



REVIEW ARTICLE

Neurotoxic disorders and medical management of patients poisoned with organophosphorus pesticides

ABSTRACT

In this article the neurotoxic disorders appearing in patients poisoned with organophosphorus pesticides (OPs) are reviewed. OPs cause four important neurotoxic effects in humans: the cholinergic syndrome, the intermediate syndrome, organophosphate-induced delayed polyneuropathy and chronic organophosphate-induced neuropsychiatric disorder. Compared to the cholinergic syndrome, that causes millions of cases of poisoning with fatality of more than 15% each year, other disorders involve much smaller number of patients. This article is focused on neurotoxic disorders appearing after acute and chronic exposure to OPs with emphasis on clinical presentation, molecular mechanisms and possibilities of medical treatment.

KEY WORDS

Organophosphorus pesticides; cholinergic syndrome; intermediate syndrome; chronic organophosphate-induced neuropsychiatric disorder; pyridinium oximes; atropine; acetylcholinesterase.

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Organophosphates (OPs) have been used as pesticides and developed as warfare nerve agents such as soman, sarin, tabun, VX and others. Some OP insecticides have found its application in human and veterinary medicine. Pesticide poisoning results from occupational, accidental, and intentional exposure. The epidemiological pattern of poisoning shows significant variation in number of deaths and form of poisoning between developing and industrial countries¹⁻³. According to the World Health Organization, about 1 million accidental and 2 million suicidal poisonings with organophosphorus insecticides are reported per year, with more than 300000 fatalities⁴. Medical management is difficult, with case fatality generally more than 15%^{4,5}.

OP esters cause four neurotoxic disorders in humans: the cholinergic syndrome, the intermediate syndrome, organophosphate-induced delayed polyneuropathy (OPIDP) and chronic organophosphate-induced neuropsychiatric disorder (COPIND). These syndromes, arising from severe exposures, may be caused by OP pesticides or and some of them by warfare nerve agents⁶. Most of the cases of poisoning can be prevented by better administrative control, restricted access to OP pesticides, effective measures of

personal protection and education of OP pesticide applicators and medical personnel.

The cholinergic syndrome

Signs and symptoms of cholinergic syndrome occurring in acute poisoning with OP pesticides are predictable from their biochemical mechanism of action and are directly related to the levels of acetylcholinesterase (AChE) activity in the central nervous system. In cases of human poisoning, general acute symptoms of peripheral nicotinic and muscarinic intoxication are clearly apparent⁷. These symptoms include miosis (unreactive to light); sweating, rhinorrhea, lacrimation, and salivation; abdominal cramps and other gastrointestinal symptoms; respiratory difficulties and cough; dyspnea, constriction sensation in the chest, wheezing; twitching of facial muscles and tongue, tremors, and fasciculations; bradycardia and ECG changes, pallor, and cyanosis; anorexia, nausea, vomiting, diarrhea, and involuntary urination and defecation. These signs and symptoms are accompanied by central effects such as dizziness, tremulousness, and confusion; ataxia; headache, fatigability, and paresthesia. Finally, seizures, convulsions, twitching, coma, and respiratory failure may occur. If the poisoned patient survives the first day of poisoning,

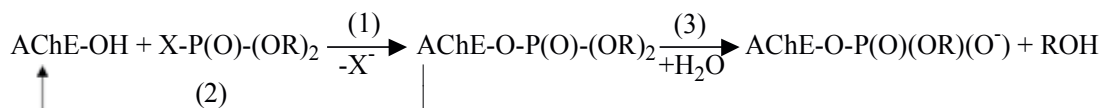


Figure 1. Interaction of acetylcholinesterase (AChE-OH) with organophosphorus compounds. Reaction 1: interaction of organophosphate molecule with the serine hydroxyl group at the active site of AChE. Inhibited AChE cannot further serve its physiological function, which causes the accumulation of acetylcholine at the nerve endings. Reaction 2: spontaneous reactivation of inhibited AChE which occurs relatively quickly for dimethylphosphates but slowly for other OP compounds. Reaction 3 (“aging”): non-enzymatic, time-dependent loss of one alkyl group (R) bound to the phosphorus. X = acyl radical (i.e. Cl⁻, F⁻, CN⁻, *p*-nitrophenol etc.).

there are personality changes, mood swings, aggressive events and psychotic episodes including schizoid reactions, paranoid delusions, and exacerbations of preexisting psychiatric problems. Sleep is poor from nightmares and hallucinations; disturbances or deficits in memory and attention, and additional delayed effects also occur. Death usually occurs due to respiratory failure resulting from a combination of central and peripheral effects, paralysis of the respiratory muscles, and depression of the brain respiratory center⁷⁻¹¹. The first four to six hours are the most critical in acute poisoning with OP pesticides. If there is improvement in symptoms after initial treatment then the patient is very likely to survive if adequate treatment is continued⁹. The data presented in Table 1 summarize the muscarinic, nicotinic and CNS effects in patients poisoned with OP pesticides observed at the National Poison Control Center in Belgrade during 1998-2007 period⁵. These findings are consistent with the results of other studies¹².

Clinical diagnosis of acute poisoning with OP compounds is relatively simple and is based on medical history, circumstances of exposure, clinical presentation, and laboratory tests. Confirmation of diagnosis can be made by measurement of erythrocyte AChE or plasma cholinester-

ase (ChE). Activities of these enzymes have been accepted as biomarkers of exposure and/or toxicity of OP. Erythrocyte AChE is identical to the enzyme present in target synapses and its levels are assumed to reflect the effects in target organs. For that reason, erythrocyte AChE is regarded as biomarker of toxicity of these compounds. On the other hand, ChE level in plasma frequently does not correlate well with clinical presentation of OP poisoned patients.

The mechanism of OP poisoning involves inhibition of AChE at synapses and neuromuscular junctions in cholinergic pathways leading to accumulation of acetylcholine and overstimulation of postsynaptic muscarinic and nicotinic receptors (Figure 1). Inhibition of AChE occurs after phosphorylation of hydroxyl group at serine at the active site of the enzyme. Following inhibition, AChE can be spontaneously reactivated at the rate that depends on chemical structure of OP. For OP having dimethyl radicals the AChE reactivation is relatively rapid with a half-time of about 1-2 hours, while that for OP having diethyl functional groups is 31-57 hours^{13,14}.

Table 1. Muscarinic, nicotinic, and CNS effects in patients poisoned with OP pesticides. From the National Poison Control Center in Belgrade (1998-2007).⁵

Muscarinic	No. (%) of Patients*	Nicotinic	No. (%) of Patients*	CNS	No. (%) of Patients*
Miosis	196 (61.8)	Fasciculations	46 (14.5)	Coma	80 (25.2)
Bronchorrhoea	164 (51.7)	Hypertension	35 (11.0)	Somnolence	23 (7.3)
GIT**	161 (50.8)	Fibrillation	32 (10.1)	Convulsions	14 (4.4)
Hypotension	88 (27.8)	Tachycardia	30 (9.5)	Sopor	13 (4.1)
ARI**	83 (26.2)	Tremor	4 (1.3)	Disorientation	4 (1.3)
Bradycardia	29 (9.1)	Arrhythmia	1 (0.3)	Agitation	1 (0.3)
ACF**	15 (4.7)				
Cardiac arrest	8 (2.5)				

*Based on total number of patients poisoned with OPs during 1998-2007 (n=317).

**Abbreviations: GIT = gastrointestinal symptoms; ARI = acute respiratory insufficiency, ACF = acute circulatory failure.

Medical management of patients with cholinergic syndrome

Medical management of patients showing symptoms of cholinergic syndrome include general and supportive measures and specific treatment. General measures in treatment of acute OP poisoning include decontamination of exposed tissues, representing a vital step in reduction of the dose of pesticide absorbed, and resuscitation when needed. The patients should be observed carefully for several days (or even weeks) because respiratory arrest may occur^{15,16}.

Supportive measures should be directed towards the cardiorespiratory system with particular emphasis on maintenance of ventilation, cardiac rhythm and blood pressure; the removal by suction of respiratory and oral secretions which may cause respiratory distress; and the oxygenation of the patient. Severely poisoned patients disconnected from the ventilator when the general condition improves, must be carefully watched for rapid deterioration and development of the intermediate syndrome during the following few days in the Intensive Care Unit^{9,15}. In addition, the patients should be warned to report to hospital if signs of organophosphate-induced delayed polyneuropathy appear 2-3 weeks after exposure.

Ingested organophosphates should be removed by early gastric aspiration and then lavage, with protection of the airway - this may be the best remedy in unconscious patients. Gastric lavage is most effective within 30 minutes of ingestion, but might be still effective up to 4 hours post ingestion, as organophosphates are rapidly absorbed from the gastrointestinal tract⁷. Administration of oral activated charcoal, in conventional doses, may be considered for reducing further absorption of some organophosphorus pesticides^{7,17}.

Specific treatment of acute poisoning with OP pesticides include administration of atropine (as direct antidote), diazepam (as anticonvulsant) and a pyridinium oxime (as specific reactivator of inhibited AChE).

Atropine acts by blocking the effects of excess concentrations of acetylcholine (ACh) at muscarinic cholinergic synapses following OP inhibition of AChE. Atropine is the initial drug of choice in acute OP poisoning. Atropine sulphate in combination with an oxime has been used in traditional therapy for OP intoxications including pesticides. Atropine can relieve the following symptoms of OP poisoning: sweating, salivation, rhinorrhoea, lacrimation, nausea, vomiting and diarrhea, and can help control of bradycardia and circulatory depressions, dilating the bronchi and abolishing bronchorrhoea. Atropine does not bind to nicotinic receptors and cannot relieve nicotinic effects in OP poisoning⁷. In addition, there is evidence on anticonvulsant properties of atropine in OP poisoning^{18,19}.

The standard dosing of atropine depends on the severity of OPC poisoning. The initial dose is usually 2 mg in an adult (0.02 mg/kg in a child) given every 5-10 min until hyperatropinization (flushing, dryness of the mouth, nose, lungs and the skin, heart rate 80-100/min, normal blood pressure, mydriasis) is reached, which should be maintained during further treatment. The dose may be increased as required. Patients poisoned with OP appear to be resistant to toxic effects of atropine and may require relatively large doses of atropine administered during prolonged periods of time. In severe OP poisoning total dose of atropine given during 5 weeks of treatment can be as high as 30000 mg¹⁵.

Diazepam is a well-known benzodiazepine most frequently used for the treatment of convulsions that appear in OP poisonings. Diazepam enhanced the clinical efficacy of low doses of atropine. In the cholinergic nervous system, diazepam appears to decrease the synaptic release of ACh. The main consequence of the action of benzodiazepines in CNS is hyperpolarization of neurons making them significantly less susceptible to cholinergically-induced depolarization. The ultimate result is cessation of propagation of convulsions^{16,20,21}.

In patients poisoned with OP, benzodiazepines may have a beneficial effect in reducing anxiety and restlessness, reducing muscle fasciculation, arresting seizures, convulsions, controlling apprehension and agitation and possibly reducing morbidity and mortality when used in conjunction with atropine and an oxime. Diazepam should be given to patients poisoned with OP whenever convulsions or pronounced muscle fasciculations are present. The recommended dose of diazepam in cases of OP poisoning is 5-10 mg intravenously over three minutes in the absence of convulsions and 10-20 mg intravenously in cases with convulsions, which may be repeated as required^{9,16,22}.

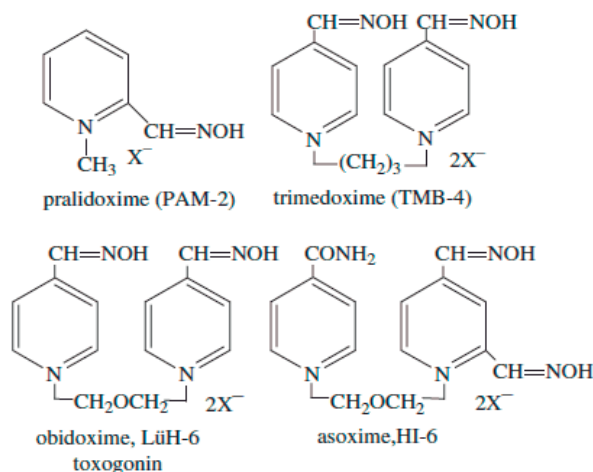


Figure 2. Chemical structures of pyridinium oximes used to treat human OP poisoning. X indicates an anion.

Pyridinium oximes accelerate the rate spontaneous reactivation of AChE inhibited by OP by displacing the phosphoryl moiety from the enzyme. The oximes can only be of benefit as long as inhibited AChE is not completely converted to the aged form which is resistant to both spontaneous and oxime-induced reactivation. Pyridinium oximes are effective against OP-inhibited AChE in the peripheral nervous system, but have a limited penetration across the blood-brain barrier (about 10% of the given dose) due to their pharmacokinetic profile and the presence of quaternary nitrogen atom(s) in their structure²³.

Among the many classes of oximes investigated so far, those with clinical application can be divided in two groups - the monopyridinium and bispyridinium oximes. Currently, the only used monopyridinium oxime is pralidoxime, while the most significant bispyridinium oximes comprise: trimedoxime (TMB-4), obidoxime (LüH-6, Toxogonin) and asoxime (HI-6), and their chemical structure is presented in Figure 2. Bispyridinium oximes are less frequently used in treatment of OP poisoned patients, due to their limited commercial availability, and may have some advantages over pralidoxime in special circumstances (i.e. poisoning with warfare nerve agents).

Pralidoxime is currently most important pyridinium oxime being used in clinical practice for about a half of a century. In poisoning with OP pesticides pralidoxime chloride should be administered to adults in a dose of 500 mg/h, continuously maintained until clinical improvement is obtained, or 30 mg/kg body weight bolus intravenously over 4 to 6 hours or 8 to 10 mg/kg/h intravenously until full recovery occurs. In children, pralidoxime chloride should be administered in a dose of 25 mg/kg intravenously for 15 to 30 minutes, followed by a continuous infusion of 10 to 20 mg/kg/h. The therapy can continue for 18 hours or longer (even several days), depending on the clinical status^{9,15} and the presence of OP or its metabolites in blood/urine.

Detailed protocols on medical treatment of cholinergic crisis are presented in several excellent reviews^{5,7,10,14,16,22,24,25}.

Intermediate syndrome

The term Intermediate Syndrome (IMS) was first described by Senanayake and Karalliedde (26) because it appeared in the interval between the end of the cholinergic crisis and the onset of OPIDP. Following exposure to various OP pesticides, clinical manifestations of IMS typically occur within 24 to 96 hours, and affect patients without fasciculation or other cholinergic signs. The reported incidence of IMS ranges from 7.7% to as high as 84%²⁷. Although IMS is well recognized as a disorder of neuromuscular junctions, its exact etiology, incidence,

and risk factors are not clearly understood. IMS generally occurred among patients with prolonged and severe inhibition of AChE, however not every patient with severe AChE inhibition develops IMS. Other risk factors of IMS include delayed metabolism of OP pesticides due to toxicokinetic factors or impaired organ function, severity of poisoning, elevated muscle enzymes, and inadequate or late oxime therapy. IMS has been linked with exposure to specific OP pesticides having dimethyl phosphate structure (e.g. fenthion, dimethoate, monocrotophos, dichlorvos, methylparathion) but also developed after exposure to parathion (ethyl phosphate) and methamidophos (phosphoramidate)^{28,29}. Two typical cases of IMS caused by fenthion and diazinon were recently described by Jokanović and coworkers⁵.

Marked weakness of neck flexion and varying degree of proximal limb muscle weakness, manifesting as weakness of shoulder abduction and hip flexion, are the regular clinical features. Respiratory insufficiency is also common and frequently draws medical attention to the onset of the syndrome. Other possible manifestations are involvement of muscles innervated by motor cranial nerves and decreased deep tendon reflexes. Studies conducted in nineties have shown that intermediate syndrome goes along with excretion of cholinesterase inhibitor metabolites in the urine and by severe depression in cholinesterase levels. It was suggested that the condition might reflect the recirculation of lipid soluble cholinesterase inhibitors from body fat compartments or gastric fluids³⁰. IMS could be explained by the reduction in number of functioning cholinergic receptors at the postjunctional membrane, or a failure of acetylcholine release. All these abnormal findings on electromyography suggested a combined presynaptic and postsynaptic defect, without sensory impairment³¹.

With appropriate therapy, recovery from IMS occurs 5-18 days after the onset of weakness. The recovery among patients who survived IMS follows a distinct pattern, starting first with muscle power recovery in cranial nerve-innervated muscles, followed by respiratory muscles, proximal muscles, and neck flexors. Since IMS carries a high risk of death among patients with respiratory failure, prompt recognition of the syndrome is the basis of IMS treatment. IMS management is mainly supportive since there are no specific antidotes available for this life threatening syndrome. As IMS generally takes place at the same time with severe OP toxicity and persistent inhibition of AChE, early gastrointestinal decontamination, followed by appropriate therapy involving atropine and pralidoxime, and prompt institution of respiratory support, should be helpful in ameliorating the magnitude and/or the incidence of IMS. The prognosis of IMS appears to be favorable if respiratory failure can be promptly recognized and treated accordingly²⁸⁻³⁰.

Table 2. Organophosphorus pesticides as a cause OPIDP in man.^{6,36,37}

OP insecticide	No of cases	Location	Year
Chlorpyrifos	2	Italy, India	1986
Dichlorvos	5	Romania, Turkey, Brazil, Korea, India	1980, 2002-2006
Ethyl parathion	1	Germany	1993
Fenthion	3	USA	1985
Isofenphos	1	Israel	1987
Isofenphos/phoxim	1	Italy	1995
Leptophos	80	USA	1974
Malathion	2	Japan, Turkey	1991, 2009
Merphos	1	USA	1977
Methamidophos	> 45	Sri Lanka, Italy, China, Turkey, USA	1981, 1998
Mevinphos	1	Serbia	2010
Mipafox	3	UK	1952
Omethoate	1	France	1972
Phosphamidon/ Mevinphos	1	China	2002
Trichlorfon	22	Romania, Iran, Japan, Hungary	1983 -1986
Trichloronat	1	Poland	1975

Organophosphate induced delayed polyneuropathy

Organophosphate induced delayed polyneuropathy (OP-IDP) is unique toxicological phenomenon in that it is caused by a single exposure to certain OP with effects usually appearing after 10 to 20 days or later. OPIDP is toxicologically different from the cholinergic syndrome in that it is based on different mechanisms which do not involve AChE and appear a few weeks after OP poisoning has been medically solved with standard therapeutic measures and patient dismissed from hospital. OPIDP is also a different syndrome from IMS.

The interest in OPIDP appeared after thousands cases of poisoning with triorthocresyl phosphate (TOCP) that occurred mainly due to beverage and food contamination in USA in 1930 and Morocco in 1959³²⁻³⁵. By the end of twentieth century, there were many cases of OPIDP due to TOCP poisoning in Romania, Sri Lanka, former Yugoslavia and China. In addition to TOCP, several other OP pesticides have been reported to cause OPIDP in man (Table 2)^{6,11,36-38}.

OPIDP is relatively rare neurodegenerative disorder in humans that is characterized by loss of function and ataxia of distal parts of sensory and motor axons in peripheral nerves and ascending and descending tracts of spinal cord. The early neurological symptoms usually are sharp, cramp-like pains in the calves, tingling in the feet and hands followed

by distal numbness and paresthesia. Pain and weakness in muscles spread rapidly and patients become unsteady and unable to keep their balance. Progressive leg weakness occurs, together with depression of tendon reflexes. Symptoms may also appear in the arms and forearms. Sensory loss may be mild. Muscle tonus of the limbs gradually increase and spasticity appears in the lower limbs. Physical examination reveals distal symmetrical mainly motor polyneuropathy, with wasting and flaccid weakness of distal limb muscles, especially in the lower limbs. In severe OPIDP quadriplegia with foot and wrist drop were observed as well as mild pyramidal signs³⁴. There may be some functional recovery in less severe cases with more distal involvement and sparing of spinal cord axons, but pyramidal and other signs of central neurological involvement may become more evident with time. The recovery affects only sensory nerves, while motor neurons may permanently lose its function as indicated by Morgan³³ who described the lack of improvement during 47 years in 11 patients poisoned with TOCP. The prognosis for functional recovery depends on the degree of pyramidal involvement with ataxia and paralysis representing a permanent outcome of severe OPIDP. It appears that clinical signs of OPIDP in children are considerably milder than in adults^{11,35,37,38}.

OPIDP is initiated by phosphorylation and subsequent aging of >70% neuropathy target esterase (NTE) in peripheral nerves. Physiological role and importance of NTE were recently discussed by Jokanović et al.¹¹.

Medical treatment of OPIDP in humans is symptomatic. Standard treatment of OP poisoned patients comprising atropine, oxime and diazepam was not effective in treatment of OPIDP. However, there were several reports in the literature describing attempts of treatment of OPIDP in animals and these studies were reviewed by Lotti³⁴ and Jokanović et al.^{11,35}, but none of these treatments have been tested in patients so far.

Chronic organophosphate-induced neuropsychiatric disorder

Chronic exposure to OPs has been associated with impaired neurobehavioral performance in some, but not all, epidemiological studies³⁹. Chronic organophosphate-induced neuropsychiatric disorders (COPIND) occur without cholinergic symptoms and apparently are not dependent on AChE inhibition^{39,40}. COPIND usually appears with a delay and persists for a long period possibly suggesting the permanent damage of the central nervous. The most common symptoms of COPIND include cognitive deficit (impairment in memory, concentration and learning, problems with attention, information processing, eye-hand coordination and reaction time), mood change (anxiety, depression, psychotic symptoms, emotional lability), chronic fatigue, autonomic dysfunction, peripheral neuropathy and extrapyramidal symptoms such as dystonia, resting tremor, bradikinesia, postural instability and rigidity of face muscles^{11,39-46}. Suicidality and alcohol intolerance have also been reported⁴². Similar clinical features have also been reported by soldiers suffering from the Gulf-War Syndrome, which led to the, so far unproven, hypothesis that the illness was caused by chronic exposure to chemical agents with similar effects to OPs⁴⁷.

Diagnostic criteria for COPIND include: 1) Repeated exposure to organophosphates; 2) At least four of the following: a) personality change and destabilization of mood, b) impairment of concentration, c) impaired exercise tolerance, d) reduced tolerance to alcohol, e) heightened sensitivity to organophosphates; 3) At least three of the following: a) exacerbation of "dippers flu", b) impulsive suicidal thinking, c) language disorder, d) heightened sense of smell, e) deterioration of handwriting⁴⁸.

In several epidemiological studies conducted among farm workers and pesticide applicators, neuropsychological damage accompanied with damage of peripheral nervous system, anxiety and depression were predominant among the poisoned group⁴⁹⁻⁵¹. Agricultural workers tested about 2 years after a pesticide poisoning episode showed significantly lower performance in verbal and visual attention, visual memory, sequencing and problem solving⁵². Levin et al.⁵³ found a high level of anxiety in commercial sprayers of insecticides. Savage et al.⁵⁴ showed abnormalities in psychometric testing and motor reflexes. Mild intoxication

can also induce COPIND, farm workers with mild OP pesticides intoxication requiring no hospitalization performed worse on tests of cognitive and psychomotor function than nonexposed workers did tested 2 years later. Epidemiological study from Spain revealed a link between exposure to organophosphates and increased suicidal rate⁵⁵. A literature review of mortality and morbidity studies related to suicide among pesticide-exposed populations, revealed high suicide rates in farming populations. Epidemiological studies conclude that acute and chronic OP exposure is associated with affective disorders^{50,56}.

The underlying mechanism of COPIND has not been established. Tan et al.⁴⁶ hypothesized that COPIND could be derived from withdrawal of OP pesticide after chronic low-level exposure or acute exposure. In addition, other scientists have suggested that mechanisms other than the inhibition of AChE might also be involved. Studies in animals suggested that cognitive enhancing action and changes in behavior of low doses of certain OPs, such as dichlorvos, in rats were unrelated to AChE inhibition^{14,57,58}. Finally, London et al.⁵⁰ reported that exposure to OP may cause serotonin disturbances in the central nervous system, which are implicated in depression and suicide in humans.

Authorship statement

Both authors contributed equally.

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Neurotoksični poremećaji i lečenje otrovanih organofosforim pesticidima

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APSTRAKT

U ovom radu opisani su neurotoksični poremećaji koji se javljaju kod pacijenata otrovanih organofosforim (OF) pesticidima. OF pesticidi izazivaju četiri značajna neurotoksična efekta kod ljudi i to holinergički sindrom, intermedijarni sindrom, organofosfatima izazvanu naknadnu polineuropatiju i hronični organofosfatima izazvani neuropsihijatrijski poremećaj. U poređenju sa holinergičkim sindromom, koji se javlja kod više miliona slučajeva trovanja svake godine u svetu sa mortalitetom većim od 15%, ostali poremećaji su opisani kod znatno manjeg broja slučajeva. Rad je fokusiran na neurotoksične poremećaje koji se javljaju posle akutne i hronične ekspozicije OF pesticidima sa naglaskom na kliničku sliku, objašnjenje molekularnih mehanizama i mogućnosti lečenja zatrovanih pacijenata.

KLJUČNE RIJEČI

Organofosforim pesticidi, holinergički sindrom, piridinski oksimi, atropin, acetilholinesteraza.