Intensive Care Management of Acute Organophosphate Poisoning: Clinical Experience and the Review of the Literature

VUČINIĆ SLAVICA¹, ANTONIJEVIĆ BILJANA², BOŠKOVIĆ BOGDAN¹, ĆURČIC MARIJANA²
National Poison Control Centre, Crnotravska 17, 11000 Belgrade¹
Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade²
SERBIA
zarkovuc@eunet.rs

Abstract: Current therapeutic scheme for management of acute poisoning with anticholinesterase pesticides includes general supportive measures (decontamination, respiratory support) and specific pharmacological treatment (atropine, oxime, diazepam). Antidote therapy is aimed to competitively antagonise overstimulation of muscarinic receptors with atropine and to reactivate inhibited AChE with oximes. Rectivation and clinical improvement of neuromuscular function are limited by aging of acetylcholinesterase and high concentrations of organophosphates. Results of our longitudinal clinical experience confirm beneficial effect of oxime administration in OP poisoning.

Key words: acute organophosphate poisoning, oxime, intensive care management

1 Introduction
Organophosphate (OP) insecticide poisoning results from occupational, accidental and intentional exposure. 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 300 000 fatalities [1].

The greatest share of poisonings come from the developing countries of the Asia-Pacific region, but OP insecticide poisonings are also a problem for countries in the developed world, although their primary concern is defense against terrorist use of these chemicals [2].

2 Problem formulation
Besides general supportive therapy, current therapeutic protocols include atropine, oxime and benzodiazepine. Atropine is the mainstay of treatment of muscarinic effects in OP poisoning worldwide. This physiologic antidote effectively antagonizes muscarinic receptor mediated effects of excessive acetylcholine, it is somewhat effective at central m-receptors, but it fails at nicotine sensitive synapses. Here, reactivating oximes can act as specific antidotes. Three actions have been attributed to oximes: 1) rectivation of cholinesterase by cleavage of phosphorylated active sites; 2) direct reaction and detoxification of unbounded organophosphorus molecules, and 3) endogenous anticholinergic effect in normal doses. While these effects have been conclusively demonstrated in experimental settings the general clinical benefit in OP poisoning is not clear yet, and the mortality is high despite the use of atropine and oxime. There are several reasons for the contradictory reports: 1) The type and dose of poison are often unknown and may vary widely. 2) The extent of decontamination may greatly differ. 3) Different oxime regimen. 4) Patients may differ with respect to enzyme polymorphisms in toxifying phosphorothioates (CYP superfamily) and hydrolytic detoxication (PON1) [3].

In this paper we present our experience related to clinical management of acute poisoning with OPs at National Poison Control Centre (NPCC), Belgrade, that were collected during the 10 years period (1998-2007). Treatment of acute poisoning caused by this class of substances will be considered through a correlation of our experience and the review of the literature.

2.1 Mechanisms of acute toxicity of organophosphate insecticides
The primary molecular mechanism of action of the OP compounds is inhibition of acetylcholinesterase (EC 3.1.1.7, AChE) producing excessive acetylcholine (ACh) accumulation and overstimulation of
cholinergic neurons. The variations in the acute toxicity of OP are the result of their different chemical structures and rates of spontaneous reactivation and aging. Even though aging occurs slowly and reactivation relatively rapidly in the case of OP insecticides, early oxime administration is clinically important in patients poisoned with these agents. In addition to reaction with AChE, OPs also react with serum cholinesterase (EC 3.1.1.8, ChE), a circulating plasma glycoprotein synthetized in the liver, in the same manner as with AChE \[3,4\].

3 Results

During the ten year period, 29723 patients were treated at the NPCC, 11174 were hospitalized, and among them 526 patients were poisoned with pesticides. OP compounds were detected in 296 patients. Poisoning with dimethyl OP was confirmed in 246 patients (malathion 153, dimethoate 69, dichlorvos 4, fenitrothion 6, monocrotophos 8), with diethyl OP in 38 patients (diazinon 21, parathion 9, phorate 1, phoxim 1, phosalone 3, chlorpyriphos 2, quinalphos 1) and in 12 patients OP could not be fully identified. Majority of poisonings (92%) were due to deliberate ingestion of cholinesterase inhibitors.

3.1 Clinical features and diagnosis of acute anticholinesterase poisoning

Acute cholinergic crisis is a medical emergency that often requires treatment in Intensive Care Unit. It consists of muscarinic, nicotinic and central nervous system effects. Muscarinic features include bronchorrhoea, bronchoconstriction, miotic pupils, abdominal cramps, involuntary defecation and urination, bradycardia, QT prolongation, hypotension. Nicotinic features include twiching of fine muscles, fasculation and hyperreflexia which may progressively lead to flaccid paralysis. The most prominent CNS symptoms are: headache, dizziness, drowsiness, nausea, confusion, anxiety, slurred speech, ataxia, tremor, psychosis, convulsions, coma and respiratory depression \[1-4\].

The most common clinical signs of poisoning in patients exposed to OPs observed at Clinic of Toxicology of the NPCC were miosis (61.8%), bronchorrhoea (51.7%), vomiting and diarrhea (50.8%), hypotension (27.8%). Acute respiratory insufficiency was registered in 83 (26.2%) and acute cardiocirculatory failure in 15 (4.7%) patients. This is consistent with the results of other studies with acute organophosphate poisoning\[1-3\].

Clinical diagnosis 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 serum ChE \[1-4\]. Many OP insecticides (e.g. chlorpyrifos, demethon, diazinon, dichlorvos, malathion, trichlorphon) appear to be more potent inhibitors of ChE than AChE and, as the consequence, ChE inhibition might occur to a greater extent than AChE inhibition. Erythrocyte AChE is identical to the enzyme present in the target synapses, thus, it is regarded as biomarker of toxicity of these compounds \[3-5\].

The majority of patients exposed to OP pesticides (46.6%) had their AChE activity between 20 and 50% (compared to mean population controls) indicating mild poisoning, about 9% patients had 10-20% of AChE activity (moderate poisoning), and there were only 2.7% patients with AChE activity lower than 10% (severe poisoning). Additional confirmation of OP poisoning was obtained after detection of these compounds and/or their metabolites in biological samples (blood, urine, lavate) by gas chromatography in 161 poisoned patients. The highest registered concentration of malathion in blood was 61.0 mg/L in a severely poisoned patient who had AChE activity lower than 10%.

3.2 Assessment of the poisoning severity

The assessment of the severity of poisoning is essential for adequate management of patients with anticholinesterase poisonings. At the NPCC for many years for this purpose we use the Poisoning Severity Score (PSS) \[6\]. PSS considers the overall clinical course where PSS 0 designates no symptoms of poisoning, PSS 1 minor (mild) poisoning, PSS 2 moderate poisoning, PSS 3 severe poisoning and PSS 4 fatal poisoning. In addition, we take into consideration other relevant data available such as the activity of AChE in erythrocytes and ChE in serum as well as good tolerance of high atropine doses.

OP were the cause of severe and fatal poisoning (PSS 3 and 4) in 129 (43.5%), and mild poisoning (PSS 1) in 70 (23.7 %) patients.
The majority of clinical manifestations resolve within a few days or weeks, but neurophysiological symptoms may remain for months. Forty-seven patients (15.9%) died. This is consistent with the findings of other authors who reported case fatality generally more than 15%. Acute respiratory insufficiency, due to weakness of respiratory muscles and central respiratory depression, was the major cause of lethal outcome in OP poisoning. Another cause of death was cardiovacular insufficiency which was even more difficult to cope with since it is often refractory to treatment [7].

3.3 Management of acute poisoning with OP pesticides

3.3.1 General supportive measures and decontamination
In our patients, respiratory support by mechanical ventilation was necessary in 97 patients (32.7%) with OP poisoning. Gastric lavage was the most commonly used (22.7%) form of decontamination in OP poisoning. Administration of oral activated charcoal, in conventional doses, may be considered for reducing further absorption of some OP pesticides [7]. This recommendation was supported by Peng et al. who conducted a randomized controlled clinical trial involving 108 patients, aimed to assess the efficacy of hemoperfusion with charcoal in treatment of acute severe dichlorvos poisoning [8]. Eddleston et al. conducted an open-label, parallel group, randomized, controlled trial in three Sri Lankan hospitals and found no benefit of multiple-dose activated charcoal [7].

3.3.2 Atropine
Atropine, an alkaloid isolated from Atropa belladonna L. by Main in 1835, was used against a cholinesterase-inhibiting agent for the first time by Fraser in 1863. It has remained the cornerstone of the therapy of OP pesticide intoxication ever since. There is a general agreement to use atropine in OP poisoning, and the only dilemma is related to the dosing regimen. Grob recommended 4-6 mg atropine, followed by 2 mg doses at 5 min intervals, until bronchial secretion was stopped [9]. Other authors found continuous infusions with atropine 1-2 mg/h, after initial atropinization, efficient as well [3,7]. The atropine dosing regimen applied in NPCC includes careful titration of atropine until appearance of signs of hyperatropinization, and individualization of dosage. The highest total administered dose of atropine at NPCC was 6400 mg. However, the most patients received total doses of atropine up to 500 mg (32%), while about 13% patients received atropine 500-1000 mg or up to 50 mg.

3.3.3 Oxime therapy
Oximes reactivate phosphorylated AChE by displacing the phosphoryl moiety from the enzyme by virtue of their high affinity for the enzyme and their powerful nucleophilicity. The rate of reactivation depends on the structure of the phosphoryl moiety bound to the enzyme, the source of the enzyme, the structure and concentration of oxime which is present at the active site, and the rate of post-inhibitory dealkylation known as aging [2-7].

It has been over five decades since Wilson and Ginsburg in the USA and Childs et al. in England published independently on the efficacy of the compound 2-PAM-iodide as a reactivator of phosphorylated cholinesterases, but this chapter has not come to a closure yet. Since then several salts of pralidoxime have been used: pralidoxime chloride, pralidoxime methanesulfonate and pralidoxime methylsulfate [3]. TMB-4 Cl₂ [1,3-Bis (4-hydroxyiminomethyl-1-pyridinio) propane dichloride] was synthesized in the United States. Lüttringhaus and Hagedorn synthesised another compound, obidoxime (Toxogonin®), in 1964 and introduced into the medical practice. Hagedorn’s group in Freiburg, Germany also synthesised an oxime named HI-6 Cl₂ [1-(2-hydroxyiminomethyl-1-pyridinio)-3-(4-carbamoyl-1-pyridinio)-2-oxapropanedi-chloride] and their most recent oxime of importance was HLö-7. Many attempts had been made so far to improve the antidotal properties of the conventional mono- and bis-pyridinium mono(di)-oximes by modifying their structure [3,10]. Despite intensive research activities on this topic, PAM-2, TMB-4, LüH-6, HI-6 and HLö-7 have remained dominant among oximes in experimental work [10].

3.3.4 Clinical Use of Oximes
A particular problem in interpreting the beneficial role and efficacy of oximes in
clinical practice is a deficiency of published data, especially those evaluated in controlled clinical trials with the proper stratification of patients with OP poisoning.

Willems et al. reported on the effects of PAM-2 methylsulphate (4.42 mg/kg as a bolus injection followed by continuous infusion 2.14 mg/kg/h) in nine patients intoxicated with organophosphorus insecticides. The therapeutic effect of the oxime seemed to depend on the plasma concentrations of ethylparathion and methylparathion [11].

In a series of five case reports, LüHy6 (Toxogonin) 250 mg was given as an intravenous bolus followed by continuous infusion of 750 mg/24 hours in cases of life-threatening parathion poisoning. This dose was effective, especially when the dose of parathion absorbed was relatively low [12].

In a clinical study of 63 patients poisoned with organophosphorus insecticides, one group of patients was treated with atropine only, while the other two groups received atropine and either PAM-2 or LüHy-6. Loading and maintenance intravenous doses for PAM-2 were 30 mg/kg and 8 mg/kg/h, respectively and 8 mg/kg and 2 mg/kg/h, respectively, for LüHy-6. Although the severity of intoxications (based on respiratory complications and duration of hospitalization) was higher in the atropine plus oxime groups, no mortality was found in the PAM-2 plus atropine group, whereas 12% and 50% of patients in the atropine and atropine plus LüHy-6 groups died, respectively[13].

3.3.5 Drawbacks and Limitations of Oxime Therapy

Experimental results have demonstrated that different oximes are not equally effective against poisonings caused by structurally different organophosphorus compounds. Pralidoxime (PAM-2), trimedoxime (TMB-4), obidoxime (LüH-6), HI-6 and HLö-7 have all been demonstrated to be very effective in experimental poisonings with sarin and VX. TMB-4 and LüH-6 may reactivate tabun-inhibited AChE, whereas HI-6 possesses the ability to reactivate the soman-inhibited enzyme. An oxime HLö-7 seems to be an efficient reactivator of AChE inhibited by any of the four organophosphorus warfare agents. According to the available literature, the oximes LüH-6 and TMB-4, although relatively toxic, are the most potent to induce reactivation of AChE inhibited by the majority of organophosphorus pesticides.

The efficacy of pyridinium oximes has also been demonstrated in many cases of patients poisoned with OP insecticides who were treated in European clinics. In those cases the recommendations for pralidoxime dosing proposed by World Health Organization were followed (30 mg/kg body weight bolus intravenously followed by 8 mg/kg/h IV) [3, 10-13].

Contrary to these findings, the reports from Asia indicated that pralidoxime treatment was not effective in their patients. These studies were apparently poorly designed due to suboptimal dose, short duration of treatment, delay between patient exposure and pralidoxime administration, and the fact that the chemical structure of OP pesticides was not taken in account [14].

3.3.6 Clinical experience with HI-6

During the different phases of development of the NPCC in Belgrade, many pyridinium oximes were used in experimental and clinical studies, as well as in routine clinical practice, such as pralidoxime chloride, pralidoxime methylsulphate, obidoxime, and HI-6. Oxime HI-6 was introduced in clinical practice in Serbia in early 1980s. Its development was initiated by Military Establishments in order to improve the treatment of chemical warfare agent poisoning.

The clinical development of HI-6 (asoxime chloride, Bosnalijek, Drug Company, Sarajevo) started in the Clinic of toxicology Military Medical Academy in 1985 and its antidotal efficacy in quinalfós poisoning was reported by Boškovic and co-workers [15].

The effects of HI-6 and PAM-2 were compared in a study of Kušić et al [16]. Sixty patients acutely poisoned with various OPs were treated with atropine, diazepam and HI-6 (500 mg every 6 hours intramuscularly) for 2 to 7 days, depending on the severity of the organophosphate poisoning. In addition, in nine patients, PAM-2 was administered (1g/6h) over the same period of time. The recovery of erythrocyte AChE was rapid in patients suffering from severe phorate, quinalphos, dichlorvos and pyridafenthion poisonings with reactivation half-lives ranging from 0.5 to 3.5 hours. Malathion-inhibited enzyme was reactivated much more slowly (reactivation half-life=10.1 hours), while HI-6 was
ineffective against AChE inhibition caused by dimethoate and phosphoramidon. While nearly 100% reactivation of the enzyme was obtained after only 2 days of HI-6 treatment, PAM-2 could reactivate only 40% of the enzyme activity by the end of the eighth day. The most reasonable explanation for this difference in the activity of HI-6 lies in the chemical structure of the OP insecticide, considering that diethoxy-type inhibited ChE in contrast to dimethoxy-inhibited enzyme, ages slowly. Slower reactivation of malathion-inhibited e-ChE could be explained in part by the effects of its impurities – isomalathion. The lack of undesirable effect even under conditions of maintaining HI-6 levels far above "the minimal effective concentrations" for oximes and being much lower for the more effective bispyridinium reactivators, for up to 7 days, confirms its exceptional tolerance in humans. In conclusion, the therapeutic use of HI-6 against poisoning by various OP insecticides showed it to be as effective as, or superior to the other oximes clinically available. Exceptional tolerance, the reactivation of acetylcholinesterase and its direct pharmacological effect make HI-6 the main contributory drug to the standard atropine-diazepam treatment of OP poisoning.

3.3.7 Experience with pralidoxime methylsulphate
Due to economic crisis in Serbia, NPCC did not have any oxime available for several years, but during the past ten years pralidoxime methylsulphate (Contrathion®) was applied with a loading dose of 400 mg (two bottles) by slow intravenous infusion: subsequently 200 mg/h continuous intravenous infusion was administered during the first day, and continued as long as clinical signs of poisoning and pesticide in urine and blood were present. In moderate poisoning 400 mg of Contrathion® followed by 400 mg/3 h were used. In our group of patients 74 (23.3 %) were treated with pralidoxime. Retrospectively four therapeutic patients' groups were analyzed: I atropine, II atropine and oxime, III atropine, oxime and bicarbonate and IV atropine and bicarbonate. There were no differences in mortality between the groups. The atropine consumption was lower in the group of patients treated with an oxime, but the difference was significant only in the group of severely poisoned patients where it was reduced for 30%. The results of other studies suggest that oximes significantly reduce atropine consumption in OP poisoning, and signs of atropinization might occur earlier when oximes were given [3,17]. Length of hospitalisation was the lowest in the group on atropine and oxime therapy (p<0.001), and when bicarbonate was added to oxime and atropine, the duration of mechanical ventilation was significantly reduced (p<0.001). Reactivation of AChE was the highest (p<0.001) in this group but bicarbonate administration did not show any benefit to reactivation of AChE.

3.3.8 Diazepam
Diazepam is used for prophylaxis and treatment of convulsions. It improves atropine tolerance, reduces CNS damage and central respiratory weakness [1-3, 10-12].

3.3.9 Sodium bicarbonate therapy
Experimental and clinical studies have shown beneficial therapeutic effect of sodium bicarbonate, when added to standard treatment for acute organophosphate poisoning, but the mechanism is unclear [18-19]. We have administered sodium bicarbonate as a loading dose of 4 mEq/kg/h followed by 4 mEq/kg/24 hours as long as OP was detected in blood in 26 (8.2 %) of patients.

4 Problem solution
There is currently insufficient evidence regarding the efficacy of oximes, however, experimental studies and limited clinical experience emphasize the need for further development of universally suitable oxime and alternative adjunct in treatment of OP poisoning.

5 Conclusions
Acute poisoning with OP esticides is not frequent in Serbia, however, it represent important clinical feature due to severity, possible complications and their impact on duration and costs of hospitalization. Management consists of prompt resuscitation, antidotes as required and selective decontamination. Oxime administration is recommended for moderate and severe poisoning. High quality medical care and ongoing monitoring in ICU are essential.
References:
[15] Boskovic