Comparative Evaluation of “Atropine Alone” and “Atropine with Pralidoxime (PAM)” in the Management of Organophosphorus Poisoning

SN Chugh*, Navneet Aggarwal**, Surekha Dabla***, B Chhabra****

Abstract

Pralidoxime (PAM) has been the treatment of choice for moderate-to-severe Organophosphorus poisoning in addition to atropine since 1956. Recently, a controversy arose which challenged the utility of PAM over atropine alone. We studied whether PAM has any utility or supremacy over atropine in treatment of OP poisoning.

Methods: 30 patients of moderate-to-severe organophosphorus poisoning, diagnosed on clinical and biochemical grounds (decreased cholinesterase levels < 50% of normal value), divided into two groups comparable in all aspects constituted the subject matter. The parameters for assessment used were: atropine profile and ventilatory profile. At the end, mortality rates were calculated in both the groups.

Results: Our data showed that PAM neither improved the atropine profile in group II patients (atropine + PAM treated) as compared to group I (atropine alone treated) nor ventilatory profile changed significantly in the two groups. Mortality was negligible in both the groups.

Conclusion: Our data does not support the widely accepted use of pralidoxime in the treatment of moderate to severe OP poisoning as it does not have any added advantage over atropine.

Introduction

Pesticide poisoning is a major public health problem in the third world because one-fourth of the total world consumption of pesticides occurs in the third world. According to WHO estimates, 70% cases of annual acute poisoning result from occupational exposure. The majority of patients of organophosphorous (OP) poisoning belong to the younger generation – less than 30 years of age – and is self-intentional. Outbreaks of mass poisoning by contamination of food such as wheat flour, or by accidents during storage have complicated the picture of OP poisoning.

In India, OP poisoning has been steadily increasing since 1963, and has become the second commonest poisoning in northern India. Ingestional poisoning is suicidal owing to easy availability and accessibility of organophosphorus compounds; while poisoning due to exposure is accidental, and occurs in agricultural and industrial workers due to neglect of protective measures.

The diagnosis of OP poisoning is mainly based on the history of ingestion or exposure, clinical features, low serum cholinesterase levels, and therapeutic response to atropine. The serum cholinesterase (pseudo ChE) has diagnostic significance, but RBC’s cholinesterase (true ChE) correlates well with the severity and follow-up treatment.

Since 1955, oximes are widely used in acute OP poisoning as specific ChE reactivators. It inhibits acetyl-ChE by removing the phosphate group bound to esteratic site of the enzyme, and reverses nicotinic effects of OP poisoning. Pralidoxime (PAM) therapy has been reviewed many times and optimistic reports have been published for the last 40 years. In 1992, DeSilva et al questioned the efficacy of PAM in the management of OP poisoning in Sri Lanka, based on the retrospective analysis of patients who received atropine plus PAM and prospective analysis of the patients who received atropine alone due to non-availability of PAM for some period in Sri Lanka. There have been similar reports from South Africa and Taiwan. Recently, similar reports of inefficacy of PAM in OP poisoning have been published from India, which concluded that infections, intermediate syndrome, and mortality were high in PAM treated patients. All these studies have been criticised either on the basis of non-
comparable groups of selected patients, or inadequate doses of PAM.

The present study was designed to critically analyse the role of PAM in patients with moderate-to-severe poisoning by dividing them into two separate comparable groups in all aspects.

**Material and methods**

The present study included 30 patients of moderate-to-severe OP poisoning. Patients with carbamate poisoning were excluded.

**Study Design:** It was a non-randomised clinico-therapeutic trial. The selected patients were non-randomly segregated into two groups in such a way that both the groups were comparable with respect to age, sex, mode of poisoning, pesticide consumed, and clinical toxicity. The treatment protocol used in the two groups was as follows:

**Group I (Atropine treated group):** It included 15 patients who received intermittent regime of atropine. Atropine was given in the doses of 2 mg IV stat, and then 2 mg after every 5-10 minutes till the signs of atropinisation appeared. After achieving atropinisation, the interval between the doses was increased so as to maintain adequate atropinisation. Atropine was then slowly withdrawn over a period of 3-5 days.

**Group II (Atropine + PAM treated group):** It included another 15 patients. Atropine was used in intermittent dosage and PAM was given in a fixed dosage of 1 g intravenous after every 6 hours. The doses were maintained continuously till clear, clinical improvement occurred, or serum ChE levels returned to normal, or upto a maximum of 5 days.

After completing the medico-legal formalities, both the groups were managed similarly in the accident and emergency ward. Patients with the following criteria were shifted to the respiratory intensive care unit (RICU).

i. History of intake of large dose.
ii. Cephalic secretions.
iii. Disturbed level of consciousness.
iv. Signs of hypoventilation or respiratory obstruction by secretions.
v. Abnormal blood gas values i.e., PaO2 < 10 kPa (75.18 mm Hg) and/or PaCO2 > 6kPa (45 mm Hg).

After receiving the patient in RICU, the need for ventilatory support was decided by the guidelines summarised here-under:

**Guidelines for ventilatory support:**

I. **Respiratory gas tensions.**
   i. **Direct indices:**
      - Arterial oxygen tension < 50 mm Hg on room air.
      - Arterial CO2 tension > 50 mm Hg in the absence of metabolic alkalosis.
   ii. **Derived indices:**
      - PaO2/FiO2 < 250 mm Hg.
      - PA-aO2 (pulmonary arterial-alveolar O2 gradient) > 350 mm Hg.
      - Vd/VT > 0.6

II. **Clinical indices.**
   - Respiratory rate (RR) > 35 breaths/minute.

III. **Mechanical indices.**
   - Tidal volume < 5 ml/kg
   - Vital capacity < 15 ml/kg
   - Maximum inspiratory force < –25 cm of H2O

The mechanical support was continued till the patients fulfilled the criteria of weaning. The patients who did not require mechanical ventilation but needed close observation and oxygen supplementation were also managed in RICU.

**Timing of serum ChE estimation**

After taking the first blood sample in accident and emergency department, the rest of the samples were collected in the ward/RICU at an interval of 24 hours, upto 5 days. Estimation was done by method of Ellman et al by using a prepared kit.

The results obtained were appropriately analysed and mortality was compared by Chi square test.

**Observations**

The most common mode of poisoning was suicidal (9 patients in Group I and 10 patients in Group II) followed
by accidental poisoning.

The clinical profile of patients in both the groups was comparable. The muscarinic manifestations were the most common presenting features in both the groups, i.e., miosis (100%), nausea (80%), vomiting, salivation, and urinary incontinence (40% each). Other symptoms, viz., sweating, lacrimation, and diarrhoea were also comparable. Nicotinic manifestations included fasciculations (40%), tachycardia (6.6%), and transient hypertension (6.6%). CNS manifestations, i.e., apnoea (33.3%), and seizures (26.6%) were also comparable in both the groups.

**Estimation of serum cholinesterase levels**

Serial cholinesterase levels from the time of admission (0 hours) daily up to 5 days are presented in the Table I.

The low values of serum ChE at 0 hour in both the groups signified moderate to severe poisoning. There was progressive rise in Serum-ChE levels in both the groups after respective treatment regimen used. However, on intra-and intergroup comparison, no statistically significant difference was found (p > 0.05). Besides this, the serum ChE levels did not correlate with clinical severity of poisoning.

**Therapeutic parameters monitored during management**

The therapeutic parameters monitored during management in both the groups are shown in Tables II and III.

**Atropine profile:** The atropine requirement and duration of atropine used in both the groups are shown in Table II. There was no statistical difference between the two groups regarding atropine requirements, total amount of atropine used and its duration.

**Ventilator profile:** The ventilator profile observed during management of patients in RICU is shown in Table III. There was no statistical difference in two groups regarding duration of ventilation and stay in ward/RICU.

**Final outcome:** The final outcome in both the groups is shown in Table IV. One patient died in Group II (6.66%), while there was no mortality in the Group I.

**Discussion**

Atropine, a physiological antidote to muscarinic effects of OP compounds, is given either as intermittent, or as continuous intravenous infusion. The recommended dose is 2-4 mg IV stat, then 2 mg at an interval of 5-10 minutes (intermittent) or by continuous IV infusion in the doses of 0.02 mg to 0.08 mg/kg/hr till atropinisation is achieved, i.e., mid-dilated pupils and pulse rate >100/min. The atropinisation is maintained for at least 24-48 hours in all cases or even longer in severe cases. Then it is gradually withdrawn over a variable period ranging from 3-5 days, depending upon the severity of poisoning and response to the treatment. Several hundred milligrams of atropine may be necessary during the first 24 hours which indirectly reflects the severity of poisoning. In this study,

<table>
<thead>
<tr>
<th>Table I: Serum ChE levels (U/L) in patients of OP poisoning</th>
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</thead>
<tbody>
<tr>
<td><strong>Time since admission</strong> (mean ± SD)</td>
</tr>
<tr>
<td><strong>mean ± SD</strong></td>
</tr>
<tr>
<td>0 hour</td>
</tr>
<tr>
<td>24 hours</td>
</tr>
<tr>
<td>48 hours</td>
</tr>
<tr>
<td>72 hours</td>
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<tr>
<td>96 hours</td>
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<tr>
<td><em>Paired ‘t’ test</em></td>
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<tr>
<td>0 vs 24 hours</td>
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<tr>
<td>0 vs 48 hours</td>
</tr>
<tr>
<td>0 vs 72 hours</td>
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<tr>
<td>0 vs 96 hours</td>
</tr>
</tbody>
</table>

N = Normal value of the kit provided (<50% of normal value is significant).
we used atropine profile for calculation of dose of atropine required in 24 hours, and total dose of atropine used. The patients who fulfilled the criteria for ventilatory support were shifted to RICU and put on ventilator.

Table II: Atropine profile in patients of OP poisoning.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Atropine profile</th>
<th>Group I Mean ± SD</th>
<th>Group II Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Atropine requirement in first 24 hours (mg)</td>
<td>78.60 ± 20.98</td>
<td>71.44 ± 21.06</td>
<td>NS</td>
</tr>
<tr>
<td>2.</td>
<td>Atropine requirement from 24 hours onwards till final outcome (mg)</td>
<td>169.40 ± 181.87</td>
<td>163.84 ± 193.39</td>
<td>NS</td>
</tr>
<tr>
<td>3.</td>
<td>Total amount of atropine used (mg) (1+2)</td>
<td>248 ± 196.53</td>
<td>235.41 ± 195.55</td>
<td>NS</td>
</tr>
<tr>
<td>4.</td>
<td>Number of days atropine used</td>
<td>7 ± 1.46</td>
<td>6.46 ± 2.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table III: Ventilator profile in patients of OP poisoning

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ventilator profile</th>
<th>Group I Mean ± SD</th>
<th>Group II Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Number of patients admitted in RICU</td>
<td>6 (40%)</td>
<td>7 (46.66%)</td>
<td>NS</td>
</tr>
<tr>
<td>2.</td>
<td>Number of patients needed ventilator</td>
<td>5 (33.33%)</td>
<td>6 (40%)</td>
<td>NS</td>
</tr>
<tr>
<td>3.</td>
<td>Number of days on ventilator</td>
<td>5.60 ± 4.27</td>
<td>4.80 ± 2.78</td>
<td>NS</td>
</tr>
<tr>
<td>4.</td>
<td>Duration of stay in RICU (days)</td>
<td>7.83 ± 4.95</td>
<td>7.57 ± 4.35</td>
<td>NS</td>
</tr>
</tbody>
</table>

Pralidoxime (PAM) is the most widely used oxime in the treatment of OP poisoning. The PAM being a cholinesterase reactivator, has been claimed to help in the early recovery of patients with organophosphorus poisoning. Treatment must be started as early as possible after exposure, ideally within 5 minutes to 2 hours. There are no definite dose recommendations, however, it has been established that the therapeutically effective oxime concentration in plasma is 4 mg/litre which can be achieved either by intermittent administration, i.e., a bolus IV dose of 15-30 mg/kg, followed by the same dose after every 6 hours to maintain a steady state concentration, or by continuous intravenous infusion at the rate of 8 mg/kg/hour; but with this schedule two initial intravenous bolus doses of 1 gm have to be given 4 hours apart to achieve the therapeutic plasma concentration.

In the present study, the mean atropine requirement during the first 24 hours did not differ significantly in both the groups (78.60 ± 20.98 and 71.44 ± 21.08 in group I and II respectively). Further, the amount of atropine used daily from 24 hours onward till final out-come, remained more or less same in both the groups. The total amount of atropine calculated in group I was 248 ± 196.33 mg, and in group II it was 235.48 ± 95.55 mg, and there was no statistically significant difference between these two groups. All these observations showed that PAM used along with atropine in group II did not lower the dose requirements of atropine. PAM is known to potentiate the effects of atropine, hence, reduces its dose requirements.

Our observations are consistent with those of other workers, who have claimed that PAM does not alter the dose requirement of atropine.

Table IV: Final outcome in patients of OP poisoning.

<table>
<thead>
<tr>
<th>Group</th>
<th>Survived</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>15 (100%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Group II</td>
<td>14 (93.33%)</td>
<td>1 (6.66%)</td>
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</tbody>
</table>

p value (Chi square test) NS NS

Respiratory failure is a known manifestation in moderate-to-severe organophosphorus poisoning, and results from weakness of respiratory muscles, and depression of respiratory centre aggravated by copious bronchial secretions and bronchospasm. The incidence of respiratory failure in acute organophosphorus poisoning is highly variable and has been reported to be 34.95% to 56%. These patients need ventilatory support if there is evidence of decreased vital capacity and fall in PaO2, and rise in PaCO2, on serial blood gas analysis. They need treatment in a RICU.

In our study, six patients (40%) in group I and seven patients (46.66%) in group II were put on ventilatory.
support in the RICU. The mean duration of use of ventilator in group I and group II was 5.60 ± 4.27 and 4.80 ± 4.7 days respectively. Data analysis for ventilatory support (Table III) showed clearly that PAM neither obviated the need for ventilatory support, nor modified the duration on ventilator. All our observations on ventilatory profile indicated that PAM in combination with atropine did not have any advantage over atropine alone (group I). The critical analysis of our study is against the usefulness of PAM, i.e., the earlier observations made between 1956 to 1992, but favour the observations made recently by other workers that PAM has no added advantage over atropine alone in treatment of OP poisoning.

The final outcome or mortality in OP poisoning depends on the severity, type of the OP compound consumed, duration of poisoning, low levels of serum ChE, development of respiratory failure and other complications. One patient died in group II, while none died in group I. Our observations clearly revealed that PAM did not influence mortality rates as there was no significant difference between the two groups.

To summarise, our data on evaluation of PAM in treatment of moderate-to-severe OP poisoning incorporating the maximal clinical parameters and comparing the two groups in an unbiased manner, revealed that this dose of PAM described in a standard text book of medicine neither decreased the dose of atropine nor prevented the development of respiratory failure, need for ventilatory support, duration of ventilation, hospital stay, and mortality rates. Our study has taken care of all these variables; hence, it is a comprehensive, useful, prospective study. Data analysis for ventilatory support (Table III) showed clearly that PAM neither obviated the need for ventilatory support, nor modified the duration on ventilator. All our observations on ventilatory profile indicated that PAM in combination with atropine did not have any advantage over atropine alone (group I). The critical analysis of our study is against the usefulness of PAM, i.e., the earlier observations made between 1956 to 1992, but favour the observations made recently by other workers that PAM has no added advantage over atropine alone in treatment of OP poisoning.

The references are as follows: