REVIEW ARTICLE

Why Do the Results of Studies on the Effectiveness of Pralidoxime for Treatment of Organophosphate Poisoning Vary?

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Abstract

Organophosphate (OP) compounds are frequently used agorchemicals for deliberate self-harm in some parts of the world resulting in high mortality and morbidity. Pralidoxime (2PAM) is the most widely used and trialed oxime for treatment of OP poisoning. There have been variations over the results of trials using 2PAM for OP poisoning. 2PAM therapy has led to favorable outcomes in some studies, whereas it has been associated with unfavorable outcomes or without benefit in the others. Why 2PAM works in some trials and why it does not in the others, has been a key question for medical toxicologists with no definite answer. In this systematic review, we sought to investigate possibilities of the variations in the results of different studies conducted on the effectiveness of 2PAM therapy for OP poisoning and we tried to provide solutions for future studies.

Keywords: Comparative Effectiveness Research; Organophosphate Poisoning; Oximes; Pralidoxime Compounds

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INTRODUCTION

Organophosphate (OP) compounds are agrochemical agents that have been frequently misused for deliberate self-harm in the world (1-5). The majority of the three million pesticide-related poisonings worldwide are due to OP compounds (1,3,6). According to large scale epidemiologic studies, mortality due to this type of poisoning varies from 9-13% irrespective of treatments given (2,3,7-10).

Oximes are nucleophilic agents that act as antidotes for treatment of poisoning with OP compounds (6,11). This class of antidotes reactivate the phosphorylated acetyl cholinesterase (AChE) by removing the phosphoryl group (6,11). Lack of an effective treatment protocol and dose regimen of antidotes might be important factors for mortality in OP poisoning (2,12). Difficulty in knowing an effective oxime regimen stem from the fact that all OP compounds are clubbed together as one group in majority of the studies, whereas they differ considerably in their toxicity. Various oximes used in different dosing regimens as well as different atropine doses in each clinical protocol also make any meaningful interpretation of the results difficult. Moreover, delayed institution of antidotes might associate with poor prognosis in the OP poisoned patients (12,13). The fact that severity of poisoning influences the antidote kinetics further confuses the picture (14,15).

Pralidoxime, also known as 2-pyridine aldoxime methyl chloride (2PAM), is the most commonly used oxime across the world. Different sets of standardized protocol of 2PAM infusion with flexible dose regimens for atropine have been used, so far, with varying results (5,8,9,12,14). Why some of them work and why the others do not, is an issue the majority of medical toxicologists have failed to resolve. The effectiveness and safety of oximes in general and 2PAM therapy in particular for OP poisoning have been matter of significant debate and controversies over the recent decades. Many clinicians needs to know whether 2PAM therapy is of any benefit for the OP poisoned patients or not. Trying to understand this important issue, in the present paper, we discuss possibilities of the variations in the results of comparative effectiveness research and observational studies conducted on the effectiveness of 2PAM therapy for OP poisoning.

METHODS

A systematic review of the studies carried out to evaluate the effectiveness of 2PAM therapy for OP poisoning was planned. Detailed literature search for randomized clinical trials (RCTs), observational historically controlled studies and observational cross-sectional studies using 2PAM as the treatment of OP poisoning in human subjects was performed by means of the academic search engines Google Scholar, Scopus and PubMed. The MeSH terms used were "Organophosphate Poisoning", "Oximes", "Pralidoxime Compounds", "Therapeutics", "Observational Study", "Historically Controlled Study", "Clinical Trials" and "Mortality". Searches were performed up to the middle of July 2015.

Articles retrieved from electronic databases (+ citations identified by other sources) were screened for eligibility according to exclusion criteria. Studies with incomplete data such as abstracts published in conference proceedings and

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articles whose full papers could not be obtained via internet and available medical libraries were excluded from analysis. Studies, in which adjunctive therapies in the form of fresh frozen plasma and magnesium sulfate were used, were excluded, as these agents could influence the outcomes.

Meta-analysis and review articles on the effectiveness and pharmacokinetics of 2PAM were also reviewed to double check that no key references were missed through the literature search undertaken by the authors. Baseline parameters of the studies including, authors, year of publication, number of patients, the country where the study took place, and study design were noted. Parameters including primary and secondary outcomes, time interval between poisoning and 2PAM therapy (time-to-treatment), and dose regimen of 2PAM were carefully looked at. For practical purposes, in some studies that the time interval between poisoning and 2PAM administration was not clearly reported, time to hospitalization was taken into account, instead.

In our analysis of the results of 2PAM therapy, no clear benefit was defined as no significantly different mortality between either of the arms the study (2PAM vs. placebo or higher dose 2PAM vs. lower dose 2PAM). Favorable outcome denotes significantly lower mortality in patients receiving 2PAM therapy either compared with placebo or lower dose 2PAM; in contrast, unfavorable outcome shows higher mortality in 2PAM treated patients (either vs. placebo or lower dose 2PAM).

RESULTS

Following literature search via electronic academic databases and search engines, 196 articles were retrieved. After excluding the articles irrelevant to the study objectives and those met exclusion criteria, 17 articles were found eligible for final analysis (Figure 1). The eligible articles comprised 9 RCTs, 1 non-randomized controlled trial, 2 historically controlled studies and 5 observational cross-sectional studies in which OP poisoned patients under treatment of 2PAM were prospectively or retrospectively studied. Among RCTs, 3 studies compared different dosages of 2PAM and 6 other compared the 2PAM therapy with placebo or no 2PAM arm. Most studies were carried out in Southeast Asian countries (14 out of 17) especially in India (10 out of 17). The notable density of studies on 2PAM therapy for OP poisoning in this region is not out of expectations, especially if we look at the magnitude of the OP poisoning problem in this part of the world (1,3,6).

Comparative studies

The main findings of the 12 comparative studies (9 RCTs, a non-randomized controlled trial and 2 observational historically controlled studies) are summarized in table 1 (4,10,12,16-24). Out of these studies, 7 studies had a placebo (saline) or no 2PAM group (10,16,17,19,21,23,24), while the rest compared two different dose regimens of 2PAM (4,12,18,20,22). Among comparative studies, in which mean time interval between poisoning and 2PAM therapy was noted, this parameter was not significantly different between either of the arms. In general, only in two studies, the use of 2PAM resulted in unfavorable outcomes (higher mortality and higher incidence of intermediate syndrome (IMS) and mechanical ventilation requirement) (10,18). In the remaining ten, 2PAM therapy was associated with either favorable outcomes (5 studies) or no clear benefit (5 studies) (Table 2). Moreover, it is important to note that in the RCT by Johnson et al that two different doses of 2PAM were examined and finally unfavorable outcomes were found (18), the daily and total dose of 2PAM in the higher dose arm was in fact low, i.e. lower than World Health Organization (WHO) recommended dose, and similar to the lower dose arm of the other studies showing favorable outcomes with much higher doses (4,12). In other words, unfavorable outcomes that Johnson et al ascertained in administration of only 3 g daily 2PAM was probably due to the fact that this dose is lower than optimum dose which is required to produce the steady plasma level of 2PAM for reactivation of inhibited AChE (4,12,22). Therefore, it can be said that except the RCT by Eddleston et al (10), the use of 2PAM for OP poisoning can be either with favorable outcomes or at least with no clear benefit. Nonetheless, it should not be overlooked that in the majority of comparative studies with placebo or no 2PAM treatment arm (5 out of 7), 2PAM therapy was associated with no clear benefit (16,17,21,23,24), while it was found to be beneficial in one study (19) and disadvantageous in another (10).

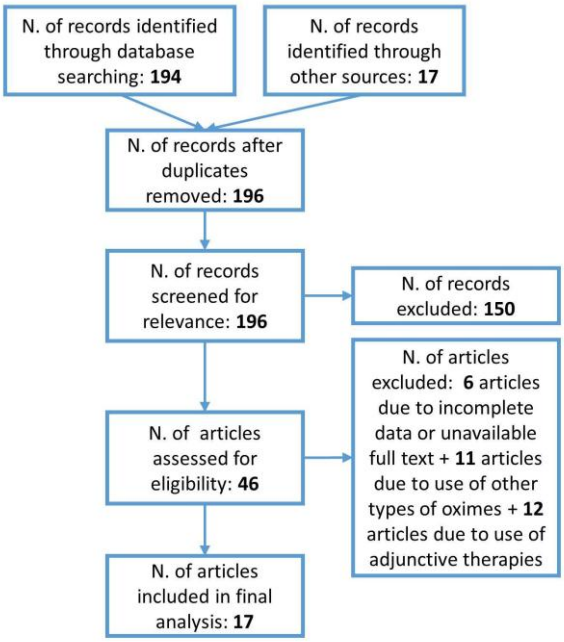

Figure 1. Flow diagram of articles analyzed according to study objectives

Observational studies

The main findings of the 5 observational cross sectional studies are summarized in table 3 (9,25-28); out of which, 3 were retrospective and the rest two were prospective. The mortality rate in these studies was 12.5 to 32%. The most attention-grabbing finding among different studies was higher mortality (28%) in patients presenting late to hospital, with a delay in institution of 2PAM ranging from 12-24

Table 1. Summary of comparative studies done on the effect of pralidoxime therapy for organophosphate poisoning

Reference n., authors, year, study location	Study design	N. of patients	2PAM given	Dose regimen of 2PAM	Mean daily dose of 2PAM	Maximum total dose of 2PAM	Mean time-to-treatment	Patients required mechanical ventilation (%)	IMS (%)	Mortality rate (%)	Conclusion according to outcomes
16, de Silva et al, 1992, Sri Lanka	HCS	24	Yes	4 g in the first 24 hours + 1 g/day for up to 5 days	1.5 g	9 g	NS	45.8	41.7	29.2	NB
		21	No	NA	NA	NA	NS	38.1	38.1	28.6	
17, Abdollahi et al, 1995, Iran	RCT	17	Yes	0.6-0.8 g q4-8h over 4 days	1.8-4.8 g	7.2-19.2 g	< 10 h	41.2	NS	17.6	NB
		17	No	Placebo	NA	NA	< 10 h	47.1	NS	17.6	
18, Johnson et al, 1996, India	RCT	36	Yes	1 g bolus + placebo infusion	NA	1 g	NA	47	39	13.9	U
		36	Yes	Bolus placebo + 1 g/8 h over 4 days	3 g	12 g	NA	67	61	22.2	
19, Balali-Mood & Shariat, 1998, Iran	RCT	8	Yes	30 mg/kg bolus + 8 mg/kg/h for up to 7 days	14.4 g	72 g	NS	25	NS	0.0	F
		43	No	NA	NA	NA	NS	5	NS	9.3	
12, Due P, 1993-2002, Vietnam	HCS	108	Yes	0.5-1 g bolus + 0.25-1 g/h until clinical response	6-24 g	NA	NA	43.5	1.9	1.9	F
		54	Yes	1-4 g/day for 3-4 days	1-4 g	NA	NA	59.3	11.1	13.0	
20, Pawar et al, 2000-2003, India	RCT	100	Yes	2 g in 30 min + 1 g/h infusion for 48 hours + 1 g/4h until weaning from ventilator	25 g daily in the first 2 days	NA	1.9 h	64.0	NS	1	F
		100	Yes	2 g in 30 min + 1 g bolus q4h for 48 hours + 1 g/4 h until weaning from ventilator	7 g daily in the first 2 days	NA	2 h	88.0	NS	8	
10, Eddleston et al, 2004, Sri Lanka	RCT	121	Yes	2 g bolus + 0.5 g/h for up to 7 days	12 g	84 g	2.9-7.8 h	21.5	NS	24.8	U
		114	No	Placebo	NA	NA	NA	21.1	NS	15.8	
21, Cherian et al, 2005, India	RCT	10	Yes	4 g /day for 3 days for moderate cases OR 12 g/day for 3 days for severe cases	4 g or 12 g	12 g or 36 g	NA	70	NS	10	NB
		11	No	Placebo	NA	NA	NA	36.3	NS	9.1	
22, Shivakumar et al, 2005, India	NCT	43	Yes	1-2 g bolus + 1-2 g q6-12h + 0.5/h infusion for maximum of 12 g	NA	4 g < total dose ≤ 12 g	NS	34.9	49	16.3	F
		15	Yes	1-2 g bolus + 1-2 g q6-12h for maximum of 4 g	NA	≤ 4 g	NS	46.7	72	46.7	
4, Mahesh et al, 2009-2012, India	RCT	37	Yes	2 g bolus + 8 mg/kg/h IV infusion for 5 days	14.4 g	72 g	5.1 h	32.4	0	10.8	F
		45	Yes	2 g bolus + 1 g q6h for 5 days	4 g	20 g	5.3 h	48.8	33.3	22.2	
23, Banerjee et al, 2014, India	RCT	60	Yes	1 g q6h for 5 days	4 g	20 g	< 12 h	5.0	NS	18.3	NB
		60	No	NA	NA	NA	< 12 h	8.3	NS	13.3	
24, Syed et al, 2015, India	RCT	50	Yes	30 mg/kg bolus + 8 mg/kg/h for up to 7 days	14.4 g	72 g	5.8 ± 3.2 h	62	20	26	NB
		50	No	Placebo	NA	NA	5.5 ± 2.8 h	58	18	28	

2PAM: Pralidoxime, IMS: Intermediate syndrome, RCT: Randomized controlled trial, HCS: Historically controlled study; NCT: Non-randomised controlled trial; NA: Not applicable, NS: Not stated, U: Unfavorable outcomes, F: Favorable outcomes, NB: No benefit

Table 2. General outline of comparative studies carried out on the effectiveness of pralidoxime therapy for organophosphate poisoning

		Study arms	
	Total	Higher dose 2PAM vs. lower dose 2PAM	2PAM vs. placebo/no 2PAM arm
N. of studies with favorable outcomes	5	4	1
N. of studies with unfavorable outcomes	2	1	1
N. of studies with no clear benefit	5	0	5
Total	12	5	7

hours, compared with patients who received 2PAM earlier in a study by Ahmed et al (28).

Generally, the lowest morbidities and mortality rates were seen in studies in which higher mean daily dose of 2PAM was given (i.e. 12.5% mortality in 16 patients who received 13.5 g daily dose in a study by Singh et al (26)) or the treatments (including 2PAM) were given to the OP poisoned patients in a very
short time after exposure (i.e. 0% mortality in 13 patients who received 2PAM in less than 6 hours post-exposure in the study by Ahmed et al (29), and 15.5% mortality in 156 patients with OP poisoning that the majority of them presented to hospital in less than 6 hours post-exposure in a study by Abedin et al (28)).

DISCUSSION

Easy availability of OP compounds is an important public health threat in South-east Asian countries (1). Role of oximes in the treatment of OP poisoning has always been controversial. Experts have different opinions on oximes, as there are evidence supporting ineffectiveness of these antidotes (6,10,14,18). It is beyond any reasonable doubt that oximes do reactivate inhibited, non-aged cholinesterase enzyme, but this reactivation may not translate into benefits in terms of either morbidity or mortality reduction (16,17,21,23,24).

OP compound formula and effectiveness of 2PAM therapy

One reason for variability of effectiveness of 2PAM therapy for poisoning can be the heterogeneity of OP compounds. OP compounds differ in their potential toxicity. Some of them are more lethal than the others. This prompted WHO to classify them according to their toxic potential (29). Peter et al demonstrated in their cohort study that mortality can be affected by the lethality of the compounds, a characteristic that in the majority of the studies were not taken into consideration (30). They found that mortality was higher with more toxic OP compounds according to WHO classification (30). In this respect, it is well recognized that the dimethyl OP compounds behave in a different manner than diethyl compounds (31,32).

Patients with diethyl OP compound ingestion generally demonstrate a lower and more sustained inhibited activity of the plasma-cholinesterase as compared to dimethyl-OP compounds (33-35). However, as Konickx et al showed, 2PAM is able to reactivate diethyl OP-inhibited plasma cholinesterase (PChE), whereas it is ineffective in reactivation of dimethyl OP-inhibited PChE (31). Likewise, Eddletson et al found significantly higher mortality and poorer response to 2PAM in poisoning with dimethoate and fention (two dimethyl OP compounds) compared with chlorpyrifos (a diethyl OP compounds) (36). Nonetheless, in a study by Hrabetz et al, patients with diethyl-OP compound ingestion developed respiratory compromise and required intubation significantly earlier compared with dimethyl-OP compound ingestion (34). In spite of these differences, clinical severity of poisoning, mortality and morbidity as

Table 3. Summary of observational studies on organophosphate poisoning cases treated with pralidoxime

Reference n., authors, year	Type of study	N. of patients	Dose of 2PAM	Mean daily dose of 2PAM	Maximum total dose of 2PAM	Mean time-to-treatment	Patients required mechanical ventilation (%)	IMS (%)	Mortality rate (%)
25, Srinivas Rao et al, 1995, India	R	593	0.5 g q6-12h	1-2 g	NA	NS	NS	NS	22.6
9, Singh et al, 2001, India	P	16	2 g bolus + 7.5 mg/kg/h (maximum 500 mg/h) until respiration improvement	13.5 g	NA	14.1 ± 27.9 h	100	6.2	12.5
26, Sungur et al, 2001, Turkey	R	31	1 g/ 6 h	4 g	NA	9.4 h	22.5	19.4	32
27, Abedin et al, 2012, Bangladesh	P	156	1-2 g q8h for 48 h	3-6 g	6-12 g	75% < 6 h	16.7	9.0	15.5
28, Ahmed et al 2014, India	R	13	2 g bolus + 1 g q6h until clinical response	4 g	NA	< 6h	100	NS	0.0
		41				6-12 h	100	NS	17.1
		32				13-24 h	100	NS	28.1
		86				NA	100	NS	18.6

2PAM: Pralidoxime, IMS: Intermediate syndrome, R: Retrospective, P: Prospective, NA: Not applicable, NS: Not stated

proven by duration of mechanical ventilation and length of stay in the ICU did not significantly differ between dimethyl- and diethyl-OP compound ingestion in the mentioned study (34). Although the sample size was small, this study demonstrated that the difference in the formula of OP compounds may influence pharmacodynamics of oximes but may not influence the severity of poisoning itself (34). Hence, when different OPs are collectively considered as a study cohort, the results would be potentially different unless the groups were matched according to the toxicity class of ingested OP compounds. Nonetheless, in practice, evaluating the class of OP compounds and their serum concentration is supposed to be futile in the immediate management of acutely OP poisoned patients, because of a longer turnaround time and wasting the vital time for saving patients' lives. However, classifying the agents according to WHO criteria may be of some prognostic value (29). In other words, identification of the compound nature may not ultimately influence the clinical management decision but may help the clinicians to anticipate prolonged/aggressive supportive care for more lethal compounds (10).

In addition, in developing countries, a lot of compounds are being used by the farmers for pest control and at times they are mixed in a container. These mixed agents are occasionally used for self-harm purpose. Peter et al raised this issue as an important confounding factor for ineffectiveness of oximes and high mortality in likely OP poisonings (30). Co-ingestion of other pesticides especially carbamates and pyrethroids must be ruled out before treating a patient with potential OP poisoning as co-ingestion has been shown to have considerable effects on mortality; and moreover, 2PAM is ineffective for poisoning with carbamates and other pesticide compounds (37).

Effectiveness of 2PAM under the influence of its pharmacokinetic and dose

Another factor that has been offered as the reason behind ineffectiveness of 2PAM for OP poisoning is the rapid re-inhibition of reactivated AChE by circulating OP particularly in the context of a massive poisoning (38). Furthermore, it is known that 2PAM plasma levels of lower than 4 μg/mL are unable to confront fast re-inhibition of reactivated AChE on the first day which then can lead to severe symptoms (21). Therefore, maintaining a steady-state higher plasma concentration was proposed (11,26,31,32,39). This could be a reason for better results in the studies using high dose 2PAM infusion (4,12,20). Moreover, continuous infusion, which produces steady 2PAM plasma levels, is superior to bolus injection of 2PAM, which is associated with frequent leaps and bounds in 2PAM plasma levels and sometimes drop to lower than 4 μg/mL (39). This fact was emphasized in the study by Pawar et al (20,39).

Beside the method of administration, some scientists considered methods to enhance pharmacokinetic of oximes. In this respect, Abbara et al proved that administration of avizafone and atropine with 2PAM can lead to faster absorption of the drug into the blood circulation and higher maximal concentrations, compared with the administration of 2PAM alone (40). Furthermore, the role of contributing enzymes in the metabolism of OP compounds should not be overlooked. Goel et al in their study looked at the importance of paraoxonases, which are a group of enzymes involved in the hydrolysis of OPs, and their genetic polymorphism in detoxification of OP compounds (41). They found significant correlation between serum paraoxonase activity and red cell AChE, and thus they proposed that individuals with low paraoxonase activity might be at higher risk for adverse health effects from OP exposure (41). Therefore, the genetic variation between patients may make them prone to poorly respond to the treatments including 2PAM.

One key element that should not be overlooked is the dose of 2PAM in the treatment of OP poisoning. In our analysis, we realized that in the majority of studies, which 2PAM was given in total doses near to or the same as the WHO recommended dose (8 mg/kg/h infusion that is equal to 14.4 g/day for an average person with 75 kg weight) the outcomes were much better (4,12,19,20). To put it in other words, if 2PAM is intended to be given to a patient, higher doses (i.e. WHO recommended dose) might be effective, while the doses lower than WHO dose (i.e. 1 g q6h which is equal to 4 g/day) are perhaps without clear benefit (4,12,18,20,23).

Timely 2PAM therapy and its effectiveness on OP poisoning

Another important factor which needs to be considered is the timing of 2PAM institution. This aspect has been addressed in a study by Ahmed et al, highlighting the fact that early institution (< 6 hours delay) in their cohort was associated with lowest mortality (0%) as compared with 17% in 6-12 hours delay and 28% in over 12 hours delay (28). Eyer and Buckley also addressed this issue as they attributed low mortality in the study by Pawar et al to short interval between admission and pralidoxime administration (median 2 h) (20,39). We noted in our study (Bhalla et al, unpublished data) that mean interval between poisoning event and patient's arrival to the nearest first aid center, where 2PAM might not be available, was just 2.14 ± 1.46 hours, whereas it was 8.52 ± 1.82 hours for delivery of patients to a tertiary care hospital, when it was probably too late for 2PAM institution. The fact that the AChE ages and the aged enzyme is difficult to reactivate, may have contributed to ineffectiveness of 2PAM therapy as evidenced in our cohort (Bhalla et al, unpublished data) and similarly in the patients with delayed admission in the study by Ahmed et al (29).

Improvement in medical facility and patients' outcomes

When we compared the reported mortality between different studies, we found a relative decrease in mortality from the turn of the century. Since the effectiveness of the antidote (2PAM) has not been adequately confirmed or refuted, this change could have simply resulted from the improvement in medical settings for poisoning care and availability of supportive care such as greater number of mechanical ventilation equipment (42). Well-equipped medical settings and experienced well-trained medical personnel are undoubtedly advantageous in patients' prognosis. Therefore, because in the majority of developing countries, there is a shortage of well-equipped facility and

trained personnel, the mortality rate in some of the reviewed studies in this paper might be high irrespective of the effect of 2PAM itself.

CONCLUSION

According to this review, we cannot still say whether 2PAM is useful for treatment of OP poisoning or not. Nonetheless, we can conclude that the reason behind variability of effectiveness of 2PAM therapy for OP poisoning is the fact that sometimes certain confounding variables have been overlooked in the studies. This paper can be a guide for designing the prospective studies on the 2PAM effectiveness for OP poisoning, in which the formula of OPs ingested as well as co-ingestants, the dose and the mode of delivery of 2PAM, the account for the delay in institution of 2PAM, and the supportive care available should be taken account. Moreover, in agreement with Due P. recommendation (12), it would be wise to perform future trials on 2PAM therapy for OP poisoning with at least three arms including placebo, standard dose of 2PAM (WHO dose) and higher/lower dose 2PAM, so that effectiveness of this antidote can be more precisely evaluated.

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