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Is there a relationship between the WHO hazard classification of organophosphate pesticide and outcomes in suicidal human poisoning with commercial organophosphate formulations?

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A B S T R A C T

The WHO classification of pesticides by hazard is based primarily on the acute oral and dermal toxicity to rats. In several Asian countries there is no legislation against the sale of Class I insecticides. We evaluated if there was an association between the WHO hazard Class I, II or III organophosphate compound and outcomes in human poisoning. Two-hundred and fifty-one patients with mean (SD) age of 30.4 (11.8) years, admitted with symptomatic poisoning and treated with atropine and supportive care, were followed up until death or hospital discharge. The admission pseudocholinesterase level of 818.8 (1368) IU/L indicated significant suppression of cholinesterase activity. Class I compounds were ingested by 126, Class II by 113 and Class III by 12 patients. The hospital mortality rate was 16.7%, 5.3% and 0% with Class I, II and III organophosphate compounds, respectively ($P = 0.01$). Ventilatory requirements were higher with Class I compared with Class II poisoning (77.0% vs. 54.9%, $P < 0.001$). Patients with Class I poisoning needed mechanical ventilation for a longer period (10.55 (7.4) vs. 7.0 (5.2) days, $P = 0.002$). The linear relationship between the WHO hazard class and mortality in acute organophosphate poisoning mandates the restriction of the sale of organophosphate compounds associated with higher lethality amongst humans.

1. Introduction

Organophosphate poisoning continues to be a major health problem in developing countries (Jeyaratnam, 1990). In several Asian countries where the sale of the highly toxic insecticides is not restricted, case-fatality is high with accidental and deliberate organophosphate exposure (Peter and John, 2008). Countries such as Sri Lanka that have banned the sale of the extremely hazardous and highly hazardous pesticides (Class I) have demonstrated a reduction in case-fatality over time (Gunnell et al., 2007). The classification of pesticides, initiated by the WHO in 1973 and periodically updated, was an endeavor to develop a tentative classification of pesticides that would distinguish between the more and the less hazardous forms of each pesticide (World Health Organisation, 2004). This classification is based primarily on the acute oral and dermal toxicity of solid or liquid formulations of compounds on the rat and takes into account the LD_{50} in rats (World Health Organisation, 2004). This classification also takes into consideration the toxicity of the technical compound as well as the formulation, making allowance for the lesser hazards from solids as compared with liquids (World Health Organisation, 2004). It is not clear if suicidal or accidental ingestion of commercial formulations of organophosphates, belonging to the different WHO hazard classes sold in the markets, bear a similar linear relationship to outcomes. A comprehensive study of this aspect in human poisoning has been limited by the restriction of sale of the more hazardous compounds in several parts of the world as well as the lack of systematic evaluation of human poisoning in countries where such pesticides are still readily available. Although a recent study set out to assess if the WHO classification system accurately predicted toxicity in humans (Eddleston et al., 2005), this was limited to the evaluation of only three WHO Class II compounds. In India, where organophosphates of all three WHO hazard classes are used by the farming community, suicide deaths due to ingestion of insecticides have reached alarming epidemic proportions (Sainath, 2007). This study was thus undertaken to evaluate if there was any relationship between the WHO class of organophosphate compound and outcomes in human poisoning in a tertiary care university hospital in India.

2. Methods

This study was a non-concurrent prospective study of organophosphate poisoned patients admitted to a tertiary care university

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teaching hospital in India between 2002 and 2007. The study was approved by the Institutional Research Board. Organophosphate poisoned patients were identified in a systematic manner. An electronically generated list of all in-patients coded as organophosphate or insecticide or pesticide poisoning was obtained from medical records. In addition, a manual search of the medical intensive care unit (ICU) register was performed and patients admitted as organophosphate poisoning were recorded. A total of 732 admissions were identified by electronic and hand search. Of these 420 in-patient charts could be retrieved for detailed assessment.

All patients over 15 years, admitted with symptomatic organophosphate poisoning and evidence of cholinesterase suppression were evaluated. Patients with ingestional poisoning were included; inhalational and skin exposures were excluded. In symptomatic patients without initial cholinesterase suppression, patients were included if a repeat cholinesterase level showed suppression. Patients with mixed overdose were excluded. Twenty-four patients were excluded. In 145 patients diagnosed as organophosphate poisoning, although patients manifested cholinergic symptoms and signs and cholinesterase suppression, the compound was not identified. The study cohort thus comprised of 251 patients in whom the compound was identified; identification based on the container brought by patients' relatives during hospitalization.

Patients were treated with atropine and supportive care including mechanical ventilation if required. Atropinisation was achieved with bolus doses targeting clear lung fields, heart rate of 110/min on Day 1 (100/min on Day 2 and 80–100/min on subsequent days) and a systolic blood pressure of >90 mm Hg. Once atropinisation was achieved, infusion was titrated to maintain the above targets. Oximes were not given as benefit has not been demonstrated with oximes in our setting of organophosphate poisoning (Peter et al., 2007). Patients requiring intubation and mechanical ventilation were usually managed in the ICU. If patient developed intermediate syndrome and/or required prolonged ventilatory support or failed extubation, a tracheostomy was performed. Intercurrent infections and complications of ventilation were treated as per standard protocols.

Patients were categorized, based on the WHO classification of pesticides by Hazard and Guidelines to Classification 2004, as Class I, II or III (World Health Organisation, 2004). Class I comprised of extremely and highly hazardous compounds, Class II of moderately hazardous compounds and Class III of slightly hazardous compounds (World Health Organisation, 2004).

The primary outcome measure was mortality. Secondary outcomes were need for ventilatory support and duration of mechanical ventilation. Discrete variables such as mortality and need for ventilation were analysed using the Fisher's exact test whilst continuous variables such as duration of ventilation were analysed using the student *t*-test. A *P*-value of <0.05 was considered significant.

3. Results

The mean (±SD) age was 30.4 ± 11.8 years with a male preponderance (181:70). There was a significant lag time to presentation to hospital (10.04 ± 15.3 h). About one-third of patients received atropine therapy outside whilst 10% received oximes. The mean APACHE II score was 15.8 ± 8.8. WHO Class I organophosphate compounds were ingested by 126 patients (50.2%), Class II by 113 patients (45.0%) and Class III by 13 patients (4.8%). The mean admission pseudocholinesterase level of 818.8 ± 1368 (reference range 3000–8000 IU/L) suggested significant suppression of pseudocholinesterase activity. Admission Glasgow coma score (GCS) was 11.24 ± 4.7.

Atropine requirements were high in the first 24 h (74.3 ± 109.1 mg). Invasive mechanical ventilatory support was needed by 169 (67.3%) patients for 9.3 ± 7.5 days. Tracheostomy was performed in 81 (32.3%) patients. The hospital length of stay was 12.1 ± 10.3 days. In-hospital mortality for the entire cohort was 10.8% (Table 1).

When outcomes were categorized by the WHO class (Table 2), mortality (Fig. 1) was found to be significantly higher (16.7%) with Class I compounds as compared with Class II (5.3%) and Class III (0%) compounds ($P = 0.01$, Fisher's exact). The need for mechanical ventilation was also significantly ($P < 0.001$) higher with Class I compared with Class II poisoning (Table 2). Despite the good outcome in Class III poisoning, it was surprising that 91% needed mechanical ventilation for 11.2 ± 14.9 days. The duration of ventilation was significantly ($P = 0.002$) lower with Class I poisoning compared with Class II poisoning.

Data on the individual compounds is presented in Table 2. Monocrotophos poisoning was associated with the highest lethality (23.8%) and need for mechanical ventilation (87.3%). Despite phosphamidon being a Class I compound, all 17 patients survived to hospital discharge, although a similar proportion of patients needed intubation when compared with other compounds of the same class. Mortality was about 5% with quinalphos, chlorpyriphos and dimethoate poisoning (Class II).

4. Discussion

This study demonstrates for the first time a linear relationship between the WHO hazard class and mortality in human organophosphate poisoning. These findings have public health implications given that several countries do not have any legislation banning the sale of the more hazardous Class I compounds. It is also likely that within a particular WHO class, the toxicity profile might be different. Although this was not formally assessed, there was evidence that monocrotophos had the highest lethality amongst Class I compounds followed by methyl parathion. It was also observed that phosphamidon, a Class Ia compound, was not associated with mortality in our cohort. A study from Sri Lanka (Eddleston et al., 2005), evaluating three Class II compounds found that dimethoate had the highest case-fatality (23.1%) followed by fenthion (16.2%) and chlorpyriphos (8.0%). The mortality with dimethoate and chlorpyriphos poisoning were similar in our cohort (4.8% vs. 5.3%). The two major differences between the studies were the absence of Class I and Class III compounds and the use of oximes in the Sri Lankan cohort. Some difference in mortality between chlorpyriphos and dimethoate in the Sri Lankan cohort may also be attributed to the lack of re-activation of acetyl-cholinesterase by oximes for dimethoate and fenthion (Eddleston et al., 2005).

In India, insecticide containers are colour coded to indicate toxicity. Red indicates most toxic, blue least toxic and yellow intermediate toxicity. It was interesting to note that monocrotophos was coded red along with other Class Ia compounds; paralleling our evidence that it is an extremely hazardous compound. This was also the impression of the shopkeeper with whom we interacted. The other Class Ib compounds were coded yellow along with the Class II compounds and had outcomes similar to Class II compounds. Whilst colour coding may alert the farmer to the level of

Table 1
Overall outcome data.

Outcome parameter	Result
Atropine requirements, 1st 24 h, mg (SD)	74.28 (109.1)
Total atropine requirements, mg (SD)	183.6 (319.8)
Number (%) requiring ventilatory support	169 (67.3)
Duration of ventilatory support, mean (SD) days	9.3 (7.5)
Time to onset of ventilation, mean (SD) days	1.2 (0.4)
Need for tracheostomy, *n* (%)	81 (32.3)
ICU length of stay[a], mean (SD) days	8.5 (7.1)
Duration of hospital stay, mean (SD) days	12.1 (10.3)
Hospital mortality, died (%)	27 (10.8)

ICU, intensive care unit.
[a] Duration of ICU stay for the 176 patients who required intensive care.

Table 2
Outcome data based on WHO hazard classification of pesticides.

Class and name of pesticide	Number of patients	Number (%) died	Number (%) ventilated	Mean (SD) duration of ventilation
CLASS I	126	21 (16.7)	97 (77.0)	10.6 (7.4)
Class I a	50	5 (10)	37 (74)	9.2 (6.9)
Methyl parathion	21	4 (19.1)	15 (71.4)	10.2 (6.9)
Phosphamidon	17	0 (0)	13 (76.5)	11.5 (7.7)
Phorate	12	1 (8.3)	9 (75)	4.2 (2.5)
Class I b	76	16 (21.1)	60 (78.9)	11.4 (7.6)
Monocrotophos	63	15 (23.8)	55 (87.3)	11.41 (7.7)
Triazophos	10	1 (10)	4 (40)	12.5 (8.3)
Dichlorvos	2	0 (0)	0 (0)	NA
Oxydemeton-methyl	1	0 (0)	1 (100)	5
CLASS II	113	6 (5.3)	62 (54.9)	6.9 (5.2)
Quinalphos	46	2 (4.3)	29 (63.0)	5.8 (4.5)
Chlorpyriphos	38	2 (5.3)	17 (44.7)	6.9 (5.2)
Dimethoate	21	1 (4.8)	10 (47.6)	7.8 (4.9)
Fenthion	4	0 (0)	4 (100)	14 (6.9)
Profenophos	2	0 (0)	1 (50)	11
Phenthoate	1	0 (0)	0 (0)	NA
Ethion	1	1 (100)	1 (100)	3
Class III	12	0 (0)	10 (83.3)	11.2 (14.9)
Malathion	11	0 (0)	10 (90.9)	11.2 (14.9)
Acephate	1	0 (0)	0 (0)	0 (0)

SD, standard deviation.

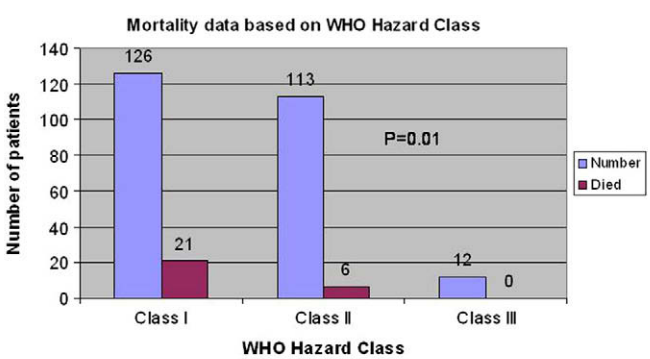

Fig. 1. Organophosphate poisoning mortality data categorized by the WHO hazard class.

toxicity in accidental exposure, it may facilitate the use of a more toxic compound in the setting of suicide.

Some limitations merit mention. We were unable to retrieve all charts for detailed audit, albeit the mortality figures of this cohort is similar to an earlier published cohort (Sudarsanam et al., 2006). Although red cell cholinesterase levels more accurately reflect the severity of intoxication, we only measured pseudocholinesterase levels as an indicator of suppression of cholinesterase activity. However all patients included in the study had significant clinical manifestations of organophosphate poisoning. It is logical that the lethality of a pesticide would not only depend on the hazard class but also the volume and concentration of compound ingested, the nature of the poison (direct or indirect acting) as well as the toxicity of the solvents. The commercially available organophosphate formulations (Table 3) are mixed with organic-based solvents (denoted as EC) or are water-based liquid suspensions (denoted SL). The animal data represents toxicity of pure organophosphate compounds in the solid or liquid state and is thus different to human poisoning data where the ingestion is of the compound along with the

Table 3
Pesticides in human poisoning and the calculated poison load.

Name of compound	WHO class	Physical state of compound	LD_{50} in rats mg/kg	Commercially available formulation in India	Number ingested volume available	Average volume ingested ml (SD)	Mortality in our cohort	Approximate amount ingested in mg/kg[b]
Methyl parathion	I a	Liquid	13	Dhanuka 50% EC	13	98 (71)	4/21 (19.1%)	980
Phosphamidon	I a	Liquid	7	Kindon Plus 40% SL	14	90 (69)	0/17 (0%)	720
Phorate	I a	Liquid	2	Umet 10% CG	4	64 (53)	1/12 (8.3%)	128
Monocrotophos	I b	Solid	14	Monocrown 36% CL	47	75 (42)	15/63 (23.8%)	540
Triazophos	I b	Liquid	82	Josh 40% EC	7	76 (51)	1/10 (10%)	608
Dichlorvos	I b	Liquid	56	Doom 76% EC	1	5	0/2 (0%)	76
Oxydemeton-methyl	I b	Liquid	65	Metasystox 25% EC	1	50	0/1 (0%)	250
Quinalphos	II	Solid	62	Ecolux 25% EC	29	115 (96)	2/46 (4.3%)	575
Chlorpyriphos	II	Solid	>3000	Force 20% EC	23	64 (54)	2/38 (5.3%)	256
Dimethoate	II	Solid	c150[a]	Rogor 50% EC	14	62 (37)	1/21 (4.8%)	620
Fenthion	II	Liquid	D586[a]	Prostar 82.5%	3	75 (43)	0/4 (0%)	1238
Profenophos	II	Liquid	358	Curacron 50% EC	1	50	0/2 (0%)	500
Phenthoate	II	Liquid	c400[a]	Aimsan 50% EC	NA	NA	0/1 (0%)	NA
Ethion	II	Liquid	208	Fosmite 50% EC	1	100	1/1 (100%)	1000
Malathion	III	Liquid	c2100[a]	Milthion 50% EC	7	100 (74)	0/11 (0%)	1000
Acephate	III	Solid	945	Asataf 75% SP	NA	NA	0/1 (0%)	NA

[a] "c" preceding the value indicates that it is a value within a wider than usual range, "D" indicates dermal LD_{50}, NA, data not available.
[b] Assuming that the average ingestion was 80 ml and the patient's average weight was 50 kg. This takes into assumption that the actual compound is taken without diluting it and that the concentrations depicted are as weight/volume.

solvent. This needs to be taken into consideration whilst comparing human data with animal data. The mean volume of pesticide ingested, noted in 165 patients, was 82.6 ± 65.2 ml. The volume of pesticide ingested was similar in the three WHO classes (Class I: 80 ± 53 ml, Class II: 85 ± 77; Class III: 93 ± 76). Although we attempted to determine the poison load for each of the compounds implicated in our cohort of patients (Table 3), this was limited by the fact that ingested volumes as stated by the relative or the patient is often inaccurate. The LD_{25} for humans, assuming a mean volume of ingestion of 80 ml and an average body weight of 50 kg, was calculated to be 540 mg/kg for monocrotophos, the compound with the highest mortality and the LD_{20} for methyl parathion was 980 mg/kg. The LD_5 for the class II compounds quinalphos, chlorpyriphos and dimethoate ranged from 250 to 620 mg/kg (Table 3). However these LD_x should be interpreted with caution given the limitations discussed above. Long term sequelae such as delayed organophosphate neurotoxicity were not assessed in the study.

5. Conclusions

This study demonstrates a linear relationship between the WHO class and outcomes in human organophosphate poisoning. Monocrotophos was associated with the highest case-fatality. These results mandate the urgent need for legislation to ban Class I compounds in countries where they are still sold.

Conflict of interest statement

There is no conflict of interest for any of the authors.

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Author's contributions

John Victor Peter was involved with the conception, study design, literature review, statistical analysis and write-up of the paper.

Jeyakumar Jerobin, Anupama Nair and Anjana Bennett collected data and helped with literature review and write-up of the paper.

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References

Eddleston, M., Eyer, P., Worek, F., Mohamed, F., Senarathna, L., von Meyer, L., Juszczak, E., Hittarage, A., Azhar, S., Dissanayake, W., Sheriff, M.H., Szinicz, L., Dawson, A.H., Buckley, N.A., 2005. Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. Lancet 366, 1452–1459.

Gunnell, D., Fernando, R., Hewagoma, M., Priyangika, W.D.D., Konradsen, F., Eddleston, M., 2007. The impact of pesticide regulation on suicide in Sri Lanka. Int. J. Epidemiol. 36, 1235–1242.

Jeyaratnam, J., 1990. Acute pesticide poisoning: a major global health problem. World Health Stat. Q. 43, 139–144.

Peter, J.V., John, G., 2008. Management of acute organophosphorus pesticide poisoning. Lancet 371, 2170.

Peter, J.V., Moran, J.L., Graham, P.L., 2007. Advances in the management of organophosphate poisoning. Expert Opin. Pharmacother. 8, 1451–1464.

Sainath, P., 2007. Farm Suicides Rising, Most Intense in 4 States. Available from; <http://www.hinduonnet.com/2007/11/12/stories/2007111253911100.htm>.

Sudarsanam, T.D., Pichaimuthu, K., Zachariah, A., John, G., 2006. Oximes in acute organophosphate poisoning. Crit. Care Med. 34, 2265.

World Health Organisation, 2004. WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2004. WHO, Geneva, ISBN 92 4 154663 8.