

EXECUTIVE SUMMARY

In agricultural societies the widespread availability of organophosphorus insecticides, which commonly are stored in houses, make them particularly common agents of poisoning, both unintentional and intentional. In India, for example, they are the most common poison in suicide attempts, and suicide may account for up to 19% of deaths in some communities. Suicide has been estimated to account for 1.4% of disability-adjusted life-years (DALYs) lost in the world, and poisonings an additional 0.5%. Rapid, specific treatment is important for recovery from organophosphorus poisoning, which interferes with nerve function by inactivating acetyl cholinesterase, a regulator of neural transmission. In this report from Vellore, India, the authors document that the standard two-drug treatment for organophosphorous poisoning can be greatly improved on. They show that the second drug, pralidoxime, not only does not add to the therapeutic efficacy of the treatment but actually increases mortality from the poisoning. In a randomized controlled trial, the authors demonstrate a 9-fold increase in survival, to 94% in their series, when only atropine is used for specific therapy and pralidoxime is withheld.

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EFFECTIVENESS OF PRALIDOXIME IN THE TREATMENT OF ORGANOPHOSPHORUS POISONING - A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL.

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Introduction

Organophosphorus compounds, organocarbamates and organochlorides are commonly used poisons in agricultural communities in India and elsewhere in the developing world. In India, organophosphorus compounds are the most common poison in suicide attempts. In our institution, organophosphorus poisoning accounted for 29% of poisonings in 1994-1995.

Oximes are nucleophilic agents which re-activate the phosphorylated acetyl cholinesterase¹ by binding to the organophosphorus molecule. There are reports to suggest that pralidoxime (P2AM) is useful in the management of patients with organophosphorus poisoning^{2,3} a fact that has led P2AM to be used routinely for treatment of organophosphorus poisoning in most Indian hospitals.

Others have not shown a significant benefit^{4,5,6,7}. The lack of effect in the study by De Silva⁶ was criticized as due to an inadequate dose⁷. As a preliminary step we conducted the first randomized controlled trial⁸ to assess the usefulness of this compound using two dosage

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schedules (1 gm bolus versus 12 gm infusion). That study demonstrated that the high dose, 12 gm infusion group had a higher incidence of intermediate syndrome and a greater requirement for assisted ventilation⁹.

Objective

To study the role of P2AM in the management of patients with organophosphorus poisoning as compared to placebo.

Patients and Methods

Patients presenting to a large university affiliated teaching institution with a history of consumption of organophosphorus compounds and sick enough to warrant admission to the Medical Intensive Care Unit were entered into the trial. Patients included in the trial had clinical evidence of organophosphorus poisoning (i.e. bronchorrhea/increased salivation, miosis or fasciculations) and had either serum pseudocholinesterase levels of less than 50% of normal values (normal 3,000 - 6,000 IU) or the report by relatives of poisoning by organophosphorus compounds. Patients were excluded if they presented after 48 hours of consumption of the compound, had taken carbamates or had systemic diseases like malignancy, chronic lung disease, renal or hepatic failure or pregnancy.

Patients were randomized using a block randomization schedule (block size of 4) to receive either a placebo infusion (normal saline) for 3 days or 12 gm of P2AM as an infusion over 3 days. The dose of atropine was titrated to maintain a pulse rate of about 100/min, pupils at mid position, normal bowel sounds, clear lungs and no signs of atropine toxicity. All other supportive measures were given as required, and the day to day decisions on management were made by the concerned unit physician.

Outcome measures analyzed were mortality, need for ventilation and duration of ventilation, development of intermediate syndrome and infections. Intermediate syndrome (or Type II paralysis) consists of weakness of proximal (neck, shoulder and intracostal) muscles, leading to respiratory paralysis. Acute (or Type I) paralysis has onset within 24 hours of exposure and is characterized by general weakness, fasciculations, respiratory failure; it generally abates within 48-72 hours of exposure. Type II paralysis, which rarely overlaps Type I paralysis, can last for weeks and necessitate assisted ventilation for that duration.

Yates-corrected Chi-square test was used for comparing two groups and Mann-Whitney Test for continuous variables. Mantel-Haenzel Chi-square test was used to see whether delay in treatment was a confounding variable. Logistic regression (excluding cases with missing values) was also used to look at other confounding variables.

Results

One hundred and ten patients were entered into the trial. The baseline characteristics of the patients (Table 1) were similar in the two groups. Thirty-seven patients (67%) in the treatment group and 27 (50%) in the placebo group had pseudocholinesterase levels of less than 500 IU/l.

Outcome parameters are presented in Table 2. The mortality was significantly less in the placebo group ($P = 0.001$). The numbers of patients developing intermediate syndrome or requiring ventilation were significantly less in the placebo group ($P = .001$ and $.004$ respectively). However, the duration of ventilation was not different in the two groups. Infections were commoner in the treatment group ($P = 0.008$). The total doses of atropine required in the two groups were similar. The times of presentation to hospital (Table 3) were similar in the two groups.

A logistic regression analysis was done to see the effect of other variables on the primary outcome - mortality (Table 4). Patients aged 30 - 39 years had a 10-times higher risk of dying ($P = 0.06$) and those 40 + years had a 21-times risk of dying ($P = 0.02$) as compared to teenagers. Females had a 4-times higher risk of dying ($P = 0.06$) as compared to males. Delay in treatment and the occurrence of infection were not significant predictors of mortality. After controlling for all these variables, patients who received P2AM had a 9-times higher risk of dying ($P = 0.006$) as compared to patients who received placebo (Table 4). Five cases from the placebo group (including the only one without a pseudocholinesterase level) and three from the treatment group did not have data on delay in treatment, and so were excluded from the regression analysis.

The mean (sd) pseudocholinesterase level was significantly ($P < 0.05$) lower in the treatment group [283.2 (243)], as compared to the placebo group [743.7 (1254)]. There was a significant ($P = 0.023$) increase in mortality when the pseudocholinesterase level was ≤ 500 IU/l as compared to > 500 IU/l: 22.5% vs. 0% respectively. In order to adjust for the effect of pseudocholinesterase level on mortality, logistic regression analysis was done including pseudocholinesterase level in the model. Table 5 shows that the pseudocholinesterase level was not significantly associated with mortality, nor did it affect the risk of P2AM on mortality.

Discussion

There have been diverse opinions on the use of P2AM in the management of organophosphorus poisoning^{3,4,5,6,7}. No randomized controlled trials had been done in this area. As a first step, we evaluated the role of P2AM in a randomized controlled trial comparing two dosage schedules (1 gm and 12 gm)⁹. This showed that the patients treated with high dose P2AM fared adversely as compared to the low dose group. This prompted us to conduct the current placebo-controlled trial. This trial shows that mortality and morbidity were significantly higher in patients who received P2AM. Mortality was higher even after controlling for other variables which could

have confounded the results.

In a previous study from our institution (MD dissertation submitted to Madras University) we have shown that pseudocholinesterase level does not correlate with severity and that true cholinesterase better correlates with severity, though both could be useful in diagnosis. Results are available only after 24 hours, and so are not available when diagnostic and therapeutic decisions must be made.

This and the earlier paper on this subject from this institution have shown a high incidence of intermediate syndrome, which may be contributing to the increased ventilatory requirements and mortality. Oximes themselves can cause muscle weakness at higher doses¹⁰. Though there are several postulates for the mechanism of intermediate syndrome, a recent study by us (to be published) has shown the presence mainly of axonal neuropathy. We presume that the randomization of this study has distributed patients at risk of intermediate syndrome equally to both arms. The acute muscle paralysis which is thought to be associated with an excess acetylcholinesterase was present only in five cases. This is a rather rare sequela. The delayed paralysis (intermediate syndrome) was more frequent in the treated group in our previous study^{8,9} and in the present study¹¹.

Wadia et al¹² suggested that the persistence of nicotinic effects due to lack of early use of P2AM contributed to the intermediate syndrome. There is evidence to say that P2AM may be ineffective once the binding of organophosphate to cholinesterase becomes irreversible and, at this stage, giving P2AM could worsen matters. Senanayaka et al¹³, however, reported ten cases with intermediate syndrome despite early administration of P2AM. Gadoth et al¹⁴ postulated that the release of previously inactivated pseudocholinesterase inhibitor acting specifically on nicotinic receptors caused this syndrome.

One way of settling this issue would be to use a protocol where a low dose P2AM (e.g. 1 gm) is compared with placebo. Since the time of administration of this compound may be crucial, a stratified randomized controlled trial of patients treated within about 12 hrs of exposure may be used to assess if this low dose P2AM is useful in binding to the free organophosphorus molecules.

These findings raise questions about the validity of the use of high dose P2AM, which in India is also a costly imported drug, in the management of patients with organophosphorus poisoning. In view of the above results, it seems reasonable to conclude that high dose P2AM has no role in the management of patients with organophosphorus poisoning, and that it does more harm than good. Since the completion of this study we have not used P2AM in the treatment of organophosphorus poisoning in our hospital and our results have improved.

The importance of a marked improvement in the treatment of organophosphorus poisoning in this part of the world can be ascertained from the work of John and Joseph, who reported that in Kaniyambodi Block of Vellore, Tamil Nadu, a community of 100,000 near our hospital, the overall mortality was 9 per 1000 per year, the proportion of deaths from suicide was 19% and the proportion of suicides due to organophosphorus poisoning was 25%¹⁵.

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Table 1: BASELINE CHARACTERISTICS

	Treatment*	Placebo+
Number of patients	55	55
Age (mean \pm SD years)	28.0 \pm 10.1	26.5 \pm 10.3
Sex (M:F)	75:25	62:38
Pseudocholinesterase levels (IU/l) (mean \pm SD)	283.2 \pm 243	743.7 \pm 1254

* Treatment group - 12 gm of P2AM administered over 3 days.

+ Placebo group - Normal saline infusion for 3 days.

Table 2: OUTCOME PARAMETERS

	Treatment	Placebo	P value
Number ventilated (n)	37 22	0.004	
Duration of ventilation (days) (mean \pm SD)	7.6 \pm 6.3	8.4 \pm 7.3	0.43
Intermediate syndrome (n)	36	19	0.001
Infections (n)	25	14	0.008
Total atropine dose (mg) (mean \pm SD)	167.2 \pm 181.2	140.9 \pm 160.9	0.33
Mortality			
Alive	39	52	
Dead	16	3	0.001

Table 3: TIME FROM INGESTION OF POISON TO START OF THERAPY

Duration in Hours between ingestion of poison & start of therapy	Treatment group (n)	Placebo group (n)
< 5 Hrs.	8	14
6 -10 Hrs.	15	13
11 -15 Hrs.	9	12
16 -20 Hrs.	9	4
> 21 Hrs.	9	10

(n) = number of patients in the group

Data not available for 5 patients in the treatment group and 2 patients in the placebo group.

Table 4: RESULTS OF LOGISTIC REGRESSION ANALYSIS

Variable	O.R of mortality	95% C.I.	P value
AGE (years)			
< 20	1.0		
20 - 29	6.8	0.6 - 77.6	0.11
30 - 39	10.1	0.9 - 109.0	0.06
≥ 40	21.3	1.6 - 282.9	0.02
SEX			
Male	1.0		
Female	4.3	0.9 - 19.9	0.06
DELAY IN TREATMENT (hours)			
1-5	1.0		
6-10	0.4	0.05 - 2.9	0.36
11-15	0.6	0.07 - 4.3	0.59
16-20	1.1	0.12 - 8.7	0.96
≥ 21	2.6	0.35 - 18.3	0.35
INFECTION			
Yes	1.4	0.40 - 5.1	0.57
No	1.0		
TREATMENT			
P2AM	9.2	1.9 - 44.7	0.006
Placebo	1.0		

O.R. - Odds Ratio **C.I.**- Confidence Interval

Table 5: RESULTS OF LOGISTIC REGRESSION ANALYSIS INCLUDING

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Variable	O.R of mortality	95% C.I.	P value
AGE (years)			
< 20	1.0		
20-29	11.4	1.01 - 129	<0.05
30-39	12.3	1.07 - 143	<0.05
≥ 40	23.5	1.71 - 323	<0.05
SEX			
Male	1.0		
Female	5.0	1.14 - 22.1	<0.05
DELAY IN TREATMENT (hours)			
1-5	1.0		
6-10	0.65	0.09 - 4.47	NS
11-15	0.62	0.07 - 4.99	NS
16-20	1.14	0.12 - 2.27	NS
≥ 21	3.02	0.37 - 24.4	NS
PCHOL (IU/l)			
≤ 500	1.61	0.44 - 7.87	NS
> 500	1.0		
INFECTION			
Yes	6.9	0.32 - 4.09	NS
No	1.0		
GROUP			
Placebo	1.0		
P2AM	9.6	1.89 - 49.1	<0.001

N.S. -Not Significant (>0.05) **O.R.** -Odds Ratio **C.I.** -Confidence Interval
PCHOL-Pseudocholinesterase level