Acute fungicide self-poisoning - a prospective case series

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ABSTRACT

Background: Pesticide self-poisoning is a global clinical and public health problem. While self-poisoning with insecticides and herbicides has been extensively studied, there is minimal literature on acute fungicide self-poisoning. We aimed to study the clinical course and outcome of fungicide self-poisoned patients recruited to a prospective cohort in Sri Lanka.

Methods: We conducted a prospective study of patients presenting with fungicide self-poisoning to nine hospitals in Sri Lanka between 2002 and 2020. Patients were enrolled by clinical research assistants, with clinical outcomes being recorded at regular review for each patient.

Results: We identified 337 cases of self-poisoning with fungicides (alcohol as only co-ingestant), including 28 different fungicides across 5 different fungicide classes. Median time from ingestion to examination was 3.1 (1.8–5.7) h. Nearly all presented to hospital fully conscious (GCS 15, 15–15)–only 27 patients (8.0%) presented with reduced GCS (<15) and only 2 (0.6%) had GCS 3/15. Most patients (333/337, 98.8%) made a full recovery, of whom only eight (2.37%) required intubation and ventilation. Four patients died (case fatality rate: 1.2%; 95% CI 0.0–23.4) after ingestion of edifenphos (n = 2), propamocarb and pyraclostrobin.

Conclusion: Fungicide self-poisoning appears to be less hazardous than insecticide or herbicide self-poisoning, with a substantially lower case fatality in the same cohort. Edifenphos is an exception to this ‘less toxic’ rule; as a WHO Class Ib highly hazardous pesticide, we recommend its withdrawal from, and replacement in, global agricultural practice. Propamocarb should be listed in the WHO hazard classification as propamocarb hydrochloride to reflect the higher toxicity of the common agricultural formulation. Pyraclostrobin currently has no WHO classification; one is urgently required now that its ingestion has now been linked the death of a patient. Additional prospective clinical data on fungicide self-poisoning is required to expand knowledge on the effects of these diverse compounds.

Introduction

The World Health Organization (WHO) considers pesticide self-poisoning to be one of the three most important means of global suicide [1]. The introduction of highly hazardous pesticides into rural households with the Green Revolution has resulted in more than 14 million premature deaths from pesticide self-poisoning [2], many of them with very little intent to die [3]. Most of these deaths have been due to highly hazardous organophosphorus (OP) insecticides, with substantial numbers from organochlorine and carbamate insecticides, bipyridyl herbicides and aluminium phosphide fumigant [4–7].

The dangers and clinical presentation of fungicides are less well established [8,9]. In contrast to most insecticide targets, few fungicide targets are present in mammals and some have argued that fungicides must be low in toxicity to mammals [10]. It is however possible that, while a fungicide works by one mechanism in fungi, it may cause injury by a different mechanism in mammals [11].

As of 2021, the Fungicide Resistance Action Committee (FRAC) have classed at least 230 fungicides into 13 groups and 63 subgroups based on their mechanism of action (MoA) [12]. The WHO has classed fungicides according to hazard, from Class Ia (extremely hazardous) to Class U (unlikely to present acute harm) [13]. The WHO Class is largely based on data on the active ingredient and rat oral LD50 toxicity studies, which have been shown at times to have only modest accuracy in predicting pesticide formulation toxicity in humans [14–16].

There is a lack of detailed literature on acute oral fungicide self-poisoning. Review of the literature for cases of acute oral toxicity with fungicides reveals mass casualty events attributed to fungicide contamination of grain [17,18] and a small number of self-poisoning cases lacking clinical details.
Fungicides with reports of acute oral toxicity but not death

Bitertanol, Binapacryl, Cosavet, Captan, Difenacoozoale, Fluazinam, Isoprothiolane, Maneb, Metiram, Picoxytrobin, Pyraclostrobin, Thiabendazole, Thiophanate-methyl, Thiram

Carbendazim [19], Carboxin [20], Chlorothalonil [21,22], Copper oxide [19], Hexaconazole [19,23], Propamocarb [24], Propiconazole [25], Proipineb [19], Pyraophos [26,31], Mancozeb [19], Tebuconazole [19,24]

Copper Sulfate [27,28,33–35] Edifenphos [19,24,29–32] Hexachlorobenzene [18]

Most of the literature focuses on just two fungicides: the OP fungicide edifenphos [19,24,29–32] and copper sulfate [27,28,33–35]. Edifenphos inhibits phosphatidylcholine biosynthesis in fungi but cholinesterases in mammals (similar to OP insecticides). Its rat oral LD50 is 150 mg/kg; it has been classified as WHO hazard class 1b to be consistent with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS)’s system of classification (Toxicity Hazard Category 3) [13]. Copper sulphate inhibits spore germination in fungi but is hemolytic in mammals causing anemia, as well as corrosion in the GI tract, renal and liver failure [27,28,33]. The WHO reports a rat oral LD50 of 300 mg/kg for copper sulphate, resulting in WHO hazard class 2 and GHS toxicity hazard category 3 classifications [13]. There are many reports of copper sulphate self-poisoning in the literature (n > 30); however, given that it is used in paint and leather industries as well as religious practice in Sri Lanka and India, many reports are unclear whether the copper sulphate used in self-poisoning was fungicidal in origin [27,28,33–35].

To better understand the clinical characteristics and outcome of fungicide self-poisoning, we analyzed patients presenting with fungicide self-poisoning to a large-scale prospective cohort study in Sri Lanka between 2002 and 2020 to identify the clinical outcomes of fungicide poisoning.

Methods

Patients

Patients were recruited from nine different secondary hospitals in Sri Lanka from 2002 to 2020 as previously described as part of the South Asian Clinical Toxicology Research Collaboration (SACTRC)’s prospective poisoning cohort [19]. Patients were included based on their history of fungicide ingestion as described by themselves, their family members, notes from the transferring doctor, or the presence of a pesticide bottle. All patients who reported ingestion/co-ingestion of a fungicide and a substance that was not a fungicide, other than alcohol, were excluded from the analysis.

Clinical data from patients were obtained regularly by research staff as described previously [14,19]. Briefly, all patients were seen regularly by full-time study doctors at least twice each day and more according to clinical need after obtaining informed consent. Significant events (intubation, seizures, and deaths) were recorded at the time of events.

Patients were seen at the medical ward first; seriously ill patients were transferred to the ICU based on Glasgow Coma Score (GCS) and cardiorespiratory function as beds became available. Criteria for intubation were tidal volume <180 mL/breath using a Wright’s respirometer, respiratory rate <10 breaths/min, or failure of a Guedel airway to preserve airway patency. Arterial blood gases were not available to guide therapy. Atropine and oximes was given to patients with cholinergic features as per published protocol [36]. Hypotensive patients who did not respond to fluid resuscitation (with 2 L of normal saline) were treated with dopamine plus dobutamine (both started at 5–10 µg/kg/min, increased as necessary) by infusion pump as per standard local practice. 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 for data collection across the cohort was obtained from the research ethics committees of University of Colombo, Sri Lankan Medical Association, University of Peradeniya, Australian National University, University of New South Wales, University of Sydney, and Oxford Tropical Medicine Ethics Committee.

Data analysis

Data were analyzed using MS Excel and GraphPad Prism (version 9). Descriptive statistics were used to summarize categorical variables. Median and interquartile ranges (IQR) were used for analysing data that did not fit a normal distribution. Figures were made using Graphpad Prism and Adobe Illustrator CS4.

Results

Out of the 80,000 patients enrolled in the South Asian Clinical Toxicology Research Collaboration (SACTRC) cohort, we identified 351 patients (0.4%) who reported ingesting 28 different fungicides between 2002 and 2020 (Table 2). Fourteen were excluded due to co-ingestion of substances other than fungicides or alcohol, including a death post co-ingestion of the fungicide thiram and OP insecticide profenofos, leaving 337 patients in this analysis.

The 28 fungicides were from five (of 13) FRAC MoA groups (Table 2 (Supplementary Table 1)). WHO classification by hazard (12) ranged from Ia (highly hazardous) to U (unlikely to cause acute harm) (Supplementary Table 1). Three fungicides (pyraclostrobin, fluazinam and cosavet) are not classified by the WHO (Supplementary Table 1). One fungicide (binapacryl) was listed as “Active ingredients believed to be obsolete or discontinued for use as pesticides” by the WHO as it had already been listed under the Rotterdam
Table 2. Fungicides by FRAC sub-group and mechanism of action.

| FRAC Subgroup and MOA | Fungicides | Cases |
|-----------------------|------------|-------|
| B1 - Inhibitor of ß-tubulin assembly in mitosis | Carbendazim, Thiabendazole, Thiophanate-methyl | 24 |
| C2 - Succinate dehydrogenase inhibitors | Carboxin | 2 |
| C3 - Quinone outside Inhibitors | Picloram, Pyraclostrobin | 5 |
| C5 - Uncouplers/Inhibitors of oxidative phosphorylation | Binapacryl, Fluazinam | 3 |
| F2 - Phospholipid biosynthesis inhibition | Edifenphos, Isoprothiolane, Pyrazophos | 26 |
| F4 - Lipid synthesis inhibitor | Propamocarb | 2 |
| G1 - Inhibition of C14-demethylase in sterol biosynthesis | Bitertanol, Difenconazole, Hexaconazole, Propiconazole, Tebuconazole | 66 |
| M - Multisite action | Chlorothalonil, Maneb, Metiram, Mancozeb, Propineb, Thiram, Copper Oxide, Copper Sulfate, Captan | 182 |
| Not classed | Cosavet, Hexachlorobenzene | 25 |
| Unknown fungicides | | |

Table 3. Baseline characteristics of all patients who ingested fungicides and of patients who ingested edifenphos.

| All Fungicides (n = 337) | Edifenphos (n = 18) |
|--------------------------|---------------------|
| **Male** | 210 (62.3%) | 14 (77.8%) |
| Age (years) | 26 (19–36) | 25 (18–37) |
| Time from ingestion to examination (hours) | 3.1 (IQR 1.8–5.7) | 4.5 (2.1–8.3) |
| Alcohol co-ingested | 70 (20.8%) | 0 |
| Glasgow coma score at admission | 15 (IQR 15–15) | 15 (IQR 15) |
| Direct admissions | 203 (60.2%) | 4 (22.2%) |
| **Pre-hospital treatment** | | |
| Forced emesis | 86 (25.5%) | 12 (66.7%) |
| Gastric lavage | 51 (15.1%) | 3 (16.7%) |
| Atropine | 22 (6.5%) | 11 (61.1%) |
| Pralidoxime | 3 (0.9%) | 2 (11.1%) |
| **Study Hospital Treatment** | | |
| Atropine | 26 (7.7%) | 9 (50%) |
| Pralidoxime | 1 (0.3%) | 0 |
| Not given gastrointestinal decontamination | 66 (19.6%) | 9 (50%) |
| **Activated Charcoal** | | |
| Single dose (only treatment) | 58 (17.2%) | 4 (22.2%) |
| Multiple doses (only treatment) | 9 (2.7%) | 5 (27.8%) |
| Single dose with other treatment | 77 (22.8) | 0 |
| **Gastric lavage** | | |
| Gastric Lavage (only treatment) | 5 (1.5%) | 0 |
| Gastric lavage with other treatment | 99 (29.4%) | 0 |
| **Outcomes** | | |
| Number of patients with seizures | 1 (0.3%) | 0 |
| Number of patients intubated | 8 (2.4%) | 5 (27.8%) |
| Number of patients intubated | 5 (62.5%) | 3 (16.7%) |
| and survived | | |
| Case fatality | 4 (95%Cİ:0.00–23.42) | 2 (95%Cİ:0.00–25.6) |

Time of ingestion was known for 313 patients across all fungicides and for 17 patients who ingested edifenphos. If alcohol was co-ingested was known for 236 patients across all fungicides and 3 patients who ingested edifenphos.

Clinical data

On admission 310 (92.0%) patients were fully conscious (GCS 15/15). The median GCS on admission was 15/15 with only 27 (8%) patients presenting with a GCS less than 15. Five patients (1.5%) presented comatose (GCS ≤8) three following ingestion of edifenphos (GCS 3/15, 3/15, 7/15) and one each following ingestion of propineb (GCS 8/15) and tebuconazole (GCS 7/15) (Table 3). Data on alcohol co-ingestion was only available for one comatose patient (GCS 3/15) who co-ingested alcohol and edifenphos. Of the five patients who presented comatose, one died following intubation, three recovered without intubation, and one patient recovered after being intubated twice.

Treatment data

Prior to study hospital admission, 86 (25.5%) patients received forced emesis and 51 (15.1%) received gastric lavage (Table 3). Once admitted to study hospitals, 58 patients (17.2%) received a single dose of activated charcoal, 9 (2.7%) received multiple doses and 135 (40.1%) received a single dose of activated charcoal alongside another treatment (Table 3). Gastric lavage was given as the only treatment to five (1.5%) patients while 99 (29.4%) received gastric lavage alongside another treatment (Table 3).

Intubation

Only eight (2.4%) of 337 patients required intubation; three (37.6%) of the intubated patients died (Table 3). Five patients were intubated after ingestion of edifenphos, while hexaconazole, pyraclostrobin, and thiram ingestion each caused one patient to be intubated. Median time from ingestion to intubation (where time of ingestion was known, n = 6) was 19.8 (IQR: 2.7 to 41.3) h; three (37.5%) were intubated within 24 h, with 14.67 h the shortest time to intubation among survivors and 2.5 h the shortest time to intubation in a non-survivor. The longest duration of ventilation in a survivor was 75.8 h; the longest duration of ventilation in a fatality was 97.8 h.

Fatalities

Four patients died (case fatality 1.2% [95%Cİ 0.03 to 23.4]) (Table 4). Two died after ingesting the OP fungicide

Patients

The median age of patients was 26 (IQR: 19 to 36) years; around two-thirds were male (63%) (Table 3). The median time from ingestion to examination (known for n = 313) at a study hospital was 3.1 (IQR: 1.4 to 5.1) hours; 203 patients arrived at study hospitals directly while 134 (40.0%) were transferred to study hospitals from peripheral hospitals (Table 3). Fungicides were co-ingested with alcohol in 70 patients (20.8%) (Table 3).
edifenphos, one died after ingesting the carbamate ester propamocarb, and one died after ingesting the carbamate ester pyraclostrobin (Tables 4 and 5). All consumed an unknown amount of fungicide. Time to death post ingestion (of the 3 with known ingestion times) ranged from 45.8 h to 95.8 h (Table 4). Two were males, and two females, aged 16, 26, 45 and 65 years (Table 4).

GCS on admission for the fatal cases was 3/15, 9/15, 15/15 and 15/15 (Table 4). Three were intubated; all presented with bilateral inspiratory pulmonary crepitations with two patients recorded as having pulmonary oedema (Table 4). Two of the intubated patients died from respiratory failure, one patient lacked a written copy of records but likely also died of respiratory failure (Table 4). One patient who ingested edifenphos was intubated for 72 h before being extubated and dying the next day (the precise reason is not stated in the notes) (Table 4). The patient who ingested propamocarb did not require intubation but presented with an irregular heart rate and died of cardiopulmonary arrest 65.5 h post-ingestion (Table 4).

Edifenphos self-poisoning
Of the 337 patients who self-poisoned using fungicides 18 (5.3%) used edifenphos. Patients ingesting edifenphos were significantly more ill than patients ingesting other fungicides.
(Table 3). Edifenphos was linked to the deaths of two patients (50%) and five intubations (62.5%) (Table 3). Median time to intubation was 8.7 (IQR: 2.6–49.2) h (ingestion time known n = 4). Although the median GCS on arrival was 15/15 (the same as for all fungicide cases) (Table 3), edifenphos cases accounted for 7/27 (25.9%) of cases presenting with GCS <15/15, including both patients presenting fully comatose (GCS 3/15). The two fatal cases were intubated 2.75 h and 2.5 h post ingestion; both received atropine (Table 4).

Of the 18 patients who ingested edifenphos; 15 (83.3%) presented with symptoms consistent with acute cholinergic syndrome while the remaining 3 (16.7%) presented with no symptoms. Eleven patients (61.1%) had respiratory symptoms: bilateral crepitations (38.8%), rhonchi (11.1%), bronchorrhea (16.7%) and respiratory arrest (22.2%). Eight (44.4%) were given atropine, one (5.6%) received atropine and pralidoxime; all patients who received atropine presented with respiratory symptoms typical of the acute cholinergic syndrome. Non-respiratory features included: tachycardia (22.2%), headache (16.7%), blurred vision (16.7%), dizziness (16.7%), epigastric pain (22.2%), and fasciculations (11.1%).

Discussion

We report a large case series of patients with fungicide self-poisoning, who had ingested 28 different fungicides from five MoA classes. Self-poisoning with 14 of these fungicides has not previously been reported. The global literature and our own case series [19] indicate that fungicides are relatively infrequently used for self-poisoning compared to other pesticide classes. In Sri Lanka, this is likely because fungicides are used less often in agriculture than insecticides and herbicides [37]. Between 2006–2011 Sri Lanka imported 5,040 metric tons (Mt) of fungicides compared to 8,940 Mt of insecticides and 24,292 Mt of herbicides [37]. They are generally also less harmful after ingestion. The case fatality for fungicide self-poisoning (1.2% [95% CI 0.0–23.4]) in this case series is significantly less than the case fatality for insecticides (6.9 [95% CI 6.5–7.3], n = 10,612) or herbicides (10% [95% CI 9.4–10.6], n = 9053) in the same cohort [19].

Despite an overall lower case fatality, edifenphos is a highly toxic exception to the finding that fungicides are generally of low toxicity. Edifenphos inhibits phosphatidylcholine biosynthesis in fungi (Table 5), but cholinesterases in animals. When ingested, edifenphos leads to acute cholinergic syndrome though an excessive buildup of acetylcholine in neuromuscular junctions, resulting in overstimulation and disruption of neurotransmission both centrally and peripherally.

In 2021, we recommended that an initial global benchmark for registration of pesticides should be a case fatality less than 5% after self-poisoning [19]. No pesticides with case fatality of 5% or greater should be permitted for agricultural use. While our data on edifenphos are limited by a small case size (n = 18), case fatality was 11.1% (95%CI 0 to 25.6). Our findings are supported by the literature which includes at least 22 cases of acute oral edifenphos self-poisoning, resulting in at least two deaths [19,24,28–32]. Edifenphos has already been withdrawn from market in Sri Lanka (our data reports no self-poisonings cases after 2009 following government ban), parts of India [38] and has never been approved for use in the EU. Our data suggests that edifenphos should be considered for a withdrawal from market globally. Much work has focused on the harm caused by OP based insecticides [3,4,6,14,15,39–41] and it would be wrong to ignore the potential harm of OP based fungicides.

The banning of the most harmful pesticides has been shown to be an effective policy in reducing self-poisoning deaths [38,40,42–45]. Since the 1995 ban of all WHO Class I toxicity pesticides and subsequent bans of endosulfan (1998), dimethoate, fenthion and paraoxan (2008) there has been a 70% reduction in the rate of suicide in Sri Lanka [40]. Restricting access to the most toxic pesticides has also reduced poisoning deaths in South Korea [45], Bangladesh [42], and elsewhere [40] with restrictions having no measurable effect on agricultural productivity [42–44,46].

Propamocarb is a carbamate ester which inhibits lipid synthesis in fungi; it is not known to inhibit cholinesterases in mammals with a rat oral LD50 8,600 mg/kg and WHO hazard class U (Table 5).

One previous case of propamocarb self-poisoning has been published; the patient developed rhabdomyolysis, but the final outcome is unclear [24]. The other, non-fatal propamocarb case presented only with a reduced GCS (14/15). Unusually, the fatal propamocarb case was not ventilated before death, with sudden cardiopulmonary arrest occurring 65 h post ingestion, preceded by rhonchi, an irregular pulse, and confusion (Table 4). Propamocarb is currently classified as ‘Unlikely to cause harm’; however, propamocarb should probably be listed as the hydrochloride salt to better reflect its more common agricultural formulation [48]. With its substantially lower rat oral LD50 value (LD50 of 2,000–2,800 mg/kg [47]), propamocarb hydrochloride’s classification would be “moderately hazardous” or “slightly hazardous”.

Pyraclostrobin is a carbamate ester that does not inhibit cholinesterases; it inhibits the mitochondrial complex III in both fungi and mammals and is a neurotoxin in chronic murine exposure experiments (Table 5). Self-poisoning with pyraclostrobin has not previously been reported in the literature. The fatal case presented with hypotension, pulmonary oedema, and bilateral inspiratory pulmonary crepitations before requiring intubation (Table 4). This presentation contrasts with the reported rat oral LD50 of >5,000 mg/kg, which would suggest low acute toxicity [13]. The three other pyraclostrobin cases reported no symptoms, other than vomiting (n = 2). Currently, pyraclostrobin is not listed in the WHO Recommended Classification of Pesticides by Hazard (Table 5) [13]; our data could encourage pyraclostrobin to be classified, at least initially as “slightly hazardous” (class III). More data on pyraclostrobin and its co-formulants would aid in understanding of its potential risk in cases of self-ingestion.

There are many fatal cases of copper sulfate self-poisoning in the literature [27, 28, 33]; however, our data includes only seven non-fatal cases. The published literature suggests a high case fatality of around 14–18.8% [34,35] in contrast to
nearly all other fungicides, suggesting that it should be considered for withdrawal and replacement. However, its additional cultural and industrial uses outside of agriculture might complicate such regulation.

**Limitations**

This study is limited by the lack of confirmed identification of the pesticide by laboratory analysis and by the lack of data on the volume of fungicide ingested for fatal cases in particular. Historically it should be noted that laboratory analysis has confirmed the history of suspected pesticide ingested in >85% of cases in this cohort [14,19]. Our conclusion that fungicide poisoning is relatively non-toxic is limited to the data available. More are required. Previous reports using this data set have listed a death post-ingestion of the C14-demethylase inhibitor hexaconazole (15). Review of the individual medical records suggests that the patient did not die from hexaconazole poisoning.

**Conclusion**

We report on fungicide self-poisoning in a large prospective cohort including 337 cases ingesting twenty-eight fungicides from 5 MoA classes. Deaths occurred from ingestion of edifenphos, propamocarb, and pyraclostrobin. Fungicides are generally less harmful than other agricultural pesticide classes with a case fatality of 1.2% compared to 6.9% for insecticides and 10.0% for herbicides. However, there are toxic exceptions. We call for the withdrawal from market of the OP fungicide edifenphos, review of whether propamocarb should be listed by the WHO hazard classification as propamocarb hydrochloride to reflect its more toxic form used in agricultural formulations, and generation of a WHO hazard classification of pyraclostrobin.

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