Differences between organophosphates in respiratory failure and lethality with poisoning post the 2011 bans in Sri Lanka

Abstract

Introduction

Self-poisoning with organophosphorus pesticides (OPs) has high morbidity and mortality. The most toxic OP formulations have been progressively banned in Sri Lanka over the past three decades. However, respiratory failure (RF) requiring ventilation remains a major contributor to fatalities. Therefore, this study was conducted to examine the frequency of RF and death after poisoning with the currently available OPs to determine if further bans might be warranted to reduce the burden of OP poisoning in Sri Lanka.

Methods

Five hundred and forty patients with confirmed OP self-poisoning were prospectively observed throughout their hospital stay following admission to Peradeniya hospital in the Central Province of Sri Lanka. Clinical data including the time and duration of intubation were documented prospectively in structured datasheets.

Results

One hundred and forty-nine patients required ventilation (27%), and 34 (23%) of those died. Males with alcohol co-ingestion were more likely to develop RF. Compared to other OPs, profenofos (Odds Ratio [OR] =2.5, 95% CI: 1.5-3.9), and quinalphos (OR= 4.5, 95% CI: 1.6-12.6) were more likely to, and chlorpyrifos (OR= 0.2, 95% CI: 0.1-0.4) less likely to lead to RF than other OPs. Profenofos was also associated with higher mortality (OR= 2.3, 95% CI: 1.1-4.6)

than other OPs. The median time to intubation was longer for profenofos, but the duration of intubation was similar for all OP formulations.

Conclusion

RF and deaths following OP ingestion continues to be a major problem in Sri Lanka, with profenofos being the major current agent of concern. Strategies to replace profenofos and quinalphos use with less toxic insecticides should be explored. Doctors should be alert to the high probability of delayed and prolonged RF after profenofos poisoning.

Key words

Organophosphorus pesticides

Profenofos

Quinalphos

Chlorpyrifos

Respiratory failure

Introduction

Self-poisoning using organophosphorus pesticides (OP) is a common clinical problem in many developing countries [1, 2, 3, 4]. These poisonings are commonly fatal and also have high morbidity, with prolonged ventilation needed for many patients [1, 2, 3, 5, 6, 7]. Initial attempts to address this problem relied heavily on the WHO classification of extremely/highly hazardous (Class I) OP, which in turn was largely based on rat lethal doses (LD50). In Sri Lanka in the 1980s there was an epidemic of poisoning with highly hazardous OP such as monocrotophos, methamidophos and methylparathion. All these Class I agents were banned in late 1990s and case fatality declined sharply [8, 9, 10]. Other Class II (moderately hazardous based on LD50) OP replaced these in Sri Lanka. However, fatal poisoning and respiratory failure (RF) remained common with a 10% case-fatality and 24% requiring ventilation post these initial bans [11, 12]. As better human toxicity data became available, the Pesticide Technical and Advisory Committee of Sri Lanka, implemented progressive bans on several Class II OP. Dimethoate and fenthion were phased out between the years 2008-2011 due to their high human toxicity [13, 14]. From 2011 onwards chlorpyrifos, profenofos and diazinon were increasingly used. In 2014, chlorpyrifos was also banned due to concerns over chronic toxicity. Since then profenofos, an S-alkyl compound, has acquired a large share of the OP market [15]. Along with these regulatory changes, the pattern of OP poisonings have changed, but no studies have examined how those changes have altered the risk of major complications from acute OP poisoning. Therefore, we conducted this prospective cohort study to describe the RF and case-fatality of the OPs that were in use from 2013-2016 in Sri Lanka.

Methods

Design and Setting

We studied a prospective cohort of acute OP self-poisoned patients from the Teaching Hospital Peradeniya in the Central Province of Sri Lanka. This is a tertiary care referral centre equipped with a specialized Toxicology Department and an ICU for the management of pesticide-poisoned patients. The in-ward toxicology ICU consists of four beds and specialized and trained nurses [16]. When the four ICU beds were occupied, subsequent patients were transferred to the main ICU of the hospital. Ethical clearance for this study was granted by the Human Research Ethics Committee, of Faculty of Medicine University of Peradeniya, Sri Lanka (2012/EC/63). Written informed consent was obtained from the patient or, in the instances where the patient was not clinically fit to do so, from the next of kin.

Data Collection

The current paper is based on data from patients with a history of OP self-poisoning recruited prospectively from 1st of March 2013 to 30th of September 2016. The OP formulation ingested was identified based on the patient's or relative's history, the bottles brought to the hospital, the transfer documents or accompanying doctor's comments, or by analysing blood samples collected on admission to hospital or by combination of the above criteria.

All patients were examined on admission for cholinergic features and vital parameters, and were treated based on a standard protocol [17]. After frequent assessments in the initial period, all patients were seen by the doctors of the medical unit at least twice daily in the routine ward rounds. In addition, the study doctors assessed the patients at least every three hours, and recorded the findings in a structured data sheet. Red blood cell acetylcholinesterase (RBC-

AChE) inhibition was measured using the Test-Mate ChE (EQM Research, Inc., Cincinnati, OH), a validated bedside method [18]. Blood samples were obtained from 385/540 patients for the identification/confirmation of the OP formulation/s they have ingested. Samples confirmed the history of the substance ingested in 87% (20/23) of samples collected within 6 hours, 84% (67/80) of samples collected within 24 hours and 113/221 overall. Further 74 agents that were from 164 patients whose history had placed them in the 'unknown OP' category were also identified. No patients were found to have ingested mixed OP formulations.

Decisions to intubate and transfer the patients into the ICU were made by the medical team, based on the clinical condition of the patient, and independent of the researchers. We considered RF to be present only if a patient was intubated and mechanical ventilation was commenced.

Data analysis

The primary data analysis was done using PRISM, version 5 (Graph Pad Software, Inc., La Jolla, CA). Continuous variables are reported as medians and inter-quartile ranges (IQR). Comparisons of continuous variables between patients with and without RF were done using the Mann Whitney U test. Odds ratios (OR) for RF and deaths for specific OPs were calculated by comparing the odds of that OP versus the odds in all other confirmed OPs combined. Odds in unknown OP were compared against the odds in all confirmed OPs. Time for the first intubation from ingestion and duration of intubation in groups of patients who had ingested different types of OPs were compared using Kruskal-Wallis test and post hoc pair-wise comparison was done using Dunn's test.

Results

From 1st of March 2013 to 30th of September 2016, 540 patients were admitted to the Toxicology Unit with OP self-poisoning. The OP compound ingested by 369 patients was identified: 138 had ingested profenofos, 106 chlorpyrifos, 48 diazinon, 37 phenthoate, 16 quinalphos, 6 azinphos methyl, 4 malathion, 4 dimethoate, 4 methamidophos, 2 monocrotophos, 2 tetrachlorvinphos, 1 carbophenothion, and 1 acephate. The other patients were categorized as 'unknown OP' (n=171) based on clinical features and persistent depression of RBC-AChE.

Intubation and ventilation were required in 149 (27%) patients overall, and 29% (106/369) of confirmed OPs. Direct admissions and referred patients had similar rates of RF (direct: 20% and transfers: 28% respectively). Thirty-four of the 46 deaths occurred in patients with RF.

The majority (130/149; 87%) of patients who required ventilation were intubated within the first 24 hours following ingestion. The median time to intubation in this group was 3.5 hours (IQR: 2-8.1), and 32 (25%) of these patients died. Fifteen of these patients (11%) were extubated within 48 hours of intubation. Nineteen (13%) patients required ventilation after 24 hours since ingestion (median time to intubation: 32 hours, IQR: 25-58) and 2 of them (11%) died. The duration of intubation was similar for patients intubated before and after 24 hours of ingestion (Early intubation group: 130 hours, IQR: 64-250 vs. Late intubation group: 168 hours, IQR: 45-223, p=0.97).

Patients who developed RF were significantly older than those who did not develop RF (mean age 42.3 (SD 16.9) vs 36.8 (SD 15.5), p=0.0006). Males (OR=1.75, 95% CI: 1.0-2.9,

p=0.030) and those who co-ingested alcohol (OR=2.87, 95% CI: 1.8-4.5, p<0.0001) were more likely to develop RF (Table 1).

The case fatality among identified and confirmed OPs was 9% (34/369). RF and mortality associated with each OP formulation are summarized in table 2. Median duration of ventilation in patients who died was 150 hours (IQR: 51-210), and 10 were ventilated for more than 200 hours. Profenofos (OR= 2.5, 95% CI: 1.5-3.9) and quinalphos (OR= 4.5, 95% CI: 1.6-12.6) ingestions were significantly more likely to be complicated by RF, and profenofos ingestion was significantly more likely to be fatal (OR=2.3, 95%CI: 1.1-4.6). In contrast, chlorpyrifos ingestion was less likely to lead to RF (OR= 0.2, 95%CI: 0.1-0.4) or death (OR=0.5, 95%CI: 0.2-1.2). Given that profenofos has been the main OP that replaced chlorpyrifos since the latter was banned in 2014 in Sri Lanka (in the middle of the recruitment period of the study), we directly compared the frequency of complications of the two formulations. Most chlorpyrifos ingestions (66/106-62%), but very few profenofos ingestions (11/138-8%) were admitted before 2014. Compared to chlorpyrifos, profenofos was 5.9 times more likely to be associated with RF (OR= 5.9, 95% CI: 2.9-12.0, p <0.0001) and 2.6 times more likely to be fatal (OR= 2.6, 95% CI: 1.0-6.9, p=0.05).

The cumulative fraction of RF for each OP formulation against post-ingestion time is shown in Figure 1. The time to event curves show a contrast between chlorpyrifos and profenofos. Most chlorpyrifos induced RF occurred within a few hours of exposure, whereas profenofos caused RF over the first 24 hours or so.

The time from ingestion to intubation (p=0.037) was longer for profenofos compared to other known OPs (Figure 2a) but the duration of intubation (p=0.99) (Figure 2b) was similar for all known OPs.

Discussion

Despite the banning of many highly toxic OP compounds in the recent past in Sri Lanka, our study found 29% of patients who ingested confirmed OPs required intubation and mechanical ventilation for RF. This is slightly greater than the 24% reported by Eddleston et al in 2006, noting that study was in a different tertiary care setting without a specialized clinical toxicology service [11]. We provide new data on the risks with several OP that have come to dominate pesticide poisoning in Sri Lanka in the last decade. We had the unique opportunity to study both chlorpyrifos and profenofos poisonings prospectively as our study commenced before chlorpyrifos was banned in 2014.

The persistent high rates of RF that we observed could be contributed by selective transfer of more severely poisoned patients to our specialized toxicology ward. However, RF among directly admitted patients in our study sample was still around 20%. This is probably a more accurate estimate of the current overall rate of RF in acute OP poisoning in Sri Lanka.

In our study, patients affected by RF were more likely to be male, older, and intoxicated with alcohol. Advancing age has previously been associated with worse outcomes [19] as has male sex [20, 21], and alcohol co-ingestion [21]. Alcohol intoxication may contribute to ingestion of larger amounts of poison [21, 22].

The pathophysiology of early RF is generally attributed to depression of the central respiratory drive, and muscarinic effects such as bronchospasm and bronchorrhoea. The pathophysiology of late RF is generally attributed to nicotinic receptor overstimulation and subsequent dysfunction in the neuromuscular junction of the respiratory muscles [11, 23, 24, 25]. In contrast to the previous Sri Lankan studies, we observed that these two entities were generally occurring in the same patients. The duration of intubation in the early RF group was similar to that in the late group, and much longer than early RF observed in previous studies [11]. This suggests that many patients with early intubation then develop the later failure in neuromuscular junctional transmission. We have recently demonstrated ongoing abnormalities in neurophysiological studies during this time with profenofos [26]. These are linked to prolonged RF and ventilation, long after the muscarinic effects have subsided [11, 24, 26, 27].

Profenofos is now the most common OP ingested, and causes RF and death more frequently than most other OPs, with rates similar to those of banned OPs such as fenthion [11, 28]. Profenofos is an S-alkyl organophosphorus compound which is widely available in Sri Lanka, formulated as a 500g/L emulsified concentrate (50%EC). It is a WHO class II 'moderately toxic' compound, but it is highly lipophilic resulting in slow elimination. This might explain the relatively delayed but prolonged requirement for ventilation. The adverse data on quinalphos were limited in our study, but previous studies have also highlighted increased risks with quinalphos poisoning [29] . In contrast, we confirmed relatively lower risks of RF from chlorpyrifos (48%EC) noted previously [11, 29].

Compared to the respiratory failure study from 2002-5 [11], our 2013-5 study shows a lower case fatality and risk of death following RF, but a much higher proportion of early (vs late) respiratory failure, with a much longer duration of ventilation for these early RF (Table 3). This

prolonged intubation is largely attributable to profenofos poisonings (Figure 2). Such prolonged intubation significantly increases morbidity and resources required to prevent death [2, 11]. The attributed mode of death in most patients was simply cardio-pulmonary failure. However, death in those with very prolonged intubation was generally attributed to aspiration pneumonia, and one patient died of a haemorrhagic stroke. Medical teams managing patients with pesticide poisoning need to be prepared to manage frequent prolonged RF with profenofos poisoning [26]. Further clinical and neurophysiological studies on predictors of prolonged RF, and predictors of successful extubation might aid in the management of these patients [30] .

Conclusions

Respiratory failure following OP ingestion persists as a problem in Sri Lanka, around one in four patients requiring prolonged ventilation. Profenofos is the current major concern being the highest OP being sold to the public in the Sri Lanka. It is now the most commonly ingested OP, and carries a significantly higher risk of RF and mortality. This more dangerous compound largely replaced chlorpyrifos following the recent ban. The pesticide regulators should consider whether further or different actions are now indicated.

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Disclosure statement

The authors have no conflicts of interest to disclose.

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Tables

Table 1: Sample characteristics

	Patients without respiratory failure (n=391)	Patients with respiratory failure (n=149)	All patients (n=540)
Median age in years (IQR)	35 (23-47)	42 (27-54)	37 (25-49)
Male	247 (63%)	127 (85%)	374 (69%)
Transfer from other hospitals	343 (88%)	138 (92%)	481 (89%)
Co-ingestion of alcohol*	112	60	172

*alcohol status was not known in all the patients, but the known numbers are given in the table

Table 2: Respiratory failure and mortality associated with different organophosphates.

	Chlorpyrifos	Profenofos	Diazinon	Phenthoate	Quinalphos	Malathion	Dimethoate	Unknown
Number	106	138	48	37	16	4	4	171
Respiratory failure (%)	11(10%)	56(41%)	11(23%)	13(35%)	10(66.7%)	2(50%)	2(50%)	43(25%)
OR (95% CI)	**0.2(0.1-0.4)***	**2.5(1.5-3.9)***	0.7(0.3-1.4)	1.4(0.7-2.9)	**4.5(1.6-12.6)***	0.8(0.08-8.0)	2.5(0.3-18.0)	1.2(0.8-1.8)
Median (IQR) time to intubate in hours	3(2.2-7)	6.7(3.5-13.3)	3(2-4.5)	3.2(1.6-7.0)	2.7(1.3-5.6)			3.7(1.5-15.1)
Median(IQR) duration of intubation in hours	142 (76-288)	141 (58-250)	92(67-252)	130 (96-204)	145(47-295)			154(63-241)
Deaths (%)	6(6%)	19(14%)	3(6.1%)	4(11%)	0%	1(25%)	2(50%)	12(7%)
OR (95% CI)	0.5(0.2-1.2)	**2.3(1.1-4.6)****	0.5(0.2-2.1)	1.2(0.4-3.6)		3.3(0.3-33.2)	**10.4(1.4-76.4)****	1.3(0.6-2.6)

Note: Bold indicates statistically significant association.* $p<0.01$, **$p<0.05$

Table 3: Comparison of the outcomes in the 2006 RF study [11] and our findings.

Outcome	2002 - 2005[11]	2013 – 2016 (this study)
Case fatality following known OP poisoning (%)	12% (46/376)	9% (34/369)
People developing RF following known OP poisoning (%)	24% (90/376)	29% (106/369)
Fatal outcome after RF (%)	51% (46/90)	31% (46/149)
Proportion of patients who required early intubation <24 hrs	58% (52/90)	87% (130/149)
Percentage of patients who required ventilation > 24 hrs	42% (38/90)	13% (19/149)
Duration of ventilation in those who developed RF before 24 hrs	Median 33hrs (Not reported)*	Median 130hrs (64-250)
Duration of ventilation in those who developed RF after 24 hrs	Median 219 hrs (154-276)	Median168hrs (45-223)
Case-fatality of chlorpyrifos poisoning	10% (21/216)	6%(6/106)

* P<0.0001 compared to late group

Figures

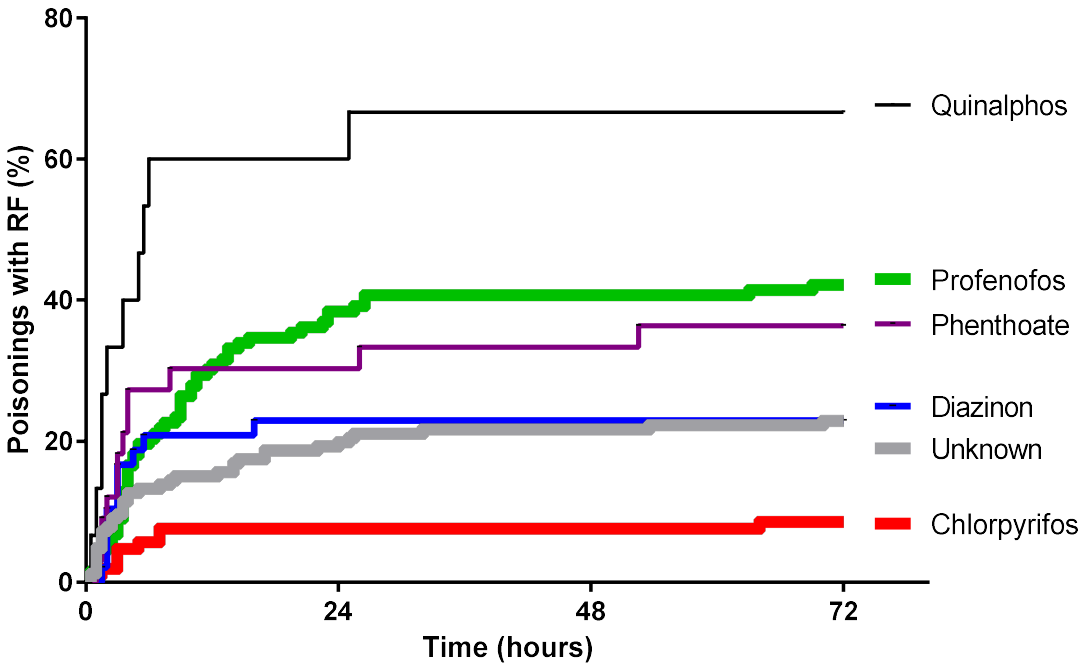

Figure 1: The cumulative proportion of patients who developed RF following ingestion of OPs. The thickness of the lines is proportional to the number of patients in each group.

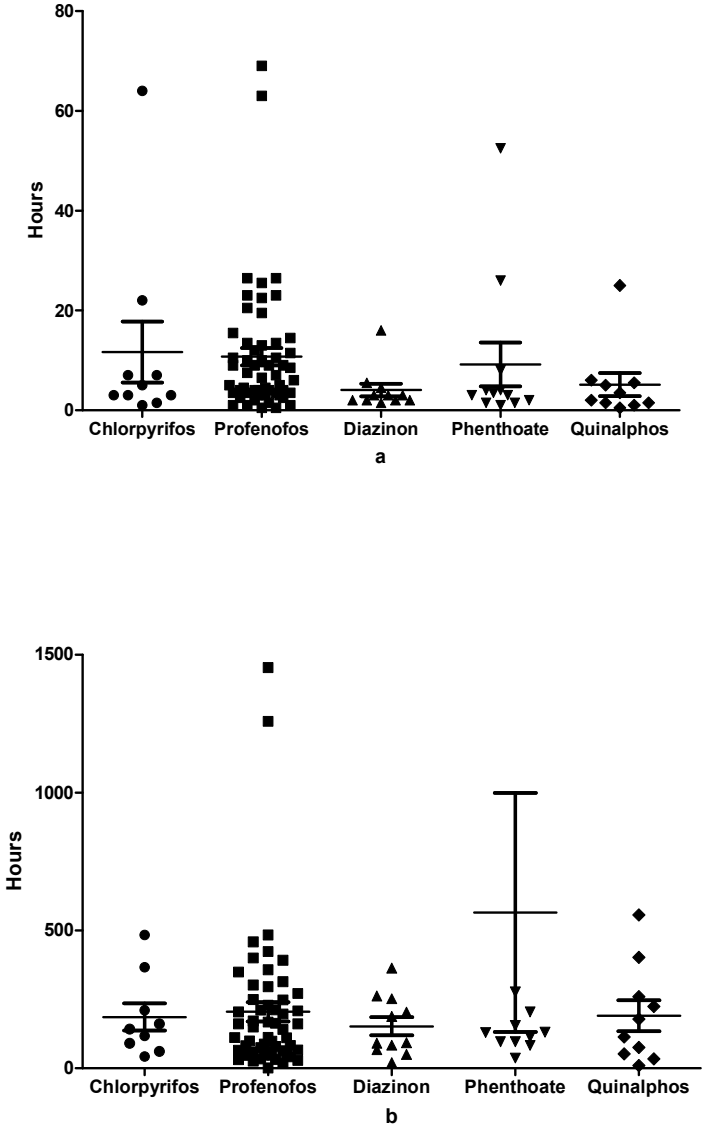

Figure 2: (a) Time from ingestion to first intubation and, (b) duration of intubation, for the five most common OPs.

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