Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study

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Summary

Background Although more than 100 organophosphorus insecticides exist, organophosphorus poisoning is usually regarded as a single entity, distinguished only by the compound's lethal dose in animals. We aimed to determine whether the three most common organophosphorus insecticides used for self-poisoning in Sri Lanka differ in the clinical features and severity of poisoning they cause.

Methods We prospectively studied 802 patients with chlorpyrifos, dimethoate, or fenthion self-poisoning admitted to three hospitals. Blood cholinesterase activity and insecticide concentration were measured to determine the compound and the patients' response to insecticide and therapy. We recorded clinical outcomes for each patient.

Findings Compared with chlorpyrifos (35 of 439, 8·0%), the proportion dying was significantly higher with dimethoate (61 of 264, 23·1%, odds ratio [OR] 3·5, 95% CI 2·2–5·4) or fenthion (16 of 99, 16·2%, OR 2·2, 1·2–4·2), as was the proportion requiring endotracheal intubation (66 of 439 for chlorpyrifos, 15·0%; 93 of 264 for dimethoate, 35·2%, OR 3·1, 2·1–4·4; 31 of 99 for fenthion, 31·3%, 2·6, 1·6–4·2). Dimethoate-poisoned patients died sooner than those ingesting other pesticides and often from hypotensive shock. Fenthion poisoning initially caused few symptoms but many patients subsequently required intubation. Acetylcholinesterase inhibited by fenthion or dimethoate responded poorly to pralidoxime treatment compared with chlorpyrifos-inhibited acetylcholinesterase.

Interpretation Organophosphorus insecticide poisoning is not a single entity, with substantial variability in clinical course, response to oximes, and outcome. Animal toxicity does not predict human toxicity since, although chlorpyrifos is generally the most toxic in rats, it is least toxic in people. Each organophosphorus insecticide should be considered as an individual poison and, consequently, patients might benefit from management protocols developed for particular organophosphorus insecticides.

Introduction

Organophosphorus insecticide self-poisoning is a major global health problem,[1,2] with hundreds of thousands of deaths each year.[3,4] Although most such deaths are in the developing world,[4] this poisoning is also an important cause of fatal self-poisoning in developed countries.[5] Organophosphorus insecticides inhibit acetylcholinesterase and butyrylcholinesterase enzymes resulting in overstimulation at cholinergic synapses.[6] Management of severe poisoning is difficult, requiring intensive care and use of atropine and oxime cholinesterase reactivators.[6,7] Management is complicated by the paucity of clinical trial evidence to guide treatment, with no clear evidence for benefit from any therapy other than oxygen, atropine, and diazepam.[8]

Although differences in human toxicity between organophosphorus insecticides were reported in 1977,[9] acute organophosphorus poisoning is regarded as a homogeneous entity in most textbooks and review or research articles. Specific treatment advice for particular organophosphorus insecticides is not supplied,[10] despite wide variation in animal toxicity, fat solubility, metabolism, selectivity for acetylcholinesterase over other serine esterases, side groups attached to the phosphate, and speed of ageing (loss of an alkyl side chain that prevents reactivation by oximes),[11] that might affect poisoning severity and response to treatment.[6,8,12] The system used most widely for differentiating organophosphorus insecticides is a WHO method based on toxic effects in rats after oral dosing.[13] This scheme was developed for occupational poisoning but has been used to ban pesticides that frequently cause death from self-poisoning[14] and to identify highly toxic pesticides.[10]

In this observational study, we aimed to determine whether the three most common organophosphorus insecticides used for self-poisoning in Sri Lanka differ in the clinical features and severity of poisoning they cause. Specifically, we aimed to compare the odds of death, intubation, and seizures, the mode of death, and the response to treatment in patients poisoned by chlorpyrifos, dimethoate, and fenthion. We also examined whether the WHO classification system accurately predicts toxicity in people.

Methods

Patients

Patients were identified at admission to three Sri Lankan hospitals as part of a cohort study of acute self-poisoning that started Mar 31, 2002, in Anuradhapura, June 4, 2002, in Polonnaruwa, and Nov 23, 2002, in Kurunegala. Patients were identified until Feb 19, 2003, in Kurunegala and May 25, 2004, in Anuradhapura and

Polonnaruwa. Patients were included in this study if they had a history of chlorpyrifos, dimethoate, or fenthion ingestion as indicated by the patient or relatives, the transferring doctor, or the pesticide bottle. Patients who ingested more than one organophosphorus insecticide or other poisons in addition to the insecticide (except for alcohol) were excluded from the study.

Patients remained under the care of the hospitals' consultant physicians who had primary responsibility for their management. Management protocols were agreed between the medical team and study team. Decisions about intubation and transfer of patients to intensive care were made by the medical team independently of study doctors. All decisions were based on the patient's clinical condition and not the particular organophosphorus insecticide ingested, as per usual hospital practice. Atropine was given according to a standard protocol.[15] Symptomatic patients received pralidoxime chloride (1 g bolus) followed by further bolus doses of 1 g every 6 h for 1–3 days. Once resuscitated, patients or their relatives were approached regarding recruitment to a randomised controlled trial of activated charcoal that was nested into the cohort; written informed consent was obtained from patients or relatives.

All patients were seen regularly by study doctors at least every 3 h or more frequently, according to clinical need, to check for changes in clinical condition, and to review atropine requirements. Important events, such as endotracheal intubation, seizures, or death were recorded at the time of the event. Patients were also seen on a study ward round twice each day and their condition over the previous 12 h recorded. Patients were first managed on the medical ward. Each hospital had two to eight such beds for medical patients. Seriously ill patients, as judged by the ward's medical staff, were transferred to the intensive care unit as beds became available.

Criteria for intubation were: tidal volume less than 180 mL per breath with a Wright's respirometer; respiratory rate less than ten breaths per min; or failure of a Guedel airway to preserve airway patency. Arterial blood gases were not available to guide therapy. Hypotensive patients (systolic blood pressure <80 mm Hg), who were not responding to 50–100 mg of atropine and fluid resuscitation (with 2 L of normal saline), were treated with dopamine plus dobutamine (both started at 5–10 $\mu g\ kg^{-1}\ min^{-1}$ and increased as necessary) by infusion pump. Norepinephrine and epinephrine infusions were not used; bolus epinephrine (1–3 mg intravenously) was administered for cardiac arrests as per standard Advanced Life Support guidelines. Ethics approval was obtained from Oxfordshire Clinical Research Ethics Committee and Faculty of Medicine Ethics Committee, Colombo.

Procedures

Blood samples were taken from all patients recruited to the randomised controlled trial until December, 2003, and used to test the accuracy of the history of the organophosphorus insecticide ingested for the cohort. Admission plasma samples (taken a median of 3–4 h after ingestion for all three insecticides) were assayed for butyrylcholinesterase activity (to show exposure) and insecticide concentration in 433 patients (240 chlorpyrifos, 136 dimethoate, 57 fenthion).

Red cell acetylcholinesterase activity was assayed in samples taken from 90 consecutive patients in the trial (57 with chlorpyrifos, dimethoate, or fenthion) during two periods (May 9 to July 10, 2002, and Dec 2 to Dec 26, 2002). Lab assay capacity limited the sample number that could be handled and determined the short period of sampling.

For acetylcholinesterase measurement, 0·2 mL of EDTA blood was diluted at the bedside into 4 mL of cooled saline and frozen to –20ºC. Plasma was separated from a second EDTA blood sample and frozen at –20ºC. All analyses were done in Munich. Acetylcholinesterase activity was assayed according to a modified Ellman method.[16] Reactivatability of acetylcholinesterase (its ability to be reactivated by supratherapeutic concentrations of oxime, showing the proportion that is not aged and therefore still potentially responsive to oximes) and butyrylcholinesterase activity were assessed as described.[11,16] Concentrations of organophosphorus insecticides in plasma were quantified by reversed phase high-performance liquid chromatography and ultraviolet detection. The lower limits of quantitation were 1 μmol/L plasma for dimethoate and 0·1 μmol/L plasma for chlorpyrifos and fenthion.

Statistical analysis

We did primary data analysis in SPSS (release 11) and Stata (release 8) software. Demographic factors and clinical characteristics were summarised with counts for categorical variables and the median (IQR) for non-normally distributed continuous variables. We

	Chlorpyrifos (n=439)	Dimethoate (n=264)	Fenthion (n=99)
Demographic characteristics			
Male	340 (77·4%)	193 (73·1%)	63 (63·6%)
Age (years)*	30 (23–40)	30 (22–42)	30 (22–38)
Time to presentation (h)*	4 (2–5)	3 (2–5)	4 (2–7)
Randomised into trial	358 (81·5%)	213 (80·7%)	82 (82·8%)
Activated charcoal treatment			
None	146 (33·3%)	98 (37·1%)	33 (33·3%)
Single dose	153 (34·9%)	87 (33·0%)	35 (35·4%)
Multiple doses	140 (31·9%)	79 (29·9%)	31 (31·3%)
Admission characteristics			
Glasgow Coma Score*	15 (14–15)	14 (6–15)	15 (15–15)
Butyrylcholinesterase activity (mU/mL)*	34 (0–304)	1129 (532–1720)	0 (0–33)
Organophosphorus insecticide plasma concentration (μmol/L)*	1·3 (0·4–3·5)	355·5 (160·0–674·0)	4·9 (0·6–16·6)

Data are number (%) unless otherwise indicated. *Median (IQR). Time of ingestion was known for 428, 259, and 95 patients, respectively. Butyrylcholinesterase and pesticide were measured in 240 and 230 chlorpyrifos patients, 136 dimethoate patients, and 57 and 51 fenthion patients, respectively.

Table 1: **Baseline characteristics following organophosphorus insecticide self-poisoning**

	Chlorpyrifos (n=439)	Dimethoate (n=264)	Fenthion (n=99)
Outcomes			
Number of deaths	35	61	16
Case fatality ratio (95% CI)	8·0% (5·8–10·9)	23·1% (18·4–28·6)	16·2% (10·2–24·7)
Number requiring intubation	66	93	31
Proportion (95% CI)	15·0% (12·0–18·7)	35·2% (29·7–41·2)	31·3% (23·0–41·0)
Number with seizures	8	0	5
Proportion (95% CI)	1·8% (0·9–3·6)	0·0% (0·0–1·4)	5·1% (2·2–11·3)
Admission characteristics for fatal cases			
Glasgow Coma Score	6 (3–14)	3 (3–7)	12 (8–15)
Butyrylcholinesterase activity* (mU/mL)	6 (0–94)	735 (269–1240)	0 (0–941)
Organophosphorus insecticide plasma concentration (μmol/L)	4·7 (3·6–5·9)	846 (657–1183)	12·3 (0·94–30·3)
Acetylcholinesterase activity over time			
Number	18	10	4
On admission (mU/μmol Hb)	63·5 (27·0–124·6)	69·0 (22·1–145·7)	64·2 (32·5–75·4)
After 1 h (mU/μmol Hb)	391·8 (294·8–507·8)	110·2 (59·4–166·9)	68·1 (53·8–122·0)
After 12 h (mU/μmol Hb)	312·5 (205·9–480·2)	42·5 (13·7–67·9)	41·9 (14·6–100·6)
Aged acetylcholinesterase on admission	19·4% (6·4–26·1)	71·9% (57·2–86·8)	70·3% (65·6–82·2)
Aged acetylcholinesterase after 12 h	19·8% (3·5–26·2)	84·5% (80·5–96·0)	85·7% (75·4–91·1)

Data are median (IQR) unless otherwise indicated. *Admission butyrylcholinesterase activity was available for 11, 25, and nine patients with fatal outcome, and organophosphorus insecticde concentration for 11, 25, and eight patients with fatal outcome, poisoned by chlorpyrifos, dimethoate, and fenthion, respectively. Butyrylcholinesterase and organophosphorus insecticide was measured in all patients who were recruited to the trial until December 31, 2003.

Table 2: **Outcomes after admission (plus admission characteristics for fatalities)**

calculated case fatality (and need for intubation) plus 95% CI in the dimethoate and fenthion groups using the Wilson method, CIA software (version 2.0),[17] and compared with chlorpyrifos by calculating odds ratios plus 95% CI. We used logistic regression models to investigate the effects of age, sex, trial recruitment, and charcoal administration on mortality and intubation.

Role of the funding source

The study sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 31, 2002, and May 25, 2004, 5585 poisoned patients were reviewed on admission to the adult medical wards. 1193 (21·4%) had a history of organophosphorus insecticide self-poisoning. All were approached for recruitment to a randomised controlled trial of activated charcoal; 937 (78·5%) were recruited. This trial was stopped in October, 2004, after the planned final interim analysis identified no effect of activated charcoal on death.[18]

About two-thirds of patients poisoned by an organophosphorus insecticide (802 of 1193) reported ingesting one of three pesticides: chlorpyrifos, dimethoate, and fenthion (table 1). The groups were similar at baseline (table 1). 147 patients (12·3%) ingested unknown cholinesterase inhibitors whereas 244 (20·5%) ingested other organophosphorus insecticides. Patients reported ingesting from a few to several hundred mL.

Using a butyrylcholinesterase level less than 50% of the laboratory mean as a cut off, we measured substantial exposure in 218 of 240 patients (90·8%) who had taken chlorpyrifos, 106 of 136 (77·9%) who had taken dimethoate, and 47 of 57 (82·4%) who had taken fenthion. Of these patients, we detected the alleged insecticide in the plasma of 208 patients (95·5%) taking chlorpyrifos, 90 (84·9%) taking dimethoate, and 45 (95·7%) taking fenthion.

There were clear differences in human poisoning effects caused by the three insecticides (table 2) despite similar lethality in rats and classification as WHO Class II moderately hazardous pesticides.[13] Dimethoate or fenthion poisoning was more severe than chlorpyrifos poisoning. Compared with chlorpyrifos, the odds ratio (OR) of death was 3·5 (95% CI 2·2–5·4) after dimethoate and 2·2 (1·2–4·2) after fenthion.

The need for endotracheal intubation was higher with dimethoate and fenthion (table 2). Compared with chlorpyrifos, the OR for intubation was 3·1 (2·1–4·4) for dimethoate and 2·6 (1·6–4·2) for fenthion, respectively.

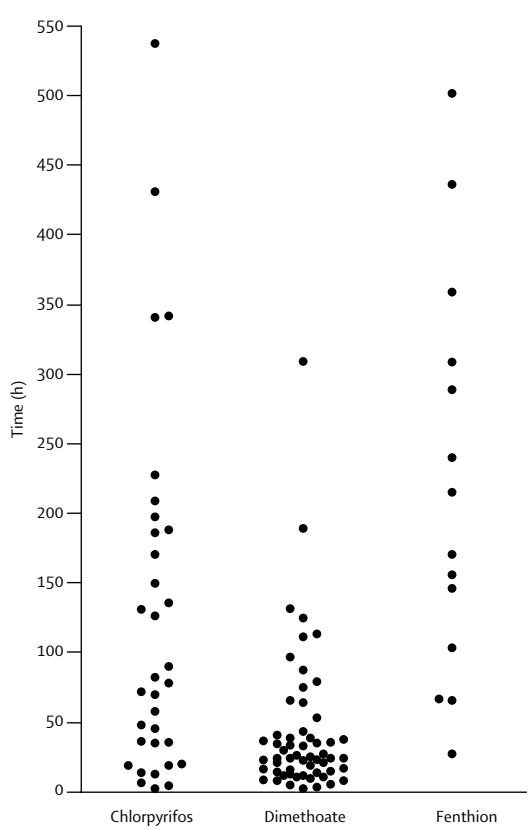

Figure 1: **Time between ingestion of insecticide and death**
Paired times of ingestion and death were available for 33 of 35 fatal chlorpyrifos cases, 60 of 61 fatal dimethoate cases, and 14 of 16 fatal fenthion cases.

Overt seizures were uncommon for all three organophosphorus insecticides (table 2).

Mode of death differed between the organophosphorus insecticides. Of the 107 cases with known times of both ingestion and death (95·5% of 112 fatal cases; figure 1), three deaths from ingesting chlorpyrifos (9% of 33) and four from dimethoate (7% of 60) were within 6 h of ingestion as a result of the acute cholinergic effects of the poisoning. By contrast, no patients poisoned by fenthion died within 24 h of ingestion. Unlike chlorpyrifos and fenthion, many deaths in patients poisoned with dimethoate (35 of 60; 58%) happened 12–48 h after ingestion from hypotensive shock (figure 1). Most presented with low Glasgow Coma Score, poor respiratory function requiring mechanical ventilation, and hypotension requiring vasopressors and atropine. Patients with fatal fenthion poisoning were often asymptomatic on admission. They initially required little atropine but ten (71% of 14) then developed cholinergic crises requiring atropine or exhibited peripheral respiratory failure (or both) and required endotracheal intubation more than 30 h after poisoning. No patients poisoned with chlorpyrifos or dimethoate with mild symptoms on admission (requiring less than 1–3 mg of atropine initially) died from delayed respiratory arrest.

Deaths from fenthion (ten of 14, 71%) or chlorpyrifos (14 of 33, 42%) were often late, after 5 days, as a result of complications of long-term ventilation or the respiratory or neurological complications of events before admission. Such late deaths were uncommon with dimethoate (four of 60, 7%).

The variability in toxic effects is unlikely to be due to differences between patients since the groups were similar. Indeed, logistic regression analysis adjusting for sex, age, recruitment to randomised controlled trial, and charcoal allocation resulted in estimates of the OR of death and intubation for dimethoate and fenthion, compared with chlorpyrifos, becoming larger.

There were clear differences on admission in the condition of patients who died (table 2). Patients with dimethoate poisoning were more deeply unconscious than those ingesting fenthion or chlorpyrifos. Seven (44%) of 16 fatal fenthion cases and six (17%) of 35 fatal chlorpyrifos cases had a normal Glasgow Coma Score on admission; only two (3%) of 61 fatal dimethoate cases had a normal score, whereas 61% had a score of 3 out of 15 on admission.

We wondered whether the variable toxicity might be due to the formulation of the organophosphorus insecticide and therefore investigated how each was prepared. We found no notable differences. Each was sold as an emulsifiable concentrate with 40–50% active ingredients (table 3). 40–50% xylene solvent was used for each insecticide; however, some chlorpyrifos and dimethoate formulators replaced part of the xylene with cyclohexanone or petroleum fractions.

	Chlorpyrifos	Dimethoate	Fenthion
WHO and EPA toxicity class	II Moderately toxic	II Moderately toxic	II Moderately toxic
Rat oral LD_{50}*			
OSHA[19]	97	250	215–245
WHO[13]	135	About 150	NG
CPH[20]	96–270	235	250
Alkyl groups	Diethyl	Dimethyl	Dimethyl
Fat solubility (log P)†	5·05	0·76	4·3
Thion or oxon	Thion	Thion	Thion
Formulation			
g/L	400	400	500
Volume (mL)	100–400	100–400	100–400
Solvents	Xylene	Xylene, or xylene and cyclohexanone	Xylene, or xylene and petroleum fractions

CPH=Crop Protection Handbook. EPA=Environmental Protection Agency. NG=not given in the source. OSHA=Occupational Safety and Health Administration, USA. *Three sources of rat oral LD_{50} values (mg/kg) given. †Log P, the logarithm of the partition coefficient between n-octanol and water, correlates with fat solubility. Values given are mean of those from two to four experimental sources.[21] Value <1·0 indicates water-soluble compound. Value >4·0 indicates a very fat-soluble compound.

Table 3: **Characteristics of the three insecticides**

Differences between the chemistry of the pesticides themselves might account for the differential toxicity. Dimethoate and fenthion are dimethyl organophosphorus insecticides, whereas chlorpyrifos is a diethyl organophosphorus insecticide (figure 2). We assessed whether variable inhibition of cholinesterases or response to oximes might explain the variable toxicity.

Considering only patients with substantial exposure (butyrylcholinesterase less than 3000 mU/mL, detectable organophosphorus insecticide), median butyrylcholinesterase activity on admission was lower after chlorpyrifos and fenthion than after dimethoate (table 1). Remarkably, despite the lesser inhibition of butyrylcholinesterase in dimethoate poisoning, the median concentration of dimethoate was much higher than that of chlorpyrifos or fenthion (table 1).

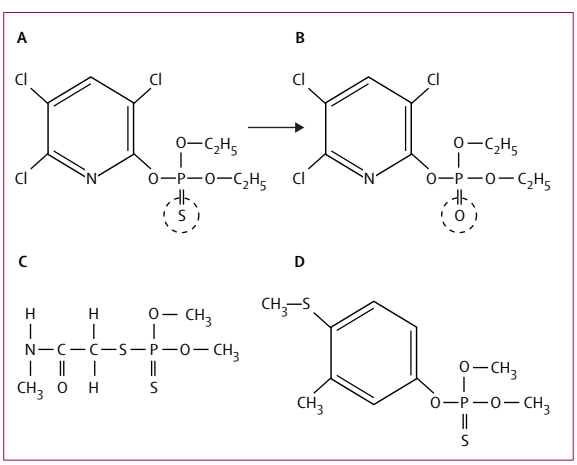

Figure 2: **Structure of the three organophosphorus pesticides**
Chlorpyrifos (A; CAS 2921-88-2) and chlorpyrifos oxon (B), the active form of chlorpyrifos after desulphuration of circled =S to =O. Dimethoate (C; CAS 60-51-5) and fenthion (D; CAS 55-38-9) must also be activated to oxon form. Note two ethyl groups attached to P in chlorpyrifos and two methyl groups attached to P in dimethoate and fenthion. Dimethoate is an aliphatic compound, chlorpyrifos and fenthion aromatic compounds.

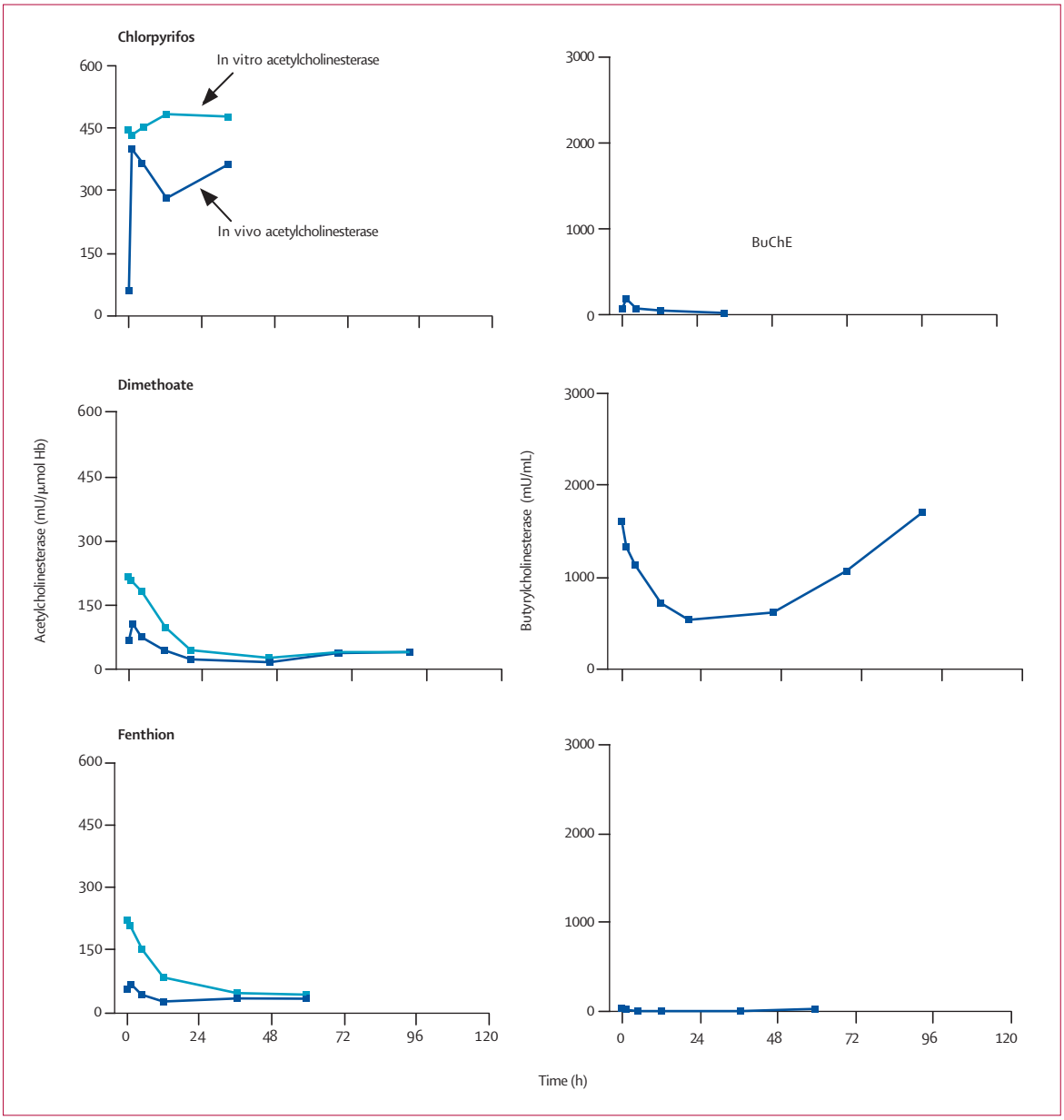

Figure 3: **Red cell acetylcholinesterase and plasma butyrylcholinesterase activities in representative cases before and after pralidoxime treatment**
Time 0=time of first pralidoxime administration. Normal acetylcholinesterase activity is around 600 mU/µmol Hb; the lower bound of normal for butyrylcholinesterase was set as 3000 mU/mL. In-vitro acetylcholinesterase assay indicates how much of inhibited acetylcholinesterase can be reactivated with supratherapeutic concentrations of oximes—ie, how much acetylcholinesterase is not yet aged and therefore responsive to oximes. Dose of oxime used in vitro is far higher than can be obtained in patients because of toxicity of oximes. Patients were chosen on basis of their similarity to median values for data. All patients followed this pattern allowing for variation due to dose and time to admission.

We analysed all 32 patients with chlorpyrifos, dimethoate, and fenthion poisoning who had less than 3000 mU/mL of butyrylcholinesterase and less than 300 mU/µmol Hb acetylcholinesterase on admission. We assayed butyrylcholinesterase, red cell acetylcholinesterase, acetylcholinesterase ageing, and plasma concentrations of organophosphorus insecticide before and after giving 1 g of pralidoxime. Median acetylcholinesterase activity on admission in these patients was similar for all three pesticides (table 2), unlike butyrylcholinesterase activity.

Response to pralidoxime differed by organophosphorus insecticide (figure 3). By 1 h, median acetylcholinesterase activity with chlorpyrifos had increased by 328 mU compared with increases of only 41 mU and 4 mU with dimethoate and fenthion (table 2). At 12 h, median acetylcholinesterase was 249 mU above admission for chlorpyrifos compared with 27 mU and 22 mU below

admission values for dimethoate and fenthion, respectively. Substantial ageing had already occurred on admission for dimethoate and fenthion compared with chlorpyrifos-inhibited acetylcholinesterase (table 2). Ageing continued for acetylcholinesterase inhibited by dimethoate or fenthion at 12 h; pralidoxime partly prevented further ageing in chlorpyrifos poisoning. Ageing was complete by 24 h in most dimethoate and fenthion cases, making oximes thereafter ineffective.

Discussion

Although the mechanism of toxicity is thought to be the same for all organophosphorus insecticides, we measured important differences in the clinical course of humans poisoned by three such compounds, despite identical treatment. We also show that the relative human toxicity of these insecticides might not be related to animal toxicity. The widely used approach of differentiating organophosphorus insecticides according to their animal LD_{50} did not accord with human toxicity, and is probably of limited value in risk assessment or management of human poisoning.

Organophosphorus insecticide self-poisoning causes hundreds of thousands of deaths each year.[3,4] Current treatment is only partly effective, with case fatality often greater than 10% in even the best intensive care units. Part of the problem is that there is little evidence on which to base management.[22] But another problem is that all organophosphorus insecticides have been grouped together, with no attempt being made to develop specific management protocols or identify particular insecticides that are difficult to treat.

Dimethoate poisoning produced a different clinical syndrome to the other organophosphorus insecticides. Some patients were deeply unconscious on admission despite having acetylcholinesterase concentrations more than 10–20% of normal. Most textbooks suggest that greater acetylcholinesterase inhibition is required for severe clinical features of poisoning. Severely poisoned patients were hypotensive on admission and died from hypotensive shock while being ventilated. The reason for this different presentation is not known. However, it may be partly due to the low fat solubility of dimethoate (table 3), causing a low volume of distribution and very high blood concentration for dimethoate.

Most fenthion deaths and many chlorpyrifos deaths occurred after several days of ventilation in intensive care. Deaths were due to complications of pesticide aspiration and hypoxic brain injury before admission or the sudden respiratory arrest of the intermediate syndrome, in addition to the complications of long-term ventilation. The rate of onset for each insecticide will determine whether respiratory arrests occur before admission or after several days in hospital.

The known toxicology of the solvents,[23] and the predominant use of xylene for all three insecticides, makes it unlikely that solvents were responsible for the variable toxicity. We were unable to find any evidence that differences in the formulations' taste and palatability might explain the differences. We did not assess the effect of acute or chronic alcohol use on organophosphorus insecticide toxicity. However, we did not note any difference in alcohol use that might account for the variable toxicity for the three insecticides.

In the absence of conclusive clinical trial data, there has been extensive debate about the effectiveness of oximes as treatment for organophosphorus insecticide poisoning.[12,24] Asian doctors have reported no benefit from pralidoxime;[25,26] however, a 250-mg bolus of obidoxime (equivalent to about 2 g pralidoxime) clearly reactivates acetylcholinesterase inhibited by the dimethyl organophosphorus insecticide parathion.[12,27] We found that patients poisoned by a diethyl organophosphorus insecticide (chlorpyrifos) responded well to pralidoxime, whereas those poisoned by two dimethyl organophosphorus insecticides (dimethoate, fenthion) responded poorly. This finding suggests that uncertainty about oxime effectiveness is likely to be due to confounding from studying these insecticides as a group rather than as individual compounds.

The dose of pralidoxime used in this cohort was lower than the current WHO recommended dose.[28] We do not think that this factor was responsible for its poor efficacy in dimethoate or fenthion poisoning—250 mg obidoxime also has a poor effect in dimethoate poisoning, with complete ageing within 20 h (figure 2, B in reference 12). The failure of pralidoxime to reactivate dimethoate-inhibited acetylcholinesterase was not due to its high blood concentration since a similar failure occurred with fenthion at a blood concentration 100 times lower.

The low dose of pralidoxime was probably sub-optimum for chlorpyrifos poisoning, allowing some acetylcholinesterase to become reinhibited and aged after the initial response. High-dose oxime was effective at obtaining sustained acetylcholinesterase reactivation and slowing ageing with parathion (figure 2, D in reference 12). However, the use of low doses of pralidoxime does not explain the variable toxicity. Higher doses might have further decreased the toxic effects and mortality of chlorpyrifos poisoning, but are unlikely to have greatly benefited patients poisoned by fenthion or dimethoate, especially those with high-dose poisoning.[11,12]

Butyrylcholinesterase activity on admission cannot be used to predict outcome or severity unless the organophosphorus insecticide is known. The degree of inhibition of butyrylcholinesterase on admission varied by insecticide: the activity was zero for many symptomatic chlorpyrifos and fenthion cases but more than 20% of normal for some severe dimethoate cases.

A limitation of this study is that a blood sample was not available from all patients to identify the pesticide

ingested. However, samples were available for 54% of patients, and, in those with substantial exposure, the reported insecticide was detected in 85–95% of patients, suggesting that the history effectively identified the ingested compound. We did not exclude patients without detectable pesticide in the blood since the lack of blood samples for some patients would have introduced bias. A further limitation is that acetylcholinesterase values were available for very few patients. However, the clear difference in response to pralidoxime in this small sample suggests the finding is likely to be robust; more patients are now being studied.

This finding of significant clinical differences between organophosphorus insecticides is important for pesticide regulation and clinical trials. Previously, regulatory decisions have sometimes been based on the WHO classification by animal toxicity.[14] However, if these findings can be generalised to all dimethyl or diethyl organophosphorus insecticides, it may be safer to allow the agricultural use of slowly activated diethyl organophosphorus insecticides, which respond well to oximes, rather than the use of dimethyl organophosphorus insecticides that are difficult to treat, irrespective of their animal toxicity.

Earlier trials of pralidoxime are confounded by the presence of both dimethyl and diethyl organophosphorus insecticides, some of which might not respond to oximes.[12] Future trials will need to identify the exact pesticide taken by each patient. Pralidoxime was not efficacious in reactivating acetylcholinesterase inhibited by the dimethyl pesticides dimethoate and fenthion. More research is needed to determine whether this poor response to oximes is a general property of dimethyl organophosphorus insecticides. Possible public health responses include banning organophosphorus insecticides that do not respond to oximes[29] and developing new therapies that allow oximes to work better.

Finally, management guidelines for organophosphorus poisoning do not differentiate between individual pesticides. Our findings suggest that it is not adequate to consider such poisoning as a homogeneous entity. The variable clinical syndromes and response to oximes suggest that future studies could lay the groundwork for developing specific management protocols for individual organophosphorus pesticides.

Contributors

M Eddleston designed and set up the cohort, designed this study, did the analysis and wrote the first draft of the report. P Eyer, F Worek, L von Meyer, and L Szinicz analysed blood and pesticide samples. F Mohamed and L Senarathna ran the trial centres and, with M Eddleston, extracted and checked patients' data for analysis. E Juszczak helped design the trial and contributed to the statistics for this paper. A Hittarage, S Azhar, and W Dissanayake had clinical responsibility for patients. M H R Sheriff and A H Dawson organised the cohort through the South Asian Clinical Toxicology Research Collaboration. N A Buckley helped design the cohort study and contributed to the analysis. All authors helped improve the study design and finalising the report.

Conflict of interest statement

We declare that we have no conflict of interest.

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