

Effect of Intensive Atropine Doses (Rapid Incremental Loading and Titration) for Management of Organophosphorus Pesticide Poisoning: a Case Series

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Abstract

Background: Acute poisoning with organophosphorus (OP) pesticides is a common method of suicide and entails considerable mortality in Bangladesh. The objective of this study was to evaluate the effects and outcomes of a protocol for treatment of OP poisoning that included titrated incremental atropine as loading dose and slow infusion for maintenance.

Methods: In this prospective descriptive case series, definitive OP poisoned patients were enrolled in an adult medicine unit of Dhaka Medical College Hospital from April 2006 to April 2007. Clinical examinations were done as soon as the patient entered the ward. Patient's demographics, comorbid conditions and the occurrence of specific clinical outcomes including death, need for assisted ventilation and clinical complications were recorded. The patients were treated according to the protocol.

Results: A total of 56 patients were enrolled over the study period. The median age of the study population was 22.5 years. Most patients were men (67.8%). The most common clinical presentation was miosis (58.9%). In total, 11 patients died (19.6%). Intermediate syndrome developed in 12 patients (21.4%) and 6 of them died. Assisted ventilation was required in 16 cases (28.5%). Patients with diastolic blood pressure ≤ 70 mmHg and/or GCS ≤ 10 were significantly less likely to survive ($P = 0.02, 0.006$, respectively). Moreover, early respiratory failure ($P < 0.001$) and the need for assisted ventilation ($P < 0.001$) were significantly higher among deceased cases. The mortality rate in this study was similar to previous studies. The frequency of atropine toxicity in the present study (1.8%) was considerably lower than conventional regimen used in previous studies.

Conclusion: Using the new protocol, lower rate of atropine toxicity developed in victims. Hence, the new protocol appears to be safer and its effectiveness should be further evaluated in case control studies in Bangladesh.

Keywords: Atropine; Bangladesh; Clinical Protocols; Organophosphate Poisoning

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INTRODUCTION

Organophosphorus (OP) compounds are commonly used for pest control and are common household items in rural areas of the developing countries. Due to easy availability and high toxicity, pesticides are a major clinical problem in many parts of the world (1-4). Intentional self-poisoning with OP compounds causes approximately 300,000 deaths every year worldwide (4-6). The case fatality of self-poisoning with OP compounds in developing world is commonly greater than 20%, but for particular pesticides it may be as high as 50-70% (7,8).

Bangladesh is dependent on agriculture for its sustained economic growth and there are more than 300 types of pesticides available for pest control (7). Very limited data are available regarding the incidence of self-poisoning with OPs in Bangladesh though it seems to be high in our clinical

experience (4,8). The epidemic proportions of deliberate self-poisoning particularly in South East Asian countries have been related to lack of strong legal prohibitions against the easy access to these compounds (9).

There is still ongoing discussion on severity grading and management of this serious life-threatening poisoning. Various management modalities for OP poisoning have been proposed around the world including Bangladesh (8,10,11). The treatment of OP poisoning requires immediate administration of sufficient amount of atropine to reverse the cholinergic excess. Varying regimens of atropinization have been proposed in different parts of the world. Eddleston et al. developed a standard protocol for treatment of self-induced pesticide poisoning (11,12). The protocol was developed in 2002 and was aimed primarily to help junior physicians to follow management guidelines for OP poisoning. The protocol included an atropine dose regimen,

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target end-points for atropine therapy, markers to assess atropine toxicity, oxime therapy and supportive treatments.

The objective of this study was to evaluate the effects and outcomes of this protocol (especially atropine therapy) for treatment of OP poisoned patients in Bangladesh.

METHODS

Patients

In this prospective descriptive case series, patients were enrolled in an adult medicine unit of Dhaka Medical College Hospital from April 2006 to April 2007. All patients had a history of OP ingestion within the maximum of past 24 hours and had clinically confirmed cholinergic features. Written informed consent was taken from patients or their close relatives. Patients were excluded if they were admitted after 24 hours of ingestion or were unwilling to give written consent. Pregnant and under 16-year-old patients were also excluded.

Procedures

A complete history was taken from each patient or entourage. Particular emphasis was given to determine the poison ingested as it is helpful in diagnosis of suspicious cases. The specific type of OP ingested was confirmed by identification of the brand name or examination of the bottle. Occasionally the poison could not be found in the vicinity, and thus, relatives were asked to purchase the same poison from the dealers. Previous studies have shown that this approach can be reliable for identification of the ingested pesticide (13). Clinical examinations were done as soon as the patient entered the ward. Toxicological screening and plasma cholinesterase measurements were not done due to limited facilities. All patients were prospectively monitored with regular measurement of their pulse rate and blood pressure by qualified physicians. The physicians also recorded patient's demographics, comorbid conditions and the occurrence of specific clinical outcomes including death, need for assisted ventilation and clinical complications.

Treatment

The treatment was started according to the protocol with quick initial assessment of main clinical features of OP poisoning including miosis, excessive sweating, wheeze or poor air entry, bradycardia and hypotension (11,12). The treatment protocol includes:

A) Rapid loading dose of intravenous atropine:

Intravenous atropine of 1.8-3.0 mg was given at the start. In case of no improvement in said 5 parameters, the doubled dose of atropine would be given every five minutes. This trend was repeated until all clinical signs of atropinization were clearly evident. If the clinical diagnosis of OP poisoning could not be clearly established, 0.6 mg intravenous atropine was administered. If all the parameters mentioned in the initial assessment were satisfactory, then the patients were considered to be "atropinized"; i.e., over 20 beats/min increase in heart rate excluded the necessity of further atropinization.

B) Maintenance dose and fluid therapy: Once the patient was atropinized with clear lungs, good heart rate (> 80 bpm), satisfactory blood pressure (systolic > 80 mmHg) and

good urine output, then atropine infusion was started and maintained at 10-20% of total atropine dose used for achieving atropinization in every hour (10-20% of loading dose/hour). The maintenance dose should be mixed with 1,000 mL of isotonic fluid and be infused at a rate of 40 micro-drops per minute as a continuous infusion for at least 24 hours after resolving cholinergic crisis.

Note: Following the initial atropinization, patients had to be reassessed for the five features of atropinization every 15 minutes. When atropinization could not be achieved (bronchospasm or bradycardia, sweating and miosis), further bolus atropine was administered. This dose was decided by the treating clinician and the maintenance infusion was subsequently adjusted by 10-20% of total bolus dose in the initial loading. After atropinization, patients were observed at least every hour for 6 hours. If atropine toxicity developed (confusion, pyrexia, absent bowel sounds; all three should be present), atropine was stopped and patients were closely monitored. Intravenous diazepam was administered in case of agitation. Atropine could be restarted at 70-80% of previous rate after toxicity resolved. Patients were also carefully monitored for development of intermediate syndrome (broken neck sign, use of accessory muscles for respiration, nasal flaring, tachypnea, sweating, cranial nerve palsies, and proximal muscle weakness).

C) Additional treatments: Pralidoxime was given to the patients with the loading dose of 30 mg/kg followed by infusion at 8-10 mg/kg/hour for 7 days or until clinical recovery (12-24 hours post-atropinization), whichever was longer. The patients also received standard medical care under the hospital admitting consultant physician.

Outcome measures

The primary outcome measure was reduction in mortality. The secondary outcome measures included the number of patients requiring assisted ventilation or life support, atropine toxicity and recovery with sequelae. These were observed side by side in every enrolled patient.

Ethics and statistical analysis

The study was approved by the ethical committee of Dhaka Medical College. Data were collected with structured questionnaire after proper management. The data were processed with SPSS-16 (SPSS Inc., Chicago, IL). Clinical characteristics were summarized using frequency (percentage) for categorical data and median (interquartile range [IQR]) for non-normally distributed continuous variables. The data on atropine dosing was analyzed using the Kruskal Wallis test. Student t-test was used for comparing the mean between two groups. Proportions were compared with the chi square test. $P \leq 0.05$ was considered as significant.

RESULTS

A total of 56 patients were enrolled over the study period. The median age of the study population was 22.5 (range = 14-50) years. Most patients were men (67.8%). The type of poison could be determined in 64.3% of cases that the most common compound used was malathion (33.9%). The clinical presentations of patients in initial assessment are shown in table 1. The most common clinical presentation was miosis (58.9%) followed by hypotension (35.7%).

Table 1. Demographic and clinical features of patients

Demographic and clinical features	Survivor (n = 45)	Death (n = 11)	P value
Mean age (year)	22.0	22.7	0.41
Female : Male, n	17 : 28	1 : 10	0.06
Miosis, n (%)	25 (55.5)	8 (72.7)	0.24
Excessive sweating, n (%)	9 (20)	3 (27.3)	0.43
Poor air entry, n (%)	11 (24.4)	5 (45.4)	0.15
Bradycardia, n (%)	5 (11.1)	1 (9.1)	0.66
Hypotension, n (%)	16 (35.6)	4 (36.4)	0.61
Pulse rate (beats/min), n (%)	90.4 (19.2)	99.6 (21.9)	0.54
Systolic blood pressure, mean (SD)	110.9 (21.5)	105.9 (26.1)	0.22
Diastolic blood pressure, mean (SD)	71.3 (11.2)	70.0 (17.9)	0.02
Body temperature (centigrade), mean (SD)	36.9 (0.7)	36.8 (1.0)	0.62
Time interval between poisoning and hospital admission (hours), mean (SD)	5.8 (5.4)	6.4 (4.8)	0.94
GCS on admission, mean (SD)	13.6 (2.7)	10.3 (4.7)	0.006

The median duration of hospital stay was 4 (IQR = 3.6 to 6) days. The median amount of atropine used was 61.2 (IQR = 27 to 122.4) mg. There was no significant difference in the total dose of atropine administered between survivor and deceased patients (Table 2). The mean dose of pralidoxime administered to all patients was 14.5 (range = 0-85.5) g. Thirty two patients (57.1%) received no pralidoxime. Intermediate syndrome developed in 12 patients (21.4%) and 6 of them died. Assisted ventilation was required in 16 cases (28.5). The majority of patients who developed intermediate syndrome (11 out of 12) required assisted ventilation. Due to limited facility, assisted ventilation could be provided only for 6 cases (10.7%). Diastolic blood pressure (DBP) and GCS were significantly different between recovered and fatal cases ($P = 0.02$, 0.006 , respectively). In this regard, patients with DBP of equal or less than 70 mmHg and/or GCS of less than 10 were less likely to survive. Moreover, death was higher among male patients ($P = 0.06$). In addition, early respiratory failure ($P < 0.001$) and the need for assisted ventilation ($P < 0.001$) were significantly higher among deceased cases.

Complications were developed in 7 cases (12.5%) and were included aspiration pneumonia in 3 cases (5.3%), hypoxic encephalopathy in one case (1.8%), ventricular tachycardia in one case (1.8%), ventricular bigeminy in one case (1.8%) and atropine toxicity in one case (1.8%). The mortality rate in overall was 19.6%; however, this rate was higher among patients who developed complications (85.7%; 6 out of 7). The mean time to discharge or death of the patients was 135.2 hours. Eight patients died due to lack of ventilatory support in the intensive care unit (ICU). By comparing the patients who received assisted ventilation and those who required but did not receive this care due to facility limitations, the risk ratio for death in patients requiring assisted ventilation due to early respiratory failure or intermediate syndrome was found to be 0.031 (95% CI: 0.005-0.19). Six patients were admitted to the ICU, of which 3 patients (50%) survived. The cause of death

in patient who died in ICU was aspiration pneumonia, hypoxic encephalopathy and refractory circulatory failure.

DISCUSSION

OP compounds are known since 1854 but their toxicity on humans has been recognized since 1930s (13,14). Pesticide poisoning is a major health problem in Bangladesh (4,8). This problem is compounded by the fact that approximately 35% of acutely poisoned patients require intensive care and mechanical ventilation (15). A uniform management guideline which can help primary care physicians to deal properly with this clinical problem was considered to be essential. In this case series, the effect of a protocol of atropine administration for OP poisoning that has been newly instituted in Bangladesh was evaluated. In the conventional method, bolus atropine was used intermittently and each patient was only managed according to physician's judgment. Hence, high dose atropine could occasionally be administered and consequently the patient would develop atropine toxicity. On the other hand, under-dosing of atropine could endanger the life of many patients (16). Notwithstanding, the new regimen that was used in this study included titration, and slow infusion of atropine as soon as achieving atropinization.

The mortality rate in this study was similar to a study done by Eddleston et al. on OP poisoned patients with this protocol (11). However, this rate still seems high which could be due to delayed transfer of patient to the hospital, injudicious use of gastric lavage that later may lead to chemical pneumonitis and aspiration pneumonia, limited number of mechanical ventilators, lack of resources, lack of trained personnel, lower socioeconomic status of the patients and negative attitudes towards patients with suicidal attempt. Mortality rate was markedly higher among those who developed complications. Early intervention to prevent complications may improve the outcomes. Besides, the frequency of atropine toxicity in the present study (1.8%) was considerably lower than conventional regimen (48%) that was used in the study by Perera et al. (16).

Table 2. Comparison of outcome parameters between deceased cases and survivors

Outcome parameter	Survivor (n = 45)	Death (n = 11)	P value
Total dose of atropine (mg), median (IQR)	51.2 (25.9-95.4)	99 (27-210)	0.11
Duration of atropine administration (hour), median (IQR)	127 (124-169)	24 (9-55.5)	< 0.001
Intermediate syndrome, n (%)	6 (13.3)	6 (54.5)	0.007
Early respiratory failure, n (%)	1 (2.2)	3 (27.3)	< 0.001
Ventilation required, n (%)	7 (15.5)	9 (81.8)	< 0.001

In the present study, the median age of the study population was 22.5 years. This finding is consistent with the other study done in Bangladesh (17). This might be due to the fact that the pesticide poisoning commonly occurs in younger age group. Miosis was present in a great number of cases. Even some patients did not have other four important features of cholinergic crisis. This finding might be explained by the fact that majority of the patients had received prehospital treatments including atropine injections.

LIMITATIONS

Although the study was performed 6 year ago, unfortunately no remarkable change in the hospital facilities has occurred in Bangladesh. Moreover, no unified protocol for OP poisoning management has been implemented and thus, in most of the emergency centers, the atropine dose is still decided by the treating physician. In that sense, the results provided in this article are still defensible. Furthermore, to evaluate the effectiveness of the new protocol, a control group was needed. However, this study was not a case-control and was only a descriptive case series. Comparing the results of cases and controls could clearly show the differences in morbidities and mortalities. Hence, conducting future studies with the design of case control for evaluation of effectiveness of the new protocol in Bangladesh is recommended.

CONCLUSION

Using the new protocol, lower rate of atropine toxicity developed in victims. Hence the new protocol appears to be safer and its effectiveness should be further evaluated in well-designed case control studies in Bangladesh.

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