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Acute intentional self-poisoning with a herbicide product containing fenoxaprop-P-ethyl, ethoxysulfuron, and isoxadifen ethyl: a prospective observational study

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Background. Herbicides are commonly ingested for self-harm, but relatively little has been published on poisoning with herbicides other than paraquat and glyphosate. We report here a case series of patients with acute exposure to a combination herbicide (brand name Tiller Gold or Whip Super) containing the selective phenoxy herbicide fenoxaprop-P-ethyl, the sulfonylurea herbicide ethoxysulfuron and the safener isoxadifen ethyl. **Method.** Clinical data on all patients presenting with Tiller Gold or Whip Super poisoning to two General Hospitals in Sri Lanka from 2002–2008 were collected prospectively until discharge. **Results.** Eighty-six patients with a history of Tiller Gold or Whip Super ingestion were included. The main clinical features were an epigastric burning sensation and vomiting; however, most of those who vomited had received gastric lavage or forced emesis. Eight patients had a reduced level of consciousness on admission (Glasgow coma scale 9–14) that resolved without intervention over several hours. Only symptomatic and supportive care was required. The median hospital stay was 1 day (IQR: 1–2) and the case fatality was zero (95% confidence interval: 0–4.2%). This low case fatality compared favorably with the case fatality of other common herbicides in our cohort: paraquat >40%, propanil >10%, 4-chloro-2-methylphenoxyacetic acid > 5%, and glyphosate >2%. **Conclusion.** This combination herbicide product appears to be safe in patients with acute self-poisoning, particularly in comparison with other herbicides, and causing few clinical features.

Keywords Fenoxaprop-P-ethyl; Gastric lavage; Tiller Gold; Acute self-poisoning; Sri Lanka

Introduction

Self-poisoning with pesticides is a major public health problem across the Asia Pacific Region.¹ It is estimated that globally 250–370,000 people die from pesticide poisoning each year.² Sri Lanka has a major problem with intentional self-poisoning with high total and youth suicide rates.³ Pesticide poisoning is the fourth leading cause of hospital deaths in agricultural districts of Sri Lanka.^{4,5}

Amongst the herbicides, there is a wide range of toxicity after acute ingestion. Although paraquat is the most lethal, its use is increasingly limited, being replaced by glyphosate and the phenoxy herbicides.⁶ In addition, many newer herbicides have recently entered the market. The effects of acute ingestion of these products have not yet been well studied, particularly in the context of acute self-poisoning.

Fenoxaprop-P-ethyl (FPPE; CAS 71283-80-2; Fig. 1) is a post-emergent phenoxy herbicide of the aryloxyphenoxy propionate group that was first registered in 1987. In Sri Lanka the commercial products Tiller Gold and Whip Super contain FPPE 69 g/L as the principal herbicide together with a less potent sulfonylurea herbicide ethoxysulfuron 20 g/L (CAS 126801-58-9; ES, Fig. 2). Isoxadifen ethyl 75 g/L (CAS 163520-33-0; IE, Fig. 3) is a safener compound that protects crops from potential adverse effects of the

Received 16 March 2009; accepted 9 July 2009.

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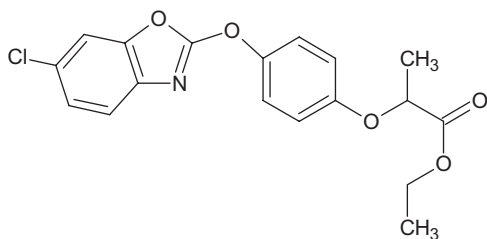


Fig. 1. The chemical structure of fenoxaprop-P-ethyl ((D+)-ethyl-2-[4-(6-chloro-2-benzoxaolxyloxy) phenoxy] propanoate).

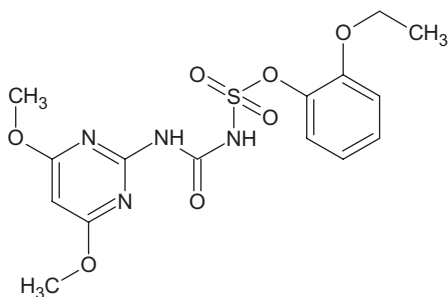


Fig. 2. The chemical structure of ethoxysulfuron (1-(4,6-dimethoxyypyrimidin-2-yl)-3-(2-ethoxyphenoxysulfonyl)urea).

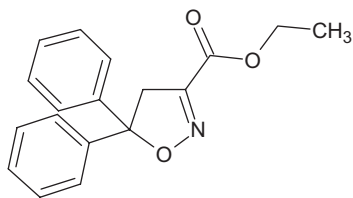


Fig. 3. The chemical structure of isoxadifen-ethyl (ethyl-4,5-dihydro-5,5-diphenylisoxazol-3-carboxylate).

herbicides.⁷ This formulation is a potent herbicide selective for broad-leaved weeds and is used in rice, cereal, and soybean crops.⁸

FPPE exerts its herbicidal action by interfering with fatty acid biosynthesis through inhibition of acetyl-CoA-carboxylase in plant chloroplast. It also inhibits this enzyme in mammalian liver and has produced reversible hepatic toxicity in laboratory studies^{9,10}; ES acts by inhibiting acetolactate synthase and blocking the biosynthesis of branched amino acids.¹¹

Acute human poisoning with this combination herbicide has not previously being reported. The more commonly used phenoxy compounds 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxyacetic acid (MCPA) have significant toxicity, with a mortality greater than 4% in the context of acute self-poisoning.^{12,13} This raises potential concerns about the safety of aryloxyphenoxy propionate herbicides such as FPPE; the toxicological effect of its coformulation with ES and IE is uncertain. Because regulatory

bans on pesticides that are highly toxic to humans may decrease overall mortality from self-poisoning^{2,5} it is essential that human exposures to newer herbicides are carefully recorded to determine their relative toxicity. This will inform regulatory authorities as well as assisting clinicians in the risk assessment and management of patients presenting with acute poisoning.

The aim of this study is to describe the clinical effects and toxicokinetics of self-poisoning with a commercial herbicide formulation containing FPPE, ES, and IE.

Methods

Study design, setting, and patients

This prospective study was nested into an ongoing cohort of all poisonings presenting to two general hospitals of the North Central Province of Sri Lanka (Anuradhapura and Polonnaruwa) between April 2002 and December 2008. We included all patients presenting with a history of poisoning with Tiller Gold or Whip Super as indicated by the history from the patient or accompanying relative and/or by positive identification of the label of the empty container when available. The data collected included demographic details, type and amount of poison, and time from ingestion to admission.

Predetermined clinical observations and complications were recorded prospectively by on-site dedicated study doctors five to six times daily on specially designed data collection forms until death or discharge up until December 2008. Data were entered into a purpose-built clinical database on a hand-held computer twice daily. In the first 51 patients we looked at the clinical notes in medical records for additional information on subjective complaints.

Clinical management of the patients was performed by the ward medical and nursing staff, independently of the research team. Blood samples were collected from all eligible patients on admission, as allowed by clinical factors, for quantification of plasma FPPE concentration. The plasma was separated off and stored at -22°C until transportation to Australia on dry ice for analysis.

Ethics approval was obtained from the Universities of Colombo and Peradeniya (Sri Lanka), Oxfordshire Clinical Research Ethics Committee (UK), Australian National University (Australia), and Sri Lankan Medical Association (Sri Lanka).

Laboratory analysis

Plasma samples were stored at -80°C and analyzed using LC/MS as follows: 50 μL of plasma and 150 μL of internal-standard (etofenprox) solution were vortex mixed and centrifuged. 20 μL of the supernatant was injected onto a Phenomenex Strata-X column ($4 \times 3 \text{ mm}$) and rinsed for 2 min at 200 $\mu\text{L}/\text{min}$ with 9:1:0.01 water : acetonitrile : formic acid. The flow was then switched and the analytes were

back-washed onto a Phenomenex Luna C18 column (2 × 50 mm 5 μm at room temperature) for the final separation. A mobile-phase gradient at 200 μL/min was used with the water : acetonitrile : formic acid ratio ramped to 1:9:0.01 over 3 min and then held at 1:9:0.01 for a further 3 min.

An API 2000 tandem mass spectrometer was used with an electrospray ionization source in positive mode. The following common instrument parameters were used: temperature = 500°C, ionspray voltage = 4,200 V, entrance potential = 10.5 V, collision cell entrance potential = 14, collision cell exit potential = 2 V. The ion-specific parameters for FPPE were MRM: 362→288, declustering potential = 71, collision energy = 23 and for etofenprox MRM: 359→183, declustering potential = 52, collision energy = 31.

Weighted quadratic regression was used to measure the FPPE concentration over the range 0.5–50 ng/mL.

Biochemical analyses were conducted by Queensland Health Forensic and Scientific Services at Princess Alexandra Hospital, Australia. This service is accredited by the National Association of Testing Authorities, Australia, and certified to International Standards (ISO 9001).

Results

During the study period 96 patients with exposure to Tiller Gold and Whip Super were identified. Ten patients (three who co-ingested MCPA, five who had insufficient clinical data, and two occupational exposures) were excluded from further analysis. There were no deaths in this group. Eighty-six cases of acute self-poisoning were analyzed. There were 57 males and 29 females; the median time to present to hospital was 4 h [inter-quartile range (IQR): 2–10 h]. Six patients co-ingested a large amount of ethanol.

The median volume ingested could be estimated in 64 patients and was 22.5 mL (IQR: 20–60). Before presentation to the study hospital, 60 and 6 patients had received forced emesis and gastric lavage, respectively, at the primary care hospitals. Sixteen of the patients received activated charcoal either as part of routine hospital management or a randomized controlled trial that did not demonstrate clinical benefits for pesticide poisoning in general.¹⁴

Symptoms and signs on admission

The reported symptoms and signs of the first 51 consecutive patients are given in Table 1. The commonest features were epigastric pain and vomiting. However, the majority of patients who were vomiting (78%) had received forced emesis or gastric lavage at the primary care hospital.

There were no serious adverse clinical sequelae on admission and thereafter. Clinical observations at the time of presentation (Table 2) and throughout hospital admission for all patients were generally within the reference range. All patients were treated with symptomatic and supportive care

Table 1. Symptoms and signs on admission from 51 patients

Symptoms and signs	Number of cases (%)
Vomiting	23 (45)
Epigastric pain	21 (41)
Difficulty in breathing	14 (27)
Diarrhea	1 (2)
Rhonchi	1 (2)

Table 2. Time to presentation and summary of clinical observations on admission from all the patients

	Number (%)
Time to presentation (h)	Median = 4 h; IQR 2–10 h (N = 86)
<2	5 (5.8)
2 to < 4	28 (32.6)
4 to < 8	25 (29.1)
8 to <12	7 (8.1)
12 to <24	17 (19.8)
>24	4 (4.6)
Glasgow coma score on arrival	Median = 15; IQR 15 to 15 (N = 86)
<7	0
7–9	3 (3.5)
10–12	0
13–14	5 (5.8)
15	78 (90.7)
Systolic blood pressure (mmHg)	Median = 110 mmHg; IQR 110–120 (N = 86)
Not recorded	0
<90	0
90–100	11 (12.8)
101–120	60 (69.8)
121–140	11 (12.8)
>140	04 (4.6)
Pulse rate (beats/min)	Median = 82 beats/min; IQR 76–92 (N = 86)
<60	2 (2.3)
60–80	41 (47.7)
81–100	35 (40.7)
101–120	5 (5.8)
121–140	2 (2.3)
>140	1 (1.2)
Respiratory rate (breaths/min)	Median = 24 breaths min; IQR 20–26 (N = 39)
Not recorded	47 (54.6)
<16	2 (2.3)
16–20	24 (27.9)
21–25	7 (8.1)
26–30	6 (7)

only. No patient required intensive care management or advanced treatments such as intubation or mechanical ventilation for a compromised airway. Most patients (91%) had a normal level of consciousness on admission; of the eight

patients (9%) with a reduced level of consciousness on admission three patients had a Glasgow coma score (GCS) of 9 and 5 patients had a GCS of 14. One patient had co-ingested ethanol and had GCS of 14. The GCS normalized within 22 h post-ingestion in all patients with no specific interventions and no complications from sedation were observed.

Cardiovascular and respiratory system examinations were normal in all patients except rhonchi in one patient and an irregular pulse because of ventricular ectopic beats in two patients on the day of admission. These minor effects resolved by the second day. The median hospital stay was 1 day (IQR: 1–2). There were no deaths giving a case fatality of 0% (95% CI: 0–4.2%).

Biochemical analyses

Routine biochemical analyses (selected electrolytes, liver, and renal function) did not identify marked variations from the usual reference range quoted for western populations.

Plasma FPPE concentration

Of the first 51 patients included in this study, 35 patients provided an admission blood sample, and in 7 of these provided serial blood samples. FPPE was detected in seven patients with a median admission plasma concentration of 2.24 ng/mL (IQR: 0.818–3.05 ng/mL). The median time to hospital presentation in these patients was 2 h (IQR: 2–3). In the remaining 28 patients the FPPE was below the lowest level of quantitation of 0.5 ng/mL and the median time to admission was 4 h (IQR: 2–9). None of the serial samples had plasma concentrations above 0.5 ng/mL.

Discussion

This is the first case series of acute human self-poisoning with a herbicide product containing FPPE, ES, and IE and our study indicates that this combination product is a relatively safe herbicide in this context. The statistical estimate of the upper end of the 95% CI for the case fatality (up to 4.2% case fatality) is very conservative. As there were no serious or life-threatening complications observed in these patients

the credible range for case fatality should be lower. This is supported by animal laboratory data, which also indicate low toxicity of each agent in the formulation and the commercial product (see Table 3 for LD₅₀ data).⁸ This product appears to demonstrate lower acute human toxicity than any of the other common herbicides for which we have prospectively collected data (Fig. 4).¹⁵

The mild clinical features observed in this case series are reassuring. The high incidence of vomiting may be due to the administration of gastric lavage or forced emesis rather than due to an inherent property of the herbicide.

Reduced level of consciousness is an important determinant of the immediate care given to patients with poisoning. Patients who present with a low GCS frequently need mechanical ventilation, which is not readily available in the developing countries. Furthermore, these patients are prone to develop complications such as aspiration pneumonitis and possibly sepsis. A small proportion (8/86) of patients in this series developed a transient reduction in the level of consciousness as measured by the GCS but all were able to protect their airway without intubation and none developed complications.

Data in rats show that FPPE is rapidly absorbed after oral ingestion and metabolized to benzoxazol mercapturic acid and hydroxyphenoxy propionic acid.^{16,17} In rats, the metabolites appear to be more persistent than the parent compounds, with an initial elimination half-life of 8.5–12.5 h followed by a terminal elimination half-life of 27–73 h in the urine.¹⁷ In this study we did not measure these metabolites to confirm

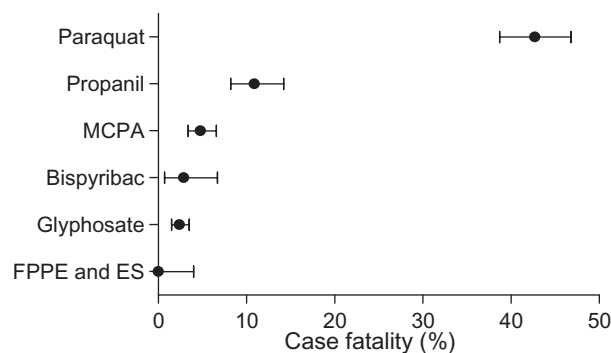


Fig. 4. The case fatality (95% confidence interval) of self-poisoning with the herbicides most commonly used for self-harm in Sri Lanka.

Table 3. Animal toxicity data on rats with different compounds co-formulated in FPPE containing commercial products

	FPPE (69 g/L)	Isoxadifen ethyl (IE) (75 g/L)	Ethoxysulfuron (ES) (20 g/L)	Commercial product (FPPE + IE + ES)
LD ₅₀ acute oral	3,150–4,000 mg/kg	1,740 mg/kg	3,270 mg/kg	>5,000 mg/kg
LD ₅₀ acute dermal	>4,000 mg/kg	>2,000 mg/kg	>4,000 mg/kg	>5,000 mg/kg
LC ₅₀	4.3 mg/L	>5 mg/L	>3.55 mg/L	4.2 mg/L

LD₅₀ and LC₅₀ are the dose and concentration, respectively, that kills 50% of the laboratory animals.

exposure. In mammals, 90% of ES is absorbed compared with between 46 and 82% of IE with oral exposure.¹¹

Only seven patients tested positive for FPPE, and none of the serial plasma samples had a concentration greater than 0.5 ng/mL. This may suggest that FPPE is rapidly absorbed and completely metabolized within 3 h, which is why FPPE was not detected in patients who presented to hospital 4 h or more post-ingestion. We found the peak plasma concentration of FPPE to be low. If absorption is indeed rapid, it is likely that the true peak concentration occurred in our patients before presentation at hospital. In addition to rapid absorption and/or elimination, the low peak FPPE concentration may also reflect the low concentration of FPPE in the formulation, small ingestion volumes, and/or a low bioavailability. Unfortunately, it is not possible to estimate the relative influence of these various factors from plasma concentration data alone. The collection of serial plasma and urine samples for quantification of the concentration of metabolites may be useful in this regard and should be considered in future studies.

Limitations

This study was conducted in two secondary hospitals in North Central Province of Sri Lanka where resources are severely limited, including radiology and laboratory services. We did not look at the mortality from this combination herbicide in primary care hospitals in this province. However, the overall mortality (for all pesticides) at peripheral hospitals is only 1.2%.¹⁸ Furthermore, such patients are usually rapidly transferred from local hospital to secondary hospitals; therefore, it can be assumed that the case fatality at the secondary hospitals is representative for this herbicide.

Conclusion

A potentially successful method for reducing deaths from pesticide poisoning is through restricting access to highly lethal pesticides. Many commercial herbicide formulations are highly toxic; whereas the case fatality for this FPPE-, ES-, and IE-containing herbicide product is relatively low. This may mean that there would be public health benefits from encouraging its use in the place of more toxic herbicide products, in particular the selective herbicides propanil (case fatality 10.5%) and bispyribac sodium (case fatality 2.7%).^{19,20}

Acknowledgments

We thank Dr. M. Suntharalingam, Dr. S.K. Kodisinhghe, and Dr. P.A.I. Wijayanayaka for their help in data collection, the hospital physicians for their assistance with the study, the medical superintendents of General Hospital Anuradhapura and Polonnaruwa for giving permission to access the medical

records, SACTRC Clinical Research coordinators and Clinical Research Assistants for their support in data collection, and Dr. Gamini Manuweera (pesticide registrar of Sri Lanka) for his advice about agricultural indications for herbicides. The South Asian Clinical Toxicology Research Collaboration is funded by the Wellcome Trust/National Health and Medical Research Council International Collaborative Research Grant 071669MA. ME is a Wellcome Trust Career Development Fellow funded by grant GR063560MA.

Declaration of interest: The work was funded by Wellcome Trust and National Health and Medical Research Council International Collaborative Research Grant 071669MA. ME is a Wellcome Trust Career Development Fellow funded by grant GR063560MA.

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