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RESEARCH ARTICLE

A STUDY ON MANAGEMENT OF ORGANOPHOSPHOROUS POISONING – OUR CLINICAL EXPERIENCE

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ABSTRACT

Background: Organophosphate compounds are the commonly used pesticides in our country. These compounds are highly toxic. Organophosphorous poisoning is therefore associated with high mortality and morbidity. Early diagnosis and treatment is the key in the management of these cases. We report our experience with the intensive care management of serious OP insecticide poisonings.
Materials and Methods: An observational study was made in 60 patients who were admitted with OP poisoning. They are treated with atropine and pralidoxime (PAM). Ventilatory and circulatory support was provided, if required.
Conclusion: Results showed that majority of cases were due to suicidal attempt and outcome improved with early intervention. However, mortality still remains high due to lack of proper guidelines in the management of such cases and probably, the limited resources in hospitals in terms of trained doctors, nurses, support personnel, laboratory facilities and finance, may be partially responsible for the high number of deaths.

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INTRODUCTION

Organophosphate (OP) insecticides inhibit both cholinesterase and pseudo-cholinesterase activities. The inhibition of acetylcholinesterase causes accumulation of acetylcholine at synapses, and overstimulation of neurotransmission occurs as a result of this accumulation. The mortality rate of OP poisoning is high. Early diagnosis and appropriate treatment is often life saving. Treatment of OP poisoning consists of intravenous atropine and oximes. The clinical course of OP poisoning may be quite severe and may need intensive care management. We report our experience with the intensive care management of serious OP insecticide poisonings. WHO estimates acute pesticide poisonings at 3 million cases/year (Eddleston and Phillips, 2004). One million accidental and two million suicidal and > 99% occur in the developing world. Organophosphate agents are commonly used as pesticides. These agents are responsible for over 70% of the cases in most of South Asia. Most deaths may occur at home and in small towns where medical facilities are not available. Hospital statistics grossly underestimate the mortality in these cases.

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MATERIALS AND METHODS

After obtaining ethical committee approval, We conducted an observational study of 60 patients admitted with Organophosphorous poisoning. They are followed in our respiratory intensive care unit (RICU). Diagnosis was made from the history taken either from the patient or from the patient's relatives, about the agent involved in the exposure. We followed a uniform protocol for management of these patients. All the patients underwent gastric lavage and treated with Atropine and Pralidoxime (PAM) depending on the severity of poisoning.

Circulatory assistance was provided with either dopamine or a combination of dopamine and nor-adrenaline. All patients were assessed for the need of artificial ventilation based on clinical severity and oxygen saturation from pulse oximetry and ABG analysis.

The following parameters were noted down for analyzing the patient course in our RICU:

1) Dose of atropine.
2) Dose of pralidoxime (PAM).
3) Time of intubation
4) Duration of mechanical ventilation.
5) Requirement of ventilatory and circulatory support.

Ventilatory support

It is indicated in stupor/coma, hypoxemia with PaO_2 < 60 mm Hg and profound muscle weakness. Ventilatory support may be needed for respiratory failure due to early acute cholinergic crisis (<24 hrs) and late intermediate syndrome (>24 hrs). In some cases, early intubation may lead to prolonged ventilatory support

The predictors for the need of ventilatory support would be

1. Delay in the initiation of specific treatment.
2. Low level of sensorium at admission
3. Pinpoint pupils and generalized fasciculations.
4. Presence of convulsions
5. Presence of respiratory failure at admission. (SpO_2< 90%; RR <8 or>30/min)
6. High initial atropine requirement for atropinization.

The patients were intubated and mechanically ventilated. Mechanical ventilation was carried out in Synchronized Intermittent Mandatory Ventilation + Pressure Support mode, either as volume or pressure control. Positive end expiratory pressure was titrated to keep SaO_2 above 94% with 40% FIO_2.

Weaning was performed using either T-piece trials or pressure support weaning.

Criteria for weaning

1. Patients who can maintain air way with a SpO_2 > 95% 0n fiO_2 of 40%.
2. Haemodynamically stable without inotropic support (i.e, dopamine or nor adrenaline)
3. Who have complete disappearance of OP poisoning symptoms (i.e salivation, lacrimation,..)

Criteria for circulatory assistance

1. Systolic blood pressure < 90 mm of Hg
2. Heart rate < 50 bpm

Weaning of circulatory assistance

1. Systolic blood pressure > 100 mm of Hg
2. Heart rate > 80-100 bpm

RESULTS

Age group * atropine dose given

Age Group		atropine dose given(mg)			Total
		<30	30-60	>60	
<15 year	Count	5	0	1	6
	% within age group	83.30%	0.00%	16.70%	100.00%
16-30 Yr	Count	29	3	4	36
	% within age group	80.60%	8.30%	11.10%	100.00%
31-60 yr	Count	11	0	7	18
	% within age group	61.10%	0.00%	38.90%	100.00%
Total	Count	45	3	12	60
	% within age group	75.00%	5.00%	20.00%	100.00%

Chi-Square value X^2 =7.3 df =4; p=0.119 NS

Age group * PAM dosage

Age Group		PAM doseage given(mg)		Total
		<5	>10	
<15 year	Count	5	1	6
	% within age group	83.30%	16.70%	100.00%
16-30 Yr	Count	31	5	36
	% within age group	86.10%	13.90%	100.00%
31-60 yr	Count	14	4	18
	% within age group	77.80%	22.20%	100.00%
Total	Count	50	10	60
	% within age group	83.30%	16.70%	100.00%

Chi-Square value X^2 =0.6 df =2; p=0.74 NS

Age group * intermediate syndrome

Age group		Intermediate syndrome		Total
		NO	YES	
<15 year	Count	5	1	6
	% within age group	83.30%	16.70%	100.00%
16-30 Yr	Count	36	0	36
	% within age group	100.00%	0.00%	100.00%
31-60 yr	Count	15	3	18
	% within age group	83.30%	16.70%	100.00%
Total	Count	56	4	60
	% within age group	93.30%	6.70%	100.00%

Chi-Square value X^2 =6.4 df =2; p=0.04 NS

Age group * duration of ventilation

Age group		Duration of ventilation(days)							Total
		0	1	2	3	5	8	10	
<15 year	No	5	0	0	0	0	1	0	6
	%	83.30%	0.00%	0.00%	0.00%	0.00%	16.70%	0.00%	100.00%
16-30 Yr	No	33	1	1	1	0	0	0	36
	%	91.70%	2.80%	2.80%	2.80%	0.00%	0.00%	0.00%	100.00%
31-60 yr	No	11	0	1	3	2	0	1	18
	%	61.10%	0.00%	5.60%	16.70%	11.10%	0.00%	5.60%	100.00%
Total	No	49	1	2	4	2	1	1	60
	%	81.70%	1.70%	3.30%	6.70%	3.30%	1.70%	1.70%	100.00%

Age group * LOC

Age group		LOC		Total
		Conscious	unconscious	
<15 year	No	3	3	6
	%	50.00%	50.00%	100.00%
16-30 Yr	No	26	10	36
	%	72.20%	27.80%	100.00%
31-60 yr	No	10	8	18
	%	55.60%	44.40%	100.00%
Total	No	39	21	60
	%	65.00%	35.00%	100.00%

Age group * outcome

Age Group		Outcome						Total
		Abscond	LAMA	Death	Discharge	Recover	Referred	
<15 year	No	0	0	0	0	5	1	6
	%	0.00%	0.00%	0.00%	0.00%	83.30%	16.70%	100.00%
16-30 Yr	No	3	5	0	1	25	2	36
	%	8.30%	13.90%	0.00%	2.80%	69.40%	5.60%	100.00%
31-60 yr	No	0	1	3	0	12	2	18
	%	0.00%	5.60%	16.70%	0.00%	66.70%	11.10%	100.00%
Total	No	3	6	3	1	42	5	60
	%	5.00%	10.00%	5.00%	1.70%	70.00%	8.30%	100.00%

Age group * religion

Age group		religion			Total
		Christian	Hindu	Muslim	
<15 year	no	1	3	2	6
	%	16.70%	50.00%	33.30%	100.00%
16-30 Yr	no	11	25	0	36
	%	30.60%	69.40%	0.00%	100.00%
31-60 yr	no	5	13	0	18
	%	27.80%	72.20%	0.00%	100.00%
Total	no	17	41	2	60
	%	28.30%	68.30%	3.30%	100.00%

Age group * sex

Age group		sex		Total
		Female	Male	
<15 year	No	4	2	6
	%	66.70%	33.30%	100.00%
16-30 Yr	No	21	15	36
	%	58.30%	41.70%	100.00%
31-60 Yr	No	7	11	18
	%	38.90%	61.10%	100.00%
Total	No	32	28	60
	%	53.30%	46.70%	100.00%

Onset of Res Arrest * atropine and PAM dose given

Onset of respiratory arrest (min)		atropine dose given (mg)			Total	PAM dosage (mg)		Total
		<30	30-60	>60		<5	>10	
<30	No	45	3	2	50	47	3	50
	%	90.00%	6.00%	4.00%	100.00%	94.00%	6.00%	100.00%
30-60	No	0	0	3	3	1	2	3
	%	0.00%	0.00%	100.00%	100.00%	33.30%	66.70%	100.00%
>60	No	0	0	7	7	2	5	7
	%	0.00%	0.00%	100.00%	100.00%	28.60%	71.40%	100.00%
	No	45	3	12	60	50	10	60
	%	75.00%	5.00%	20.00%	100.00%	83.30%	16.70%	100.00%

Onset of Res Arrest * intermediate syndrome

onset of respiratory arrest (min)		Intermediate syndrome		Total
		NO	YES	
<30	Count	49	1	50
	%	98.00%	2.00%	100.00%
>60	Count	6	1	7
	%	85.70%	14.30%	100.00%
30-60	Count	1	2	3
	%	33.30%	66.70%	100.00%
	Count	56	4	60
	%	93.30%	6.70%	100.00%

Onset of Res Arrest * Duration of Ventilation

Onset of respiratory arrest(min)		Duration of Ventilation (days)							Total
		0	1	2	3	5	8	10	
<30	Count	49	0	0	0	1	0	0	50
	%	98.00%	0.00%	0.00%	0.00%	2.00%	0.00%	0.00%	100.00%
30-60	Count	0	0	0	1	1	0	1	3
	%	0.00%	0.00%	0.00%	33.30%	33.30%	0.00%	33.30%	100.00%
>60	Count	0	1	2	3	0	1	0	7
	%	0.00%	14.30%	28.60%	42.90%	0.00%	14.30%	0.00%	100.00%
Total	Count	49	1	2	4	2	1	1	60
	%	81.70%	1.70%	3.30%	6.70%	3.30%	1.70%	1.70%	100.00%

Onset of Res Arrest * Loss of Consciousness (LOC)

Onset of respiratory arrest (min)		LOC		Total
		Conscious	unconscious	
<30	Count	32	18	50
	%	64.00%	36.00%	100.00%
>60	Count	5	2	7
	%	71.40%	28.60%	100.00%
30-60	Count	2	1	3
	%	66.70%	33.30%	100.00%
	Count	39	21	60
	%	65.00%	35.00%	100.00%

Onset of Res Arrest * outcome

Onset of respiratory arrest (min)		outcome						Total
		Abscond	LAMA	Dead	Discharge	Recover	Referred	
<30	Count	3	6	0	1	37	3	50
	%	6.00%	12.00%	0.00%	2.00%	74.00%	6.00%	100.00%
>60	Count	0	0	0	0	5	2	7
	%	0.00%	0.00%	0.00%	0.00%	71.40%	28.60%	100.00%
30-60	Count	0	0	3	0	0	0	3
	%	0.00%	0.00%	100.00%	0.00%	0.00%	0.00%	100.00%
	Count	3	6	3	1	42	5	60
	%	5.00%	10.00%	5.00%	1.70%	70.00%	8.30%	100.00%

Onset of Res Arrest * religion

Onset of Respiratory Arrest (min)		religion			Total
		Christian	Hindu	Muslim	
<30	No	13	35	2	50
	%	26.00%	70.00%	4.00%	100.00%
30-60	No	2	1	0	3
	%	66.70%	33.30%	0.00%	100.00%
>60	No	2	5	0	7
	%	28.60%	71.40%	0.00%	100.00%
Total	No	17	41	2	60
	%	28.30%	68.30%	3.30%	100.00%

Chi-Square value X^2 =2.62 df =4; p=0.623 NS

Onset of Res Arrest * sex

Onset of Respiratory arrest (min)		sex		Total
		Female	Male	
<30	No	29	21	50
	%	58.00%	42.00%	100.00%
30-60	No	1	2	3
	%	33.30%	66.70%	100.00%
>60	No	2	5	7
	%	28.60%	71.40%	100.00%
Total	No	32	28	60
	%	53.30%	46.70%	100.00%

Chi-Square value X^2 =2.6 df =2; p=0.267 NS

There were 32 female and 28 male patients in our study out of which, 68% were suicide attempts and 32% were accidental exposure and the most frequent signs were miosis, change in mental status, hyper salivation and fasciculations. Gastric lavage was done in all cases. In our study, 30% patients has Low level of sensorium at admission, 10% had convulsions, 40% patients had Pinpoint pupils (size less than 2mm) and generalized fasciculations and 20% of patients had high initial atropine requirement for atropinization(5mg). Mean time of intubation is 6.6 hrs (3-12hrs) and mean duration of stay in RICU was 6.6 days (2-11days). In the management - atropine starting dose varied from 0.6-5mg and PAM dosage varied from 2-5 gm/day. Complications occurred in course of treatment include - intermediate syndrome in 3 patients and 3 patients succumbed to death (In that one is ARDS, one is septic shock and one is due to hypotension and cardiac arrest). Data are presented as mean +/- standard deviation

DISCUSSION

Pesticide poisoning is a major clinical problem in the rural districts with thousands of poisonings and hundreds of deaths every year. Case fatality is high. Despite the limitations of an observational study without laboratory confirmation of the ingested poison, two major reasons are clear: highly toxic pesticides being used for self-harm and difficulties with patient management. The case fatality for self-poisoning in the developing world is commonly 10–20% (for particular pesticides it may be as high as 50–70%) in contrast to < 0.3% case fatality ratio normally found for self-poisoning from all causes in Western countries.

The cause of the high case fatality is multifactorial –

1. The high toxicity of locally available poisons,
2. Difficulties in transporting patients across long distances to hospital,
3. The paucity of health care workers compared with the large numbers of patients and
4. The lack of facilities, antidotes, and training for the management of pesticide poisoned patients.

Pesticides are currently classified by the WHO on the basis of their toxicity in untreated animals from Group I (extremely hazardous) to Group III (slightly hazardous) and compounds unlikely to cause ill health (World Health Organization 2001). It is not yet clear whether this system is applicable for self-poisoning. The data from our case series suggest that it may not be applicable. The most toxic organochlorine was endosulfan, which although having only Group II toxicity, is practically untreatable in humans and associated with high mortality (Roberts *et al*., 2003). These observations should be interpreted conservatively as this is a retrospective study without laboratory identification or inclusion of out of hospital deaths. Nor should it be dismissed, as work in Sri Lanka has shown that identification of the pesticide by patient or relatives is confirmed by laboratory analysis in over 80% of cases[(1)]. A further complication may be differences in the commonly ingested formulations or concentrations of each pesticide. Current UN Food & Agriculture Organization (FAO) guidelines suggest that all Group I and II compounds should be withdrawn from agricultural practice. Group I pesticides and endosulfan have been banned in Sri Lanka (Eddleston *et al*., 2003; Ballantyne and Marrs, 1992; Batra *et al*., 2003).

Timing of admission and outcome

Patients presented to the hospital remarkably quickly, with 89% being admitted directly to Fatima institute of Medical Sciences and 55% of these patients arrived within 1.5 hrs. This contrasts with the situation in the Christian Medical College, Vellore, in which most patients presented to hospital 10 (Johnson *et al*., 1996) or 12 (Ballantyne and Marrs, 1992) hrs post-ingestion. This delay may explain the lack of pralidoxime effectiveness in their studies.

Use of antidotes

A large amount of hospital resources went into treating pesticide poisoning and yet the overall mortality was high. Optimal treatment for OP poisoning should involve pralidoxime and atropine (Eddleston *et al*., 2003; Johnson *et al*., 2000; Bismuth *et al*., 1992). Oximes are cholinesterase reactivators that also increase the rate of elimination of OP (Thompson *et al*., 1987). There were a number of difficulties with the way these antidotes were used in the hospital. The WHO recommends much higher doses of pralidoxime than those used here – a bolus of at least 30mg/kg of pralidoxime chloride followed by an infusion of 8mg/kg per hour (Bismuth *et al*., 1992). These doses of pralidoxime chloride are equivalent to 45mg/kg bolus (2 to 3 g) and 12mg/ kg/hour (0.6 to 1.0 g/hour) infusion of the Iodide salt. Thus, patients received pralidoxime doses as much as ten-fold lower than the WHO recommended dose. Furthermore, the use of a bolus dosing regimen will result in sub-therapeutic pralidoxime concentrations for more than half of the time (Bismuth *et al*., 1992; Eddleston *et al*., 2002b). However, it must be noted that, as yet, there is no hard evidence that oximes produce clinical benefit (Samuel *et al*., 1996). Furthermore, recent Indian studies suggest that low doses of oximes may be harmful to patients (Samuel *et al*, Cherian, Peter, Samuel, Jaydevan) (Risher *et al*., 2004), although the results of these studies are subject to debate (Eddleston *et al*., 2002b; Lotti 2003; Samuel *et al*., 1996). The only oxime available in the district during the study was pralidoxime iodide. In most other areas of the world, chloride or sulfonate salts are the standard pralidoximes used (Bismuth, Inns & Marrs) (American Academy of Clinical Toxicology and European Association of Poisons Centresand Clinical Toxicologists 1997). Administration of WHO recommended doses of pralidoxime (Johnson, Jacobsen, Meredith, Eyer, Heath, Ligtenstein, Marrs, Szinicz, Vale, & Haines) (Bismuth *et al*., 1992) as an iodide salt would provide around twenty times the average daily intake of iodine. While this has not been reported to cause problems in this setting, adverse effects have been reported at these doses of iodine. (Risher *et al*.; Karalliedde *et al*., 2004) The doses of atropine used may have been appropriate in many cases - it is not possible to determine retrospectively from the notes how successful the atropine dosing was. However, there are two reasons to suspect that it may be possible to improve use of atropine. Firstly, the doses used were similar in most patients, suggesting that titration to an appropriate level of atropinisation was not generally done. Secondly, the overall death rate was higher than in some other series (Eddlestonetal) (Samuel *et al*., 1996) and early deaths were common. This may partly reflect the high toxicity of the substances, but also suggests possibilities for improvement in the stabilization of patients. Administering pralidoxime and atropine to patients poisoned with organochlorines and pyrethroids may be harmful, is unlikely to provide any beneficial effect and wastes resources.

It may be a widespread problem in the overstretched developing world hospitals that globally see the majority of the patients. Further education and training of doctors may be able to reduce this problem.

General management

Diazepam or phenobarbitone should usually be sufficient to control seizures from pesticide poisoning, although patients with severe organochlorine poisoning may require general anesthesia. The value of prophylactic anticonvulsant therapy is not yet clear. Gastrointestinal decontamination usually involved gastric lavage using normal saline. Although some patients (possibly those who present within 1 hour of ingestion) may benefit from decontamination, there is currently no evidence for clinical benefit (American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists) (Karalliedde *et al*., 2004). Furthermore, gastric lavage can be dangerous when it is performed without intubation in patients at risk of seizures or rapid loss of consciousness, or in patients who do not consent to the procedure (American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists 1997) (Karalliedde *et al*., 2004). The lack of good evidence for the management of poisoned patients, and the consequent conflicting recommendations of many textbooks (Eddleston *et al*., 2004), do not help the situation. There are also probably too few doctors and nursing staff to adequately care for patients and increasing the doctor to patient ratio may lead to better care.

However, there may also be opportunities for improved care using existing resources. The development of national, regional and/or institutional guidelines for early diagnosis of pesticide poisoning and appropriate use of antidotes may be helpful. More attention to the problem during undergraduate medical training is also warranted given the importance of the problem in Indian and other Asian hospitals. A better understanding of the pathophysiology of pesticides might stop doctors using inappropriate antidotes. There may also be considerable benefit from the development of postgraduate training programmes in clinical toxicology. This would potentially provide the clinical leadership and high-level expertise necessary to aid in the development of guidelines and to promote the training of junior doctors throughout the Asia-Pacific region. More clinical research on the natural history of pesticide poisoning and the effectiveness of antidotes should also help guide therapy (Buckley *et al*., 2004; Karalliedde *et al*., 2004)

Conclusion

OP insecticide poisoning is a serious condition that needs rapid diagnosis and treatment. Since respiratory failure is the major reason for mortality, careful monitoring, appropriate management may decrease the mortality rate. The limited resources in government hospitals in terms of trained doctors, nurses, support personnel, laboratory facilities and finance, may be partially responsible for the high number of deaths. Improving the availability of antidotes is an important factor that could improve outcomes. At the same time, discussions should be opened with the state Agricultural Ministry concerned for targeted bans of pesticides. Finally, we believe a prospective study is required to more accurately identify the total number of deaths and cases in the district and in the state of Andhra Pradesh, India. Such a study could be used to assess the impact of instituting the simple measures we have outlined above on the mortality and morbidity from pesticide poisoning.

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