Pharmaceutical Sciences
March 2018, 24, 79-82
doi: 10.15171/PS.2018.12
http://journals.tbzmed.ac.ir/PHARM

Short Communication

Evaluation of Pralidoxime Use in an Iranian Teaching Referral Hospital

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Article Info

Article History:
Received: 5 April 2017
Revised: 30 June 2017
Accepted: 24 August 2017
ePublished: 15 March 2018

Keywords:
-Antidote
-Organophosphate
-Poisoning
-Pralidoxime

ABSTRACT

Background: Organophosphorus (OP) poisonings, a common source of pesticide poisoning, are an important cause of morbidity and mortality in the developing countries. Combination therapy with atropine and oxime is a common practice in the management of OP poisoning. However, the additive benefit of using pralidoxime in addition to atropine remains controversial. Due to inappropriate and widespread use of this relatively expensive and low available antidote, we aimed to evaluate its usage in an Iranian teaching hospital.
Methods: Medical files of patients with pesticide poisoning who had been admitted to the poisoning ward between September 2013 and September 2014 were reviewed. Patients with definite diagnosis of OPs poisoning were selected to evaluate rational use of pralidoxime in their treatment regimen. Data were collected using a checklist containing demographic, clinical, and para clinical characteristics, as well as the type of pesticide poisoning. Appropriateness of the pralidoxime therapy was determined based on clinical practice guideline and endorsed by an attending medical toxicologist.
Results: 68.8% of patients had been poisoned with insecticides, 27.1% with aluminum phosphide, 2.1% with herbicides, and 2% with rodenticides, respectively. OPs were responsible for 43.8% of all poisoning. All patients with OPs poisoning received pralidoxime after they had been admitted to emergency department, while only 55% of them were eligible to receive pralidoxime. Moreover, pralidoxime had been administered for 59% of patients with non-OPs poisoning, which all of them were clinically inappropriate.
Conclusion: The use of pralidoxime in the northwest of Iran is not appropriate and thus, it is highly recommended that a patient-tailored treatment guideline be provided and implemented regionally.

Introduction

Organophosphorus (OP) compounds are a common source of pesticide poisoning and an important cause of morbidity and mortality in the developing world.[1,2] Based on the World Health Organization (WHO) estimates, there are almost three million OP poisoning per year, with a death rate of roughly 10%.[3] Environmentally, OPs are less harmful than other existing pesticides such as organochlorines,[4] as well as they are very effective insecticides.[5] Thus, they are used preferentially and widely for insects control in several fields such as horticulture, agriculture, and homes, particularly in South America, Asia, and Africa.[6] Additionally, they are used domestically and in public sanitization to control diseases vectors. Some OPs are used to cure human infestation with head lice, scabies, and crab lice. Also OPs have been used as nerve agents in warfare and terrorist attacks.[7] This widespread usage has made exposure to these highly toxic compounds common and inevitable.[5,8] Due to extensive use as well as poor surveillance for human exposure to pesticides, health consequences including intentional poisoning are reported more frequently in developing countries.[6,9] However, in the developed countries and United States, the risk of poisoning with OPs is much lower.

All cases of poisoning with OPs should be considered as an emergency cases and any patient with more than minor symptoms should quickly be admitted to a critical care unit. Antidotes including atropine, oximes, and diazepam are used widely in OPs poisoning. Combination therapy with atropine and oxime is a common practice in the management of OPs pesticide poisoning. The principal role of the pyridinium oximes is reactivation of enzyme acetylcholinesterase (AChE) inhibited by OPs, consequently permitting ACh to be hydrolyzed in the routine manner and continuation of normal cholinergic neurotransmission. Since atropine is unable to bind to nicotinic receptors, it is not effective in treatment of neuromuscular dysfunction. Therefore, useful effects of oximes are primarily on neuromuscular transmission, and

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thus there is little impact on CNS effects as well as parasympathetic effects such as bronchoconstriction, bronchorrhea, and rhinorrhea.[7] Pralidoxime should be administered concurrently with atropine to avoid worsening of symptoms due to temporary oxime-induced AChE inhibition.[10] Oxime therapy should be considered in all patients with evidence of moderate to severe cholinergic features, neuromuscular dysfunction, or exposure to OPs known to result in delayed neurotoxicity.[7] Pralidoxime is an available, relatively expensive, and widely used oxime in the treatment of patients with OPs poisoning. Unfortunately, this agent is not appropriately used in human OPs poisoning. According to a comprehensive literature review, no study has yet investigated rational use of praldoxime and the cost of its inappropriate utilization in OPs poisoning. Thus, we aimed to evaluate rational utilization of pralidoxime for OP poisoning in a teaching referral hospital affiliated to Tabriz University of Medical Sciences, Tabriz, Iran.

Materials and Methods

Current study was conducted as a retrospective, descriptive, exploratory study at Sina Hospital, a referral poisoning hospital, affiliated to Tabriz University of Medical Sciences, Tabriz, Iran. Medical files of patients with pesticide poisoning who had been admitted to the poisoning ward of Sina Hospital between September 2013 and September 2014 were reviewed. All patients with definite diagnosis of OPs poisoning were selected to evaluate rational and indication based use of pralidoxime in their treatment protocol. Also patients with non-OPs pesticide poisoning who had erroneously received pralidoxime before transferring to poisoning ward at Sina Hospital were included to evaluate overuse and misuse of pralidoxime. Data collection was performed using an already designed checklist containing demographic, clinical, and para clinical characteristics, as well as the type of pesticide caused poisoning. Based on clinical studies, pralidoxime is indicated for the treatment of nicotinic symptoms and moderate to severe muscarinic features following OPs poisoning.[11] Thus, indication for pralidoxime administration was remarked in the checklist as "Yes" or "No". Lastly, decision on the appropriateness of the pralidoxime administration was checked and endorsed by an attending medical toxicologist, and then frequency or percentage of appropriate or inappropriate use of pralidoxime was summarized as proper in tables or figures.

Data were summarized as frequency (%) or mean ± SD and analyzed descriptively by SPSS statistical software, version 17 (SPSS Inc., Chicago). Our study obtained approval of Hospital authority before reviewing medical files, and identity and clinical data of patients remained anonymous all over the study.

Results

During the predefined review period, we found 96 subjects with pesticide poisoning. Mean age of the study patients was 36.71 ± 18.5 years old (range: 15- 92 years) and 56/96 (58.3%) were males. Considering the type of pesticide poisoning, 68.8% of patients had been poisoned with insecticides, 27.1% with aluminum phosphide, 2.1% with herbicides, and 2% with rodenticides, respectively (Table 1). Among all pesticide poisoning, OPs were exclusively responsible for 43.8% of poisoning. Systemic features of OPs poisoning including muscarinic and nicotinic symptoms have been summarized in Table 2. Almost all patients had fairly experienced a combination of muscarinic and nicotinic features. All cases of OPs poisoning (42 patients) received pralidoxime after they had been admitted to emergency department, while regarding the clinical indications, only 55% (23 subjects) of patients were eligible to receive pralidoxime.

Table 1. Patients' demographics and type of pesticide poisoning.

Characteristics	Value*
Age (years) (min - max)	36.71 ± 18.5 (15-92)
***Gender*, *n* (%)**	
Females	40 (41.7%)
Males	56 (58.3%)
***Type of poisoning*, *n* (%)**	
Insecticides	
Organophosphates	42 (43.8%)
Non- Organophosphates	24 (25%)
Herbicides	2 (2.1%)
Rodenticides	2 (2%)
Aluminum phosphide	26 (27.1%)

*Mean ± SD (range) for age; Frequency (%) for other nominal variables.

Table 2. Muscarinic and nicotinic symptoms in patients with OPs poisoning.

Symptoms	Value
***Nicotinic* (%)**	
Muscle weakness and Paralysis	55%
Seizure	25%
Fasciculations	20%
***Muscarinic* (%)**	
Diarrhea	32.1%
Diaphoresis and Salivation	28.3%
Miosis	17%
Lacrimation	15.1%
Urination	7.5%

Table 3. Appropriateness of pralidoxime administration in pesticide poisoning.

Indication	Value
Organophosphate Poisoning (n=42)	
Appropriate use, *n* (%)	23 (55%)
Inappropriate use, *n* (%)	19 (45%)
Other Pesticide Poisoning (n=54)	
Inappropriate use, *n* (%)	32 (59%)

In addition, pralidoxime had been administered for 59% (32) of patients with non-OPs poisoning (54 subjects) which all of them were clinically inappropriate (Table 3).

Discussion

Self-inflicted and accidental poisoning with OPs pesticides have yet remained a major global clinical problem, particularly in developing countries, approximating to 3 million cases in each year.[12] OPs compounds act by irreversible inhibition of the enzyme

AChE, resulting in the accumulation of the neurotransmitter ACh and therefore unrestrained stimulation of cholinergic nerves. The ensuing impacts include slower heart rate, dilation of blood vessels, bronchoconstriction and in severe poisoning, death caused by respiratory failure.[13] Pralidoxime and atropine have been used as antidotes for the treatment of patients with acute OPs poisoning.[7] Pralidoxime regenerates functional enzyme AChE following inactivation by OPs, while atropine blocks exaggerated effects of excessively accumulated Ach at cholinergic synaptic sites.[14] However, the additive benefit of using pralidoxime in addition to atropine remains controversial in some clinical trials.[11] The WHO-recommended regimen for pralidoxime in adults (30 mg/kg bolus intravenous over 30 min followed by 8 mg/kg/hr continuous infusion to quickly achieve and maintain a serum concentration of > 4mg/L) has been simply determined based on animal studies;[15] while the type and dosage of OP pesticide should be considered in dosing strategy and treatment effects of pralidoxime in OP poisoning.[16] Therefore, it seems reasonable to consider severity and clinical presentations of OP poisoning to decide whether pralidoxime administration is indicated. Due to the low lipid solubility and consequent limited entry into the CNS, majority of the pralidoxime effects are mounted on the peripheral nervous system.[11]

Although relative advantage of add-on therapy with pralidoxime over atropine has yet remained to be clarified in the management of OP poisoning, it is predicted that pralidoxime might be effective in the recovery of the nicotinic neuromuscular transmission (such as resolution of muscle fasciculations, weakness, paralysis, etc.) and reversing moderate to severe muscarinic symptoms.[11] Our study retrospectively evaluated rational use of pralidoxime under a direct consult and observation of an attending medical toxicologist in a teaching hospital. As demonstrated in the Table 1, and evident in the previous studies,[14,17] majority of pesticide poisoning occurs in young and economically active age group of patients in developing countries. This may be explained by availability of highly toxic OP poisons, widespread usage of OP pesticides in the developing countries' agricultural activities, lower socioeconomic status, and poor education. Almost all of the patients studied in our investigation exhibited both muscarinic and nicotinic symptoms. A range of clinical features, termed as acute cholinergic crises, manifests in acute OP toxicity. Depending on the type and location of cholinergic receptors, clinical picture may comprise muscarinic (bronchorrhea, bronchospasm, lacrimation, miosis, diarrhea, urination, bradycardia, hypotension, salivation, and vomiting), nicotinic (muscle weakness, fasciculation, paralysis, mydriasis, hypertension, tachycardia, and sweating) and CNS presentations (agitation, confusion, seizure, coma, and respiratory failure).[12]

In the present study, the percentage of OP poisoned patients who received pralidoxime inappropriately was 45% (19 out of the 43 patients). In addition, fifty nine percent of patients with other pesticide poisoning also received pralidoxime which was not appropriate or indicated at all. Despite wasting resources due to irrational use, such medical errors expose patients to life-threatening side effects of pralidoxime including hypertension, arrhythmias, and respiratory arrest.[18-20] In a meta-analysis performed by Buckley et al,[11] it was mentioned that there is insufficient evidence to illustrate whether oximes are beneficial or harmful. Also the findings of this meta-analysis did not support the pralidoxime regimen recommended by the WHO. However, patient tailored dosing strategies were suggested by the authors for pralidoxime therapy. In a study by Lin et al,[21] it was shown that the treatment of OP poisoning should be directed toward the severity of the each patient intoxication. Their results suggested that more severe OP poisoning should be treated with higher doses of pralidoxime. Moreover, Pawar et al proposed that high-dose pralidoxime therapy consisting of a 2 g loading dose followed by a constant drip of 1 g/h for 48 hours decreases the morbidity and mortality of patients with acute moderately severe OP poisoning.[22] Taken together, it seems essential to at least implement patient tailored treatment guideline for pralidoxime therapy in OPs intoxication treatment.

Alongside of imposing life-threatening side effects of pralidoxime upon patients with OPs or non-OPs poisoning, special attention should be paid to wasted cost in irrational use of pralidoxime. According to the dosage regimen recommended by WHO and the length of emergency ward stay, the number of pralidoxime vials (average price of each 200mg vial equal to 5.85 $) inappropriately used for OPs poisoning was 608 and for non-OPs poisoning 1024. Altogether, the losses attributable to irrational use of pralidoxime in this survey had been 9547.2 $.

Finally, there were some limitations in our retrospective study including unknown identity of OPs caused poisoning, morbidity and mortality of patients with OP poisoning, effectiveness of pralidoxime when indicated, side effects of pralidoxime.

Conclusion

Based on our survey, the use of pralidoxime in the northwest of Iran is not appropriate and thus, it is highly recommended that a patient-tailored treatment guideline for pralidoxime indication, doses, and length of therapy based on patient's OPs poisoning severity be provided and implemented regionally until sufficient evidence supporting additional benefit of oxime therapy in addition to atropine monotherapy would be available.

Conflict of interests

The authors claim that there is no conflict of interest.

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