisoning in young children. *Pediatr Emerg Care* 1999;15(2):102–3.
68. Davies JO, Eddleston M, Buckley NA. Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. *QJM* 2008;101(5):371–9.
69. Yager J, McLean H, Hudes M, et al. Components of variability in blood cholinesterase assay results. *J Occup Med* 1976;18(4):242–4.
70. Thiermann H, Szinicz L, Eyer P, et al. Correlation between red blood cell acetylcholinesterase activity and neuromuscular transmission in organophosphate poisoning. *Chem Biol Interact* 2005;157–8:345–7.
71. Macintyre AG, Christopher G, Eitzen E Jr, et al. Weapons of mass destruction events with contaminated casualties: effective planning for health care facilities. *JAMA* 2000;283(2):242–9.
72. Kales SN, Christiani D. Acute chemical emergencies. *N Engl J Med* 2004; 350(8):800–8.
73. Sidell FR, Borak J. Chemical warfare agents II nerve agents. *Ann Emerg Med* 1992;21(7):865–71.
74. Koenig, KL, Boatright CJ, Hancock JA, et al. Health care facility-based decontamination of victims exposed to chemical, biological, and radiological materials. *Am J Emerg Med* 2008;26(1):71–80.
75. Konickx LA, Bingham K, Eddleston M. Is oxygen required before atropine administration in organophosphorus or carbamate pesticide poisoning? - a cohort study. *Clin Toxicol (Phila)* 2014;52(5):531–7.
76. Eddleston M, Buckley NA, Checketts H, et al. Speed of initial atropinisation in significant organophosphorus pesticide poisoning—a systematic comparison of recommended regimens. *Clin Toxicol* 2004;42(6):865–75.
77. Sener EB, Ustun E, Kocamanoglu S, et al. Prolonged succinylcholine-induced paralysis in OP insecticide poisoning. *Acta Anaesthesiol Scand* 2002;46(8):1046–8.
78. Selden BS, Curry SC. Prolonged succinylcholine-induced paralysis in organophosphate insecticide poisoning. *Ann Emerg Med* 1987;16(2):215–7.
79. Shih T, McDonough JH Jr, Koplovitz I. Anticonvulsants for soman-induced seizure activity. *J Biomed Sci* 1999;6(2):86–96.
80. Eddleston M, Juszczak E, Buckley NA, et al. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet* 2008;371(9612): 579–87.
81. Mizutani T, Naito H, Oohashi N. Rectal ulcer with massive haemorrhage due to activated charcoal treatment in oral organophosphate poisoning. *Hum Exp Toxicol* 1991;10(5):385–6.

82. Shih TM, Koviak TA, Capacio BR. Anticonvulsants for poisoning by the organophosphorus compound soman: pharmacological mechanisms. *Neurosci Biobehav Rev* 1991;15(3):349–62.
83. Shih TM, Rowland TC, McDonough JH. Anticonvulsants for nerve agent-induced seizures: the influence of the therapeutic dose of atropine. *J Pharmacol Exp Ther* 2007;320(1):154–61.
84. McDonough JH Jr, Jaax NK, Crowley RA, et al. Atropine and/or diazepam therapy protects against soman-induced neural and cardiac pathology. *Fundam Appl Toxicol* 1989;13(2):256–76.
85. Eddleston M, Buckley NA, Eyer P, et al. Management of acute organophosphorus pesticide poisoning. *Lancet* 2008;371(9612):597–607.
86. Choi PT, Quinonez LG, Cook DJ, et al. The use of glycopyrrolate in a case of intermediate syndrome following acute organophosphate poisoning. *Can J Anaesth* 1998;45(4):337–40.
87. Perrone J, Henretig F, Sims M, et al. A role for ipratropium in chemical terrorism preparedness. *Acad Emerg Med* 2003;10(3):290.
88. Shemesh I, Bourvin A, Gold D, et al. Chlorpyrifos poisoning treated with ipratropium and dantrolene: a case report. *J Toxicol Clin Toxicol* 1988;26(7):495–8.
89. Buckley NA, Eddleston M, Li Y, et al. Oximes for acute organophosphate pesticide poisoning. *Cochrane Database Syst Rev* 2011;(2):CD005085.
90. Eddleston M, Eyer P, Worek F, et al. Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. *PLoS Med* 2009;6(6):e1000104.
91. Eddleston M, Szinicz L, Eyer P, et al. oximes in acute organophosphorus pesticide poisoning a systematic review of clinical trials. *QJM* 2002;95(5):275–83.
92. Worek F, Bäcker M, Thiermann H, et al. Reappraisal of indications and limitations of oxime therapy in organophosphate poisoning. *Hum Exp Toxicol* 1997;16(8):466–72.
93. Kurtz PH. Pralidoxime in the treatment of carbamate intoxication. *Am J Emerg Med* 1990;8(1):68–70.
94. Petroianu G, Ruefer R. Poisoning with organophosphorus compounds. *Emerg Med (Fremantle)* 2001;13(2):258–60.
95. Shih TM, Skovira JW, O'Donnell JC, et al. Treatment with tertiary oximes prevents seizures and improves survival following sarin intoxication. *J Mol Neurosci* 2010;40(1–2):63–9.
96. Ahmed SM, Das B, Nadeem A, et al. Survival pattern in patients with acute organophosphate poisoning on mechanical ventilation: a retrospective intensive care unit-based study in a tertiary care teaching hospital. *Indian J Anaesth* 2014;58(1):11–7.
97. Thiermann H, Szinicz L, Eyer F, et al. Modern strategies in therapy of OP poisoning. *Toxicol Lett* 1999;107(1–3):233–9.
98. Schexnayder S, James LP, Kearns GL, et al. The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. *J Toxicol Clin Toxicol* 1998;36(6):549–55.
99. Willems JL, De Bisschop HC, Verstraete AG, et al. Cholinesterase reactivation in organophosphorus poisoned patients depends on the plasma concentrations of the oxime pralidoxime methylsulphate and of the organophosphate. *Arch Toxicol* 1993;67(2):79–84.
100. Dawson RM, Poretski M. Carbamylated acetylcholinesterase: acceleration of decarbamylation by bispyridinium oximes. *Biochem Pharmacol* 1985;34(24):4337–40.

101. Medicis JJ, Stork CM, Howland MA, et al. Pharmacokinetics following a loading plus a continuous infusion of pralidoxime compared with the traditional short infusion regimen in human volunteers. *J Toxicol Clin Toxicol* 1996;34(3):289–95.
102. Thompson DF, Thompson GD, Greenwood RB, et al. Therapeutic dosing of pralidoxime chloride. *Drug Intell Clin Pharm* 1987;21(7–8):590–3.
103. Noshad H, Ansarin K, Ardalan MR, et al. Respiratory failure in organophosphate insecticide poisoning. *Saudi Med J* 2007;28(3):405–7.
104. Altintop L, Aygun D, Sahin H, et al. In acute organophosphate poisoning, the efficacy of hemoperfusion on clinical status and mortality. *J Intensive Care Med* 2005;20(6):346–50.
105. Richardson RJ, Hein ND, Wijeyesakere SJ, et al. Neuropathy target esterase (NTE): overview and future. *Chem Biol Interact* 2013;203(1):238–44.
106. Senanayake N. Tri-cresyl phosphate neuropathy in Sri Lanka: a clinical and neurophysiological study with a three year follow up. *J Neurol Neurosurg Psychiatry* 1981;44(9):775–80.
107. Lotti M, Moretto A. Do carbamates cause polyneuropathy? *Muscle Nerve* 2006;34(4):499–502.
108. Yang PY, Tsao TC, Lin JL, et al. Carbofuran-induced delayed neuropathy. *J Toxicol Clin Toxicol* 2000;38(1):43–6.
109. Umehara F, Izumo S, Arimura K, et al. Polyneuropathy induced by m-tolyl methyl carbamate intoxication. *J Neurol* 1991;238(1):47–8.
110. Dickoff DJ, Gerber O, Turovsky Z. Delayed neurotoxicity after ingestion of carbamate pesticide. *Neurology* 1987;37(7):1229–31.