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ORGANOPHOSPHATE POISONING: A NARRATIVE REVIEW OF MECHANISMS, CLINICAL PRESENTATION, AND MANAGEMENT

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ABSTRACT Organophosphate and carbamate compounds are widely used as insecticides and have medical applications as well. Global exposure to these agents results in millions of cases annually, with hundreds of thousands of fatalities. Clinical manifestations of poisoning involve cholinergic excess, cardiac issues, respiratory failure, intermediate neurologic syndrome, and delayed neuropathy. Diagnosis is based on clinical findings, and laboratory testing includes RBC acetylcholinesterase activity. Management involves prompt intervention with atropine and oxime therapy. Prognosis depends on factors such as Glasgow Coma Score and the specific agent involved. Further research is needed to understand the complex mechanisms underlying these toxicities and improve treatment strategies.

KEYWORDS : Organophosphates, Pesticide poisoning, Cholinesterase inhibitors, Organophosphate poisoning intermediate syndrome, Pralidoxime.

INTRODUCTION

Organophosphate (OP) poisoning is a significant public health concern worldwide, particularly in agricultural countries where these chemicals are widely used as insecticides and pesticides. These chemical compounds are employed to control pests in crops and can also be found in household products, increasing the risk of accidental exposure in the general population (1).

OP poisoning is a medical emergency that can lead to a wide range of clinical manifestations, from mild symptoms such as headaches and nausea to severe complications, including respiratory failure, seizures, and coma. This toxicity primarily occurs due to irreversible inhibition of the enzyme acetylcholinesterase, which is essential for the degradation of the neurotransmitter acetylcholine, resulting in an excessive accumulation of acetylcholine in neuronal synapses and leading to a state of cholinergic hyperactivity (2).

METHODS

The methods for this narrative review on organophosphate poisoning were conducted using systematic searches in major medical databases (PubMed, EMBASE, and Scopus) with relevant MeSH terms and DeCS keywords, including "Organophosphate Poisoning," "Toxicity," "Cholinesterase Inhibitors," and "Pesticides." The search covered literature published from inception to the present. We also included non-indexed sources and grey literature. Inclusion criteria comprised articles in English, with a focus on clinical aspects, diagnosis, and management. Data were synthesized qualitatively to provide a comprehensive overview of the topic. The review's goal was to consolidate current evidence and insights into organophosphate poisoning for clinical practitioners and researchers.

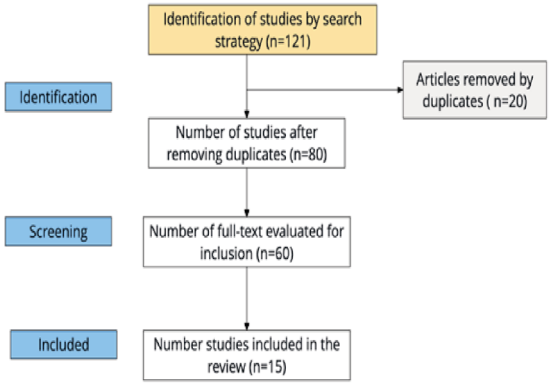

Figure 1. PRISMA.

Overview of Organophosphate and Carbamate Exposure

Organophosphates have been widely used as insecticides for over 50 years, but their use has decreased in recent decades due to the development of carbamate insecticides with similar toxicities. Additionally, organophosphates and carbamates find medical applications in the reversal of neuromuscular blockade and the treatment of various conditions such as glaucoma, myasthenia gravis, and Alzheimer's disease (2).

Globally, an estimated 3,000,000 people are exposed to organophosphate or carbamate agents annually, resulting in up to 300,000 fatalities. In the United States, there were over 8000 reported exposures to these agents in 2008, with fewer than 15 deaths. Exposure primarily occurs through accidental or intentional ingestion of agricultural pesticides. Other potential sources include consuming contaminated food or wearing pesticide-laden clothing (3).

Specific agents linked to human poisoning include carbamates like methomyl and aldicarb, as well as organophosphates such as parathion, fenthion, malathion, diazinon, and dursban. Despite restrictions, some household insecticides still contain chlorpyrifos, a derivative of dursban. The concern over organophosphorus nerve agents like sarin and Novichok has increased due to terrorist activities and assassination attempts involving these agents (4).

Neurotoxic Mechanisms of Organophosphorus and Carbamate Compounds

Organophosphorus and carbamate compounds, widely used as insecticides and in medical applications, exert their toxic effects through intricate mechanisms of action. These compounds readily penetrate the skin, lungs, and gastrointestinal tract, binding irreversibly to acetyl cholinesterase (AChE) - an enzyme responsible for breaking down acetylcholine at neuronal synapses and neuromuscular junctions (5).

Upon binding to AChE, the organophosphorus compound induces a conformational change termed "aging," making the enzyme resistant to reactivation by antidotal oximes. Notably, plasma cholinesterase (BuChE) and neuropathy target esterase (NTE) inhibition also occurs, though their clinical significance remains less understood (6).

Carbamates, derived from carbamic acid, share similarities in absorption and cholinesterase inhibition. However, unlike organophosphates, carbamates are transient inhibitors, spontaneously hydrolyzing from cholinesterase sites within 48 hours. This unique characteristic confers shorter duration of toxicity, yet comparable mortality rates as seen with organophosphate exposures (7).

Clinical features

Organophosphorus (OP) and carbamate compounds, widely used as insecticides and medical agents, can cause significant toxicity in humans. These toxicities are influenced by various factors, including the rate of acetylcholinesterase (AChE) inhibition, the route of absorption, and the lipophilicity of the agents (7).

Acute toxicity from OP agents manifests as cholinergic excess, affecting the autonomic nervous system, neuromuscular junction, and central nervous system (CNS). Clinical signs include bradycardia, miosis, lacrimation, salivation, bronchorrhea, bronchospasm, urination, emesis, and diarrhea. However, the mnemonic SLUDGE/BBB and DUMBELS used to recall these symptoms overlook critical CNS and nicotinic effects, such as fasciculations, muscle weakness, and paralysis (8).

Cardiac issues, such as arrhythmias and myocardial ischemia, may occur in some cases of OP poisoning, with older patients at higher risk. Respiratory failure due to CNS depression, neuromuscular weakness, and bronchoconstriction contributes to fatalities. Around 10-40% of OP-poisoned patients develop the "intermediate syndrome" 24-96 hours after exposure. This disorder is characterized by neurologic abnormalities, including neck flexion weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, and respiratory insufficiency. Risk factors for its development may include exposure to highly fat-soluble OP agents (8).

Delayed neuropathy, known as OPIDN, typically occurs one to three weeks after ingestion of specific OP agents. Patients experience painful "stocking-glove" paresthesias followed by a symmetrical motor polyneuropathy. Survivors may face neurobehavioral deficits and Parkinsonism, while severe cases result in permanent disability. In addition to these manifestations, severe OP poisoning has been associated with acute kidney injury requiring renal replacement therapy and acute pancreatitis (9).

Understanding the diverse clinical presentations and long-term effects of OP and carbamate poisoning is crucial for effective management and patient outcomes. Further research is needed to elucidate the complex mechanisms underlying these toxicities. Improved knowledge will aid in the development of targeted treatments and preventive strategies, ultimately reducing the impact of these toxic compounds on human health (10).

Diagnosis

The diagnosis of organophosphate or carbamate poisoning relies on clinical findings, given the variable nature of toxicity among these agents. Recognition of cholinergic excess is crucial, with symptoms such as bradycardia, miosis, salivation, and bronchospasm indicating the possibility of poisoning. The distinct odor of some organophosphorus agents can aid in identification (11).

To precisely identify the agent and determine the appropriate treatment, distinguishing between dimethyl and diethyl poisons is essential. Dimethyl compounds age rapidly, necessitating prompt oxime therapy, while diethyl compounds may exhibit delayed toxicity and require prolonged treatment. Conducting a trial of atropine can further support the diagnosis. The absence of anticholinergic effects after atropine administration confirms poisoning with an acetylcholinesterase inhibitor (12).

Laboratory evaluation involves measuring RBC acetylcholinesterase (RBC AChE) activity, providing insight into the degree of toxicity and the effectiveness of oxime therapy. Plasma cholinesterase activity is a less accurate marker and should not guide treatment decisions. Unfortunately, RBC AChE testing is not widely available in hospital laboratories (13).

Management

Management of organophosphate or carbamate poisoning requires prompt and appropriate intervention. In cases of severely depressed mental status, immediate endotracheal intubation and 100 percent oxygen are essential. Respiratory failure can develop rapidly due to multiple factors, necessitating early intubation even in patients with normal vital signs.

Cholinergic toxicity is treated with atropine and oxime therapy. Atropine competes with acetylcholine at muscarinic receptors, alleviating muscarinic signs and symptoms. The dose of atropine should be titrated to achieve the therapeutic endpoint of respiratory secretions clearing and bronchoconstriction ceasing. For severe poisoning, high doses of atropine may be required, and epinephrine can be added if needed (14).

Pralidoxime (2-PAM) is an effective cholinesterase reactivating agent that treats both muscarinic and nicotinic symptoms. It should be given to patients with cholinergic toxicity, neuromuscular dysfunction, or exposures to organophosphorus agents known to cause delayed neurotoxicity (14).

Seizures resulting from organophosphate poisoning are managed with benzodiazepines like diazepam. Decontamination is crucial in cases of topical exposure. Aggressive removal of clothing and thorough irrigation of affected areas should be performed. Gastric lavage is generally not recommended, and activated charcoal may be given to patients presenting within one hour of ingestion. Forced emesis is contraindicated. Monitoring for cardiac complications is advisable, and aspirin can be considered for non-occlusive myocardial ischemia (15).

Overall, the management approach should be tailored to each patient's condition and response to treatment, considering the varying clinical responses among individuals affected by organophosphate poisoning.

Prognosis

Prognosis in acute OP or carbamate poisoning depends on factors such as Glasgow Coma Score (GCS) and specific OP agent involved. A GCS below 13 indicates a poor prognosis. Clinical scoring systems like APACHE-II, SAPS-II, and MPM-II can help predict outcomes, but their accuracy may vary based on the OP agent. Lipophilic OPs, like fenthion and parathion, may cause delayed and prolonged symptoms, warranting careful attention. Larger prospective studies are needed to better assess prognosis accurately (15).

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