

Pharmacokinetic Studies on Oximes in Organophosphate Poisoning: A Mini Review

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Abstract

Organophosphate (OP) poisoning is one of the most common causes of poisoning in developing countries especially in Southeastern Asia. Poisoning with phosphorus-containing organic chemicals or OP compounds can be managed with antidotes like oximes which are potential reactivators of acetylcholinesterase (AChE). The efficacy of oxime therapy in OP poisoned patients mainly depends upon various factors such as different dose plans, infusion rate of oximes, genetic differences of patients, type of oxime used and chemical nature of the OP compound ingested. Studies on pralidoxime kinetics in OP poisoned patients have shown that reactivation of AChE depends on the plasma concentration of oximes as well as OP compounds. The plasma concentration of oximes mainly depends on the dose plan from intermittent injection to continuous infusion after a loading dose. The incontrovertible fact is that the intermittent dosing of oximes results in deep troughs in blood pralidoxime/oxime levels (BPL) whereas continuous infusion of oximes maintains steady state plasma concentrations. Many published literature also highlighted pralidoxime via continuous infusion results in better outcomes with minimum fluctuation in BPL compared to intermittent dosing. At therapeutic doses, adverse effects of oximes are reported to be minimal. But high BPL is associated with some common adverse effects including dizziness, blurred vision and diastolic hypertension. Considering all the facts, it is important to note that kinetic studies of oximes are useful not only in deciding the dose regimen, but also in predicting the possible side-effects.

Keywords: Organophosphate Poisoning; Oximes; Pharmacokinetics; Pralidoxime Compounds

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INTRODUCTION

Organophosphate (OP) poisoning is one of the major causes of poisoning reported from developing countries especially in Southeastern Asia (1-4). In OP poisonings, the accumulation of acetylcholine in neurologic synapses occurs due to the inhibition of acetylcholinesterase (AChE) caused by deposition of a phosphoryl group at the enzyme active sites (1). This results in orchestra of clinical manifestations known as cholinergic syndrome (5). Oximes are the nucleophilic agents which act as antidotes in poisoning with phosphorus-containing organic chemicals or OP compounds (1). They reactivate the phosphorylated AChE by removing the phosphoryl group (1). Pralidoxime, the most widely used oxime, was discovered in mid-1950s by Wilson et al (6), and was soon successfully introduced into clinical practice for patients with parathion poisoning. Other oximes which were later developed are obidoxime, trimedoxime, HI-6, and HLo7 (1,7,8).

The benefit of oxime therapy for OP poisoning has always been under significant questions. Some research showed the positive effects of this class of medications to

improve the patients (9-11), while the others yielded contrary results (12,13). This is probably due the different dose plan and infusion rate of oximes, genetic differences of patients, type of the oxime used and chemical nature of the OP compound ingested in different studies. In this review, we aimed to evaluate the kinetic studies done on oxime therapy for OP poisoning with a brief look at their adverse effects.

Necessity of kinetic study on oximes

Two major determinants of the degree of AChE reactivation are the specific identity and concentrations of both oxime and OP compound (1). Oximes differ according to their potency and spectrum of activity. Obidoxime and HI-6 are the most potent compounds while pralidoxime is generally less potent compared to other oximes (7,8). In addition, based on the chemical nature of the OP compound, dimethylphosphoryl- or diethylphosphoryl-AChE complex might be formed. Reactivation and aging of the diethyl compounds occurs remarkably slower than dimethyl compounds (1,7,8,14-17). A study by Worek et al, in 1997 showed that obidoxime is the most potent oxime in reactivation of 2-diethylphosphoryl-AChE which is the

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resultant of poisoning with parathion, chlorpyrifos, chlorfenvinphos, diazinon and other OP compounds (7). Efficacy of obidoxime in reactivating dimethylphosphoryl-AChE was shown to be forty, nine and three times higher than HI-6, pralidoxime and HLo-7, respectively, and its efficacy was found to be concentration dependent (8,16).

Worek et al, in 2004 in an in vitro study showed that all oximes differ in their potency (17). They found that inhibited AChE by phosphoramidates was resistant to be reactivated with oximes while phosphorylated AChE could be easily reactivated. HLo7 was found to be the most potent against phosphorylated AChE and obidoxime was the most potent oxime against inhibited AChE by organophosphates and phosphoramidates (17). In another study by Worek et al in 1998, it was observed that obidoxime and pralidoxime are weak antidotes in cyclosarin poisoning; and HLo7 was shown to be an extremely potent reactivator of human true and pseudo-cholinesterases (8). The slight discrepancy in the results of these studies might be due to the difference in the plasma concentration of these oximes administered in different doses and infusion rates.

In severe OP poisoning, the pralidoxime plasma concentration of 4 µg/ml was shown to be unable to confront fast re-inhibition of reactivated AChE on the first day following poisoning. Therefore, maintaining a steady-state plasma concentration was proposed (7). Rios et al in 2005 showed that maintenance of higher plasma concentration of pralidoxime was beneficial even if the patient was admitted 24 hours post-ingestion, particularly for organophosphates with half-life of longer than one day (19). Another study on OP poisoned patients demonstrated that AChE reactivation with pralidoxime methylsulphate, depends not only on the plasma concentration of the oxime but also on the plasma concentration of the OP agent (20). Correspondingly, Willems et al showed that oxime concentration of about 4 mg/L was effective only when the plasma concentrations of ethyl and methyl parathion were below 30 µg/L (18). Thus, it is necessary to study the role of plasma concentration of oximes and their potency in reactivation of inhibited AChE with different OP compounds.

Moreover, the kinetics of oximes in OP poisoned patients is entirely different from healthy volunteers. In this respect, Jovanovic showed that OP poisoned patients had higher plasma concentration of pralidoxime, larger volume of distribution as well as longer effective half-life compared to healthy volunteers (20). Furthermore, different formulations of an oxime may possess different efficacy. For example, pralidoxime is available as chloride, iodide, metasulfate and mesylate salts, while the most widely used forms are chloride and iodide salts. The chloride salt has advantages over iodide, as in particular, its less molecular weight makes it 1.5 times more active, and additionally, higher doses of pralidoxime iodide put patients at the risk of thyroid toxicity, especially if given for a long period (7,16). Considering all these, studying on kinetics, specificity and clinical benefits of existing dosage regimen of oximes in OP poisoning is necessary.

Kinetic studies on blood level of pralidoxime according to dose regimens

Various dose regimens for oxime therapy in OP

poisoning have been recommended from intermittent injection to continuous infusion following a loading dose (1,9-14,21-24). The incontrovertible fact is that the intermittent dosing results in deep troughs in blood pralidoxime/oxime levels (BPL). A study by Medicis et al showed that rapid infusion of 1 g pralidoxime within 30 minutes resulted in 30 mg/L BPL and was associated with increase in diastolic blood pressure of 20 mmHg in healthy volunteers, while a deep trough occurred within a short period; whereas, in continuous infusion constant BPL was maintained and no adverse effect was seen (22). Casey et al similarly found that pralidoxime methanesulfonate administered with 30 mg/kg bolus injection every 4 hours resulted in BPLs between 4.31 mg/L and 145 mg/L (trough and peak levels); whereas, continuous infusion at 10 mg/kg/h, resulted in BPLs ranging from 22.4 mg/L to 36.26 mg/L (23). This narrowed range of BPL in continuous infusion compared to intermittent dosing is one of advantages of the former method that delivers a steady-state concentration to counter the OP agent. In a recent study, it was found that by intermittent 1g 8 hourly dosing of pralidoxime the BPL peaked at 34.2 µg/mL on average 30 minutes post-injection, and dropped to 4.63 µg/mL on average in trough just before the next dose (24). On the other hand, by continuous 500 mg per hour infusion and continuous 1 g per hour infusion of pralidoxime, mean BPL of 20.76 and 38.86 could be maintained, respectively (24). It was also noticed that the reactivation rate of AChE was higher and the rate of intermediate syndrome was lower in continuous infusion compared to intermittent dosing (24). Pawar et al, Mahesh et al and Due similarly supported continuous infusion of pralidoxime against intermittent bolus doses (9-11).

Overall, it seems that OP poisoned patients receiving pralidoxime via continuous infusion obtain better outcomes compared to intermittent dosing that is accompanied with considerable fluctuations in BPL.

Pharmacokinetic analysis and adverse effects of oximes

At therapeutic doses, adverse effects of oximes are reported to be minimal (22,25,26). The well-known adverse effects of pralidoxime including dizziness, blurred vision and diastolic hypertension, have been attributed to high BPL or rapidness of infusion of the drug (25,26). The high BPL is shown to be associated with minor side effects in healthy volunteers. Medicis et al showed that traditional rapid infusion of 16 mg/kg over 30 minutes produces dizziness or blurred vision in the healthy volunteers along with increases in the diastolic blood pressure (22). Volunteers experienced dizziness and blurred vision when BPL approached 80 µmol/L, corresponding to 14 mg/L pralidoxime chloride. These adverse reactions were not seen in continuous infusion of 4 mg/kg over 15 minutes followed by 3.2 mg/kg/h for 3.75 h (for a total dose of 16 mg/kg). The adverse effects in rapid infusion group might be due to high BPL within a short period (22). Other adverse effects due to pralidoxime injection in normal volunteers include headache, drowsiness, nausea, tachycardia, increased systolic blood pressure, decreased renal function, muscular weakness and elevations in liver enzymes (25-27). In a

randomized controlled trial by Eddelston et al, it was revealed that tachycardia, hypertension (especially diastolic) and vomiting were significantly higher in patients who received pralidoxime (2 g/20 min + 0.5 g/h for up to 7 days) compared to placebo group (12). On the other hand, Mahesh et al (2 g bolus + 8 mg/Kg/h infusion for 5 days), Pawar et al and Due (a flexible dose regimen) did not report substantial adverse effects attributable to pralidoxime (9-11). In addition, in a study by Schexnayder et al on OP poisoned children treated with a loading dose of 15-50 mg/kg over 30 minutes, followed by a continuous infusion of 10-20 mg/kg/h, pralidoxime did not produce any side effect at mean serum concentration of 22 ± 12 mg/L (28). However, in the study by Pawar et al, both diastolic and systolic blood pressure were significantly higher over the first 24 hour in patients receiving pralidoxime by continuous infusion (2 g in 30 min + 1 g/h infusion) than in patients receiving via intermittent injections (2 g in 30 min + 1 g bolus every 4 hours) (9). In this sense, a recent study established an apparent link between higher BPL and higher systolic blood pressure (24).

The most serious adverse effect of pralidoxime therapy, which has been reported to date, was observed in a coumaphos-poisoned patient who was treated with pralidoxime iodide infusion (0.4 g over 2 minutes) (29). The patient developed repeated asystole and subsequently cardiac arrest (29); nevertheless, these complications cannot be directly attributed to pralidoxime due to the concomitant treatment of the patient with atropine and also the effect of OP compound itself. It has been reported that rapid injection of pralidoxime can provoke impairment of respiration (slow and shallow breathing), which might be due to peripheral effect at the neuromuscular junction (30).

Altogether, it can be said that excessive BPL, either by rapid infusion or high doses of pralidoxime, exposes the OP poisoned patients to more adverse effects and risks.

CONCLUSION

Considering all the facts, it is important to note that kinetic studies of oximes are useful not only in determining the dosage regimen, but also in predicting the possible adverse effects. While the beneficial role of oximes for OP poisoning is still uncertain, further clinical trials and kinetic studies should be done to bring the fact to light.

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