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Original Article

Clinical study of continuous micropump infusion of atropine and pralidoxime chloride for treatment of severe acute organophosphorus insecticide poisoning

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Abstract

Background: Our study sought to assess the effectiveness of a constant micropump infusion of atropine and pralidoxime chloride compared with repeated-bolus doses in patients with severe acute organophosphorus insecticide poisoning (AOPP).
Methods: A total of 60 patients with severe AOPP, defined as cholinergic crisis with respiratory failure or cerebral edema, were randomly divided into two groups of 30 patients each. In the experimental group, patients received a continuous micropump of atropine and pralidoxime chloride; in the control group, patients were given intermittent injections of atropine and pralidoxime chloride. Primary outcome measures were the dose of atropine required for atropinization, Acute Physiology and Chronic Health Evaluation II (APACHE II) score at atropinization, time to atropinization and acetylcholinesterase (AchE) recovery time. Additionally, the case fatality rate was measured as a secondary outcome.
Results: Compared to patients in the control group, the time to atropinization, AchE recovery time, dose of atropine when atropinization occurred, and APACHE II score in the experimental group showed a statistically significant therapeutic effect ($p < 0.05$), and the case fatality rate of the experimental group was lower than that of the control group ($p < 0.05$).
Conclusion: Continuous micropump of atropine and pralidoxime chloride combined is more effective than the use of repeated-bolus injection in the treatment of severe acute organophosphorus insecticide poisoning.

Keywords: atropine; organophosphorus poisoning; pralidoxime chloride

1. Introduction

Acute organophosphorus insecticide poisoning (AOPP) is a major cause of self-poisoning in developing countries, responsible for the deaths of an estimated 200,000 people each year.[1] It is a common emergency accident in China with an average mortality rate of 10%. Furthermore, severe AOPP rapidly leads to acute cholinergic crisis and includes symptoms resulting from hyperstimulation of the central and peripheral muscarinic and nicotinic receptors. Death is usually caused by respiratory failure resulting from paralysis of the diaphragm and intercostal muscles and cerebral edema, with a case fatality rate of up to 30%.[2] The standard treatment for AOPP is to give intravenous atropine and oximes.[3] Treatment with atropine is well established, which inhibits the effect of acetylcholine at muscarinic receptors. It has been reported that continuous micropump injection of atropine can significantly reduce the case fatality rate of severe AOPP.[4] Reactivation of inhibited acetylcholinesterase (AchE) occurs after treatment with oximes, such as pralidoxime chloride, and the minimum concentration in plasma at which this treatment is effective is

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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thought to be 4 mg/L. A dose of 1 g of oximes every 4–6 hours has been the standard regimen in Asian district hospitals, but many clinicians remain unconvinced of its effectiveness.[5] Evidence suggests, however, that the concentration of pralidoxime in the blood might need to be higher to antagonize the toxic effects of many insecticides. Thus, a bolus-loading infusion followed by a maintenance infusion may be the best regimen. Because the study of continuous micropump infusion of oxime in treating AOPP has rarely been reported,[6] the effect of a continuous micropump of atropine and pralidoxime chloride combined in the treatment of severe AOPP has not been tested. In the current study, we aimed to assess the effectiveness of a constant micropump infusion of atropine and pralidoxime chloride compared with repeated-bolus doses in patients with severe AOPP.

2. Methods

2.1. Patients

Patients were enrolled in our study from July 2007 until May 2012. A total of 60 patients received a diagnosis of severe AOPP based on a history of oral consumption of organophosphorus insecticide, the presence of characteristic signs of acute cholinergic crisis (in particular: sweating, pinpoint pupils, urinary and fecal incontinence, bronchorrhoea, bronchospasm, and hypotension) with respiratory failure or cerebral edema, and plasma erythrocyte AchE activity less than 30% of normal. Exclusion criteria consisted of patients who received cardiopulmonary resuscitation during emergency admission, the presence of chronic disease such as heart and lung disease, and concomitant ingestion of other toxicants. Sixty patients with severe AOPP were randomly divided into a continuous micropump atropine and pralidoxime chloride group (experimental group) and an intermittent injection of atropine and pralidoxime chloride group (control group).

This research was approved by the Ethics Committee of The Songjiang Central Hospital and was undertaken in accordance with the principles of the Declaration of Helsinki.

2.2. Treatment

2.2.1. General supportive treatment

All patients with AOPP were assessed and resuscitated in the emergency room before admission to the intensive care unit. Sixty patients received intratracheal intubation and mechanical ventilation in order to maintain airway patency and ensure adequate arterial oxygen saturation. According to the standard treatment plan in China,[7–9] gastric lavage with 20,000 mL of warm water was immediately performed after intubation until the returning fluid was clear and odorless. After gastric lavage, crushed tablets of activated charcoal were left in the stomach and replaced every 8 hours for the next 48 hours. Meanwhile, every patient also received supportive treatment such as hepatoprotection (daily 1.8 g of reduced glutathione), rehydration, diuresis, and hemoperfusion (run immediately after admission, 2 hours daily for 2 days). Patients were monitored continuously by noninvasive means to measure their blood pressure, heart rate, respiratory rate, and arterial oxygen saturation.

2.2.2. Specific antidotal treatment

Every patient was given an initial loading dose of 20 mg of atropine and 2 g of pralidoxime chloride intravenously.[8,10] After the loading dose of atropine and pralidoxime chloride was administered in the experimental group, a continuous micropump atropine infusion was set up at a speed of 20 mg/hour to keep the patient atropinized without reaching toxic levels, using frequent adjustments of dose (usually adjusting the dosage every 5 minutes with the rate of 2 mg/hour declining according to the clinical symptoms of patient). When the patient achieved most of (at least 4 out of 5) the target endpoints[11] (i.e., heart rate > 80 beats/minute, dilated pupils, dry axillae, systolic blood pressure >80 mmHg, clear chest with absence of wheeze) for atropine therapy, an intravenous infusion of the minimum dose of atropine was maintained. Meanwhile, a continuous micropump of pralidoxime chloride infusion was also set up at a speed of 8 mg/kg/hour[10] until the AchE value recovered to 60% of normal.

In the control group, a subsequent dose of 5 mg of atropine injection every 10 minutes was given until atropinization was achieved. Patients also received an intravenous dose of 1 g of pralidoxime chloride every 6 hours until the AchE value recovered to 60% of normal.

2.2.3. Outcomes

The primary outcomes were the atropine dose needed for atropinization, the time to atropinization, the time to AchE recovery, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at atropinization. Case fatality rate in the whole hospitalization period was considered a secondary outcome.

2.3. Statistical analysis

All analyses were performed using SPSS 11.0 software (SPSS Inc, USA). Continuous variables were investigated for departure from normality by use of the Shapiro–Wilk test. For the normally distributed data, we calculated the mean difference and performed Student t tests to compare the experimental group and the control group. For the skewed data, we performed nonparametric Mann–Whitney U tests to investigate differences between the two groups. The significance of the case fatality rate difference between two groups was determined by a Chi-square test, and $p < 0.05$ was used to determine statistical significance.

3. Results

There were a total of 60 patients including 28 men and 32 women with a mean age of 32.5 years, and an age range of 14–56 years. Among the 60 cases of poisoning, there were 18 cases of methamidophos, 17 cases of omethoate, 11 cases of dichlorvos, 5 cases of trichlorfon, and 9 cases of composite

organophosphorus. The mean poisoning volume of organophosphorus insecticides was 50 mL (range 20–100 mL), and the time interval between exposure and admission to the hospital ranged from 30 minutes to 2 hours. There was no statistically significant difference in sex and age, organophosphorus insecticide composition, time interval between exposure and admission to hospital, and AchE activity after poisoning between the two groups (Table 1).

Table 2 shows that continuous micropump of a combined atropine and pralidoxime chloride infusion was a greater benefit to patients with severe AOPP than the intermittent injections of atropine and pralidoxime chloride given to the control group. During the course of treatment, the time to atropinization and time to AchE recovery was shorter in the experimental group than the control group, leading to a lower amount of intravenous atropine needed for atropinization given to the experimental group than to the control group. The APACHE II score at atropinization was also significantly better in the experimental group than in the control group. Compared with that in the control group, there was a lower case fatality rate (10% vs. 26.7%) in patients given a micropump infusion of atropine and pralidoxime chloride.

4. Discussion

AOPP accounted for more than 70% of the total number of insecticide poisonings in China, ranking first in acute chemical poisoning among adult Chinese. Oral administration of large doses of organophosphorus insecticides can cause severe AOPP, because of the rapid inhibition of AchE activity, leading to the accumulation of acetylcholine at cholinergic synapses. The excess acetylcholine causes constant acetylcholine receptor triggering, resulting in serious muscarinic, nicotinic, and central nervous system symptoms, and is life threatening.[12] Therefore, finding ways to improve the survival rate of severe AOPP is an important concern for emergency and critical care workers.

Currently, there is a consensus that comprehensive measures for treating severe AOPP consisting of the administration of muscarinic antagonists (usually atropine) and oximes (usually pralidoxime) are specific antidotes for organophosphorus insecticide poisoning. Early administration of sufficient doses of atropine may create conditions for oximes to play a more substantial role. Pralidoxime chloride can be highly effective in restoring skeletal muscle strength and improving diaphragmatic weakness where atropine has virtually no effect.[13] In actual clinical work, atropine has some features such as the ability to be quickly effective, a short half-life, and a rapid metabolism. However, residual organophosphorus insecticides are stored in fat tissue and continue to be released into circulation. Therefore, the amount of atropine can suddenly appear inadequate or excessive, leading to a variety of clinical manifestations, making it difficult to control the dose of atropine. It is worth noting that insufficient dosage, excessive reduction, or premature withdrawal of atropine can cause a rebound in symptoms. At the same time, there is a tendency to

Table 1
Baseline characteristics of the two treatment groups.

Baseline characteristics	Control (n = 30)	Experimental (n = 30)	p
Men (n)	15	13	> 0.05
Age (y)	32.53 ± 10.02	32.46 ± 10.06	> 0.05
Types of poisons			
Methamidophos	9 (30)	9 (30)	> 0.05
Omethoate	9 (30)	8 (26.7)	> 0.05
Dichlorvos	5 (16.7)	6 (20)	> 0.05
Trichlorfon	3 (10)	2 (6.6)	> 0.05
Composite organophosphorus	4 (13.3)	5 (16.7)	> 0.05
Volume of poisons (mL)	49.66 ± 24.24	50.16 ± 24.26	> 0.05
Time to hospital after exposure (h)	1.21 ± 0.44	1.22 ± 0.39	> 0.05
AchE level (U/L)	19.83 ± 8.35	20.5 ± 7.46	> 0.05
Intubated during resuscitation	30 (100)	30 (100)	> 0.05

Data are expressed as mean ± standard deviation or n (%).
Reference value for acetylcholinesterase (AchE; colorimetric method): 130–310U/L.
AchE = acetylcholinesterase.

Table 2
Outcome comparison of the two treatment groups.

Group	n	Atropinization (min)	AchE recovery (d)	Atropine dose for atropinization (mg)	APACHE II score	Case fatality rate (%)
Experimental	30	49.3 ± 26.5	3.5 ± 0.8	40.3 ± 6.0	10.2 ± 2.0	10.0
Control	30	64.5 ± 29.5	5.8 ± 0.4	53.5 ± 7.3	19.3 ± 6.0	26.7
t or X^2		2.09	14.08	4.43	7.88	13.11[a]
p		< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Data are presented as mean ± standard deviation.
AchE = acetylcholinesterase; APACHE = Acute Physiology and Chronic Health Evaluation; X^2 = Chi square value.
[a] = X^2.

administer excess atropine, which can be dangerous. Atropine toxicity can result in agitation, confusion, hyperthermia, and severe tachycardia.[14] It has been reported that 10.78% of mortality was due to atropine poisoning in the analysis of 1403 cases of organophosphorus insecticide poisoning deaths in China.[15] Consequently, close observation and dose adjustment are essential to avoid both under- and over-atropinization. Pralidoxime chloride has a short half-life of 1.0–1.5 hours. If treatment with oximes is delayed by 2 hours, the phosphate bound to the inhibited AchE loses an alkyl group and becomes resistant to pralidoxime therapy.[16] In addition, high doses of pralidoxime chloride administration can inhibit AchE, resulting in respiratory arrest.[17] Therefore, it is essential to explore the rational and effective use of the treatment in order to maintain an appropriate balance of treatments.

In the current study, we have reported that a continuous micropump of atropine and pralidoxime chloride combined reduced the amount of atropine needed for atropinization, time to atropinization, and time to AchE recovery compared to an intermittent injection regimen. Thus, the number of deaths was also reduced in the experimental group. Therapy requires immediate administration of sufficient atropine to reverse signs of cholinergic excess together with airway and ventilatory support. Current guidelines recommend the use of bolus doses to attain atropinization, followed by an infusion.[18] In our study, we administered a continuous micropump of atropine infusion at a speed of 20 mg/hour after the loading dose was provided in the experimental group.[19] The amount administered was similar to the hourly dosage of atropine used in the control group in order to reduce research bias. The experimental treatment was shown to be beneficial for avoiding both underatropinization and overatropinization due to close observation and dose adjustment. The current data showed that the time to atropinization and dosage of atropine used were more optimal in the continuous micropump infusion group than in the control group, suggesting the importance of achieving early atropinization and maintaining a stable plasma atropine concentration in the treatment of organophosphate insecticide poisoning.

To our knowledge, the exact role of pralidoxime in treatment of AOPP remains a matter of debate. It has been reported that two small uncontrolled case series suggested that pralidoxime could have a possible benefit if given according to the World Health Organization dosage regimen.[5] By contrast, two meta-analyses concluded that pralidoxime causes harm such as increased the risk of death and incidence of intermediate syndrome.[20,21] A systematic review reported that there was insufficient evidence to establish the effectiveness of oximes in AOPP.[22]

A randomized controlled trial including 200 patients with moderately severe AOPP showed reduced mortality in patients treated with continuous pralidoxime infusion (1 g/hour for 48 hours after a 2 g loading dose) compared to repeated-bolus injection.[23] It is the first known trial of dosing oximes as recommended by the World Health Organization, using a dose of 8 mg/kg/hour of pralidoxime after a loading dose of 2 g.[10] Similar to the aforementioned research, our data also support the efficiency of continuous micropump pralidoxime chloride and atropine infusion in treating severe AOPP. Compared to the traditional method of intermittent intravenous administration, the use of a continuous micropump intravenous antidote not only maintains the effective drug concentration in circulation, but also is conducive to the observation of disease changes. This leads to a stable state of atropinization for patients with severe AOPP, therefore avoiding atropine overdose. We also demonstrated that the APACHE II score, which is commonly used to assess the severity of critically ill patients, was better in the experimental group than in the control group during atropinization, strongly indicating that sustained and effective drug maintenance is an important means to stabilize the progression of the disease. It is worth mentioning that a randomized controlled trial, which was performed in Sri Lanka, was reported in 2009 to compare the World Health Organization-recommended regimen of pralidoxime to a placebo in the treatment of AOPP.[24] No evidence was found that this regimen improved survival or reduced the need for intubation in patients with organophosphorus insecticide poisoning. However, there were two key differences from our study. First, the median time from organophosphorus insecticide ingestion to hospital in that study was 4.4 hours, significantly longer than the 1.2 hours in our study. Second, only 17.4% of cases were intubated in that study, compared to 100% in our study. There was a trend toward worse outcomes in patients not intubated before pralidoxime administration, suggesting that intubation may be protective against adverse effects such as respiratory arrest. In contrast, we believe that an earlier application of pralidoxime chlorine and strong supportive therapy is necessary for our regimen to play the biggest role in the treatment of severe AOPP.

This study had several limitations. First, the number of patients was small. The minimum sample size calculated for each group was 50 (one-sided significance level of 5%, power 80%, a 20% difference of mortality between two groups). It is relatively difficult to include more patients with severe AOPP due to the relatively high level of civilization in the Shanghai area. It should be noted that the results of the current study provide evidence that the method of micropump infusion of atropine and pralidoxime chloride may be the better choice for treatment of severe AOPP. However, more cases are required in the future to better support the aforementioned results. Second, we are unable to assess the relationship between plasma atropine and/or pralidoxime concentrations and the study outcomes because those concentrations are not measured in this study. Third, we did not measure serum/urine concentrations of organophosphorus insecticide. Moreover, we did not conduct a comprehensive toxicological screen to completely exclude the possibility of concomitant toxicant exposure. Therefore, although all patients in this study had a clear history and overt manifestations of acute organophosphorus insecticides poisoning, there remains a possibility of exposure misclassification. The aforementioned limitations shall be evaluated in future research.

In conclusion, the method of continuous micropump infusion of atropine and pralidoxime chloride after a loading dose

is considered to be an effective strategy in the treatment of severe AOPP. This is due to its ease of operation, precise control of speed, and dose of antidote into patients, fast time to reach atropinization, a shortening of the AchE recovery time, and a significant reduction in the case fatality rate. Because our study incorporated a small sample size, we believe that further multicenter trials are required to provide clearer evidence supporting the efficacy of the continuous infusion of drugs in patients with severe AOPP.

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