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A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning

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Context. The case fatality from acute poisoning with glyphosate-containing herbicides is approximately 7.7% from the available studies but these have major limitations. Large prospective studies of patients with self-poisoning from known formulations who present to primary or secondary hospitals are needed to better describe the outcome from acute poisoning with glyphosate-containing herbicides. Furthermore, the clinical utility of the glyphosate plasma concentration for predicting clinical outcomes and guiding treatment has not been determined. **Objective.** To describe the clinical outcomes, dose–response, and glyphosate kinetics following self-poisoning with glyphosate-containing herbicides. **Methods.** This prospective observational case series was conducted in two hospitals in Sri Lanka between 2002 and 2007. We included patients with a history of acute poisoning. Clinical observations were recorded until discharge or death. During a specified time period, we collected admission ($n = 216$, including five deaths) and serial ($n = 26$) blood samples in patients. Severity of poisoning was graded using simple clinical criteria. **Results.** Six hundred one patients were identified; the majority ingested a concentrated formulation (36%, w/v glyphosate). Twenty-seven percent were asymptomatic, 63.7% had minor poisoning, and 5.5% of patients had moderate to severe poisoning. There were 19 deaths (case fatality 3.2%) with a median time to death of 20 h. Gastrointestinal symptoms, respiratory distress, hypotension, altered level of consciousness, and oliguria were observed in fatal cases. Death was strongly associated with greater age, larger ingestions, and high plasma glyphosate concentrations on admission ($>734 \mu\text{g/mL}$). The apparent elimination half-life of glyphosate was 3.1 h (95% CI = 2.7–3.6 h). **Conclusions.** Despite treatment in rural hospitals with limited resources, the mortality was 3.2%, which is lower than that reported in previous case series. More research is required to define the mechanism of toxicity, better predict the small group at risk of death, and find effective treatments.

Keywords Toxicokinetics; Suicide; Pesticide; Mortality; Prognosis

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ME, NAB, and AHD designed the clinical studies to which the patients were recruited. DMR, NAB, ME, FM, and AHD contributed to the collection of data and coordination of these studies. DMR, DAG, and FM arranged the collection and transport of plasma samples from Sri Lanka to the United States. DAG coordinated the analysis of the plasma samples which were conducted by AM and MSB who take responsibility for these data. DMR and FM coordinated the chart review. DMR extracted and analyzed the data and drafted the initial manuscript. All authors contributed to the final version of the manuscript and approve its submission. DMR coordinated the development of the manuscript, retains full access to the data presented, and had final responsibility for the decision to submit for publication.

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Introduction

Glyphosate-containing herbicides are used extensively and increasingly in both domestic and agricultural contexts worldwide.¹ They have favorable toxicity with occupational and accidental exposures, broad-spectrum efficacy including herbicide-tolerant crops, and favorable environmental impact data.^{2,3} In the United States, for example, in 2001 glyphosate-containing herbicides were the most commonly used pesticide compared with 17th in 1987.⁴

Reflecting their widespread use, there are frequent reports of exposure to glyphosate-containing herbicides. U.S. poison control center data between 2001 and 2007 report glyphosate to be the most common herbicide exposure. Each year there were more than 4,000 exposures to glyphosate-containing herbicides of which approximately 800 were evaluated in a health care facility. However, only 373 of these cases were intentional (suicidal) ingestions. If we assume that only these exposures lead to significant poisoning, the case fatality was 3.8%, with another 11.8% suffering major poisoning.^{5–11} However, poison center data studies usually underestimate deaths^{12–14} and therefore case fatality.

Series of intentional ingestions of glyphosate-containing herbicides from Asia suggest greater lethality. Aggregated data from Taiwan,^{15–20} Korea,²¹ and Japan^{22,23} report a combined case fatality of 7.7% (range 6.7–29.3%, $n = 2727$). Approximately 20% of these cases were considered accidental exposures, suggesting that the case fatality with intentional poisoning might be even higher. These Asian data were largely derived from retrospective studies in tertiary hospitals or poison centers. Such study designs are prone to both selection/referral and reporting biases that may have led to substantially over- or underestimated case fatality. No previous large studies have been prospective or examined the concentration of glyphosate as a biomarker of exposure.

Different clinical outcomes may also relate to the type of product used. Globally, glyphosate-containing herbicides are available in various formulations ranging from ready-to-use formulations (~1–5% glyphosate acid equivalent) to concentrates requiring dilution before use (~30–50%). Products also contain co-formulants, in particular surfactants that improve penetration of the herbicide into the plants and that appear to contribute substantially to the toxicity profile.²⁴ In the context of acute poisonings, it is generally considered that surfactants are the most toxic component in the product and that concentrated products are more hazardous than dilute ones^{3,25} although the glyphosate-salt may also contribute.²⁶

Here, we describe the clinical toxicology of glyphosate products in a large prospective sequential observational case series of adults with acute intentional self-poisoning. Clinical outcomes, relationship with plasma glyphosate concentration, and glyphosate toxicokinetics are presented.

Methods

Clinical

We have prospectively established a large clinical database of every patient with an acute poison exposure presenting to Anuradhapura and Polonnaruwa Hospitals in Sri Lanka following direct admission or through transfer from a remote hospital where they were medically assessed. These are regional referral hospitals that provide 24-h medical and nursing care to patients in dedicated medical wards.

Every patient presenting to these study hospitals with a history of an acute exposure between April 4, 2002 and June 2, 2007, was reviewed by on-site study doctors. Following an initial clinical assessment and resuscitation, the history of exposure (including co-ingestants) was obtained on presentation for each patient. The exposure for each patient is determined based on the history provided by the patient or their relatives and/or the commercial preparation found with the patient. An admission blood sample to confirm the history of exposure was provided, their eligibility for various substudies was considered, and written informed consent was obtained. All patients received supportive care, including supplemental oxygen, intravenous fluids, and ventilatory and hemodynamic (dopamine) support as required.

Patients presenting to study hospitals between April 2002 and October 2004 were eligible for enrollment in a randomized controlled trial assessing the efficacy of activated charcoal in the treatment of acute poisoning. This study did not show a difference in clinical outcomes between activated charcoal and control.²⁷ Patients who were not enrolled in the charcoal trial were eligible for enrollment in a toxicokinetic study. Here, in addition to the admission blood sample, serial samples were provided by patients at 1, 4, 12, and 24 h, then once daily until discharge or death, as allowed by clinical factors. Blood was collected into an EDTA tube that was promptly centrifuged and the plasma was removed and frozen at -23°C until the time of analysis.

Patients were regularly reviewed (at least four times daily for new admissions and while clinically unstable) and routine bedside clinical observations were recorded prospectively by on-site study doctors until discharge or death. Resources are severely limited at these rural hospitals, so laboratory analyses, invasive clinical measurements, and endoscopic procedures are usually unavailable. To obtain additional clinical information on the deaths, the hospital medical notes were retrospectively reviewed (if available) using a predesigned data collection sheet by a clinical trial coordinator at each center.

We analyzed patients with a history of ingestion of a glyphosate-containing herbicide in this database. Patients were excluded if they had co-ingestion of another poison (excluding ethanol). We graded the severity of poisoning on the basis of predetermined clinical criteria using a simple system (Table 1) based on clinical features of glyphosate poisoning

Table 1. Clinical grading of severity of poisoning

| | |
|--------------------|--|
| Asymptomatic | |
| Minor | Spontaneously resolving minor poisoning (e.g., nausea, vomiting, abdominal pain, sedation) with stable vital signs and no other organ involvement |
| Moderate to severe | Poisoning requiring intervention, for example, hypotension (MABP < 70 mmHg), respiratory failure requiring intubation, ventricular dysrhythmias or cardiac arrest, marked sedation or coma (GCS < 10), seizures, or oliguria |
| Fatal | |

that are included in the Poisoning Severity Score that was developed, tested,²⁸ and subsequently validated.²⁹ The patient was classified to the most severe poisoning category depending on clinical signs and symptoms documented at any time during admission.

The amount ingested was quantified according to the history using methods described previously.^{15,16} Here, “a little” or “teaspoon” was 5 mL, a “mouthful” was 25 mL, a small cup was 100 mL, a glass was 300 mL, and a bottle was 400 mL. If the patient reported a range of possible exposures (e.g., 2–4 mouthfuls), the mean value was taken.

For the duration of this study there were no major changes in clinical management of patients with acute poisoning with a glyphosate-containing herbicide. There are no effective specific interventions for patients with acute glyphosate-containing herbicide poisoning.

Laboratory

Blood samples from patients presenting between May 8, 2002, and August 30, 2005, inclusive were sent for quantification of the concentration of glyphosate by Monsanto (St. Louis, MO, USA). Control samples (nonpesticide poisoning) were also sent and the analysts were blinded to the identity of the patient, the time of collection, and clinical outcomes.

Blood samples were centrifuged and 0.1 mL portion of the supernatant was mixed with 0.9 mL of deionized water. The diluted plasma was passed through a C18 solid-phase extraction cartridge (300 mg) followed by serial rinses with additional deionized water to a total volume of 3 mL. Glyphosate was quantitated using high-performance liquid chromatography equipped with a postcolumn reaction system specific for primary amines.³⁰ In the postcolumn reactor, addition of sodium hypochlorite oxidized glyphosate to glycine, which reacted with *o*-phthalaldehyde to form a fluorescent derivative. A fluorescence detector measured the resulting product with excitation at 340 nm and emission at 455 nm. This method was validated to quantify glyphosate concentrations from 1.5 to 9,000 µg/mL with a sample size of 0.1 mL of plasma.

Thirty-two spiked plasma samples with concentrations ranging from 1.5 to 6,000 µg/mL were included in the analytical runs and the median recovery in these samples was 95.9%.

Kinetics and the dose–response relationship of glyphosate

The toxicokinetics of glyphosate were determined in serial blood samples provided by patients presenting between April 11 and August 30, 2005, who provided a sample on two or more occasions. Because of uncertainty in the dose and bioavailability in humans, the only kinetic parameter that could be determined was the apparent half-life, presumed for purposes of discussion to represent elimination. Concentration–time data from six individuals providing four or more samples were plotted on a semilogarithmic graph to confirm that elimination was first order. Then, data from all patients providing two or more samples were combined to determine the best-fit apparent elimination half-life and 95% CI for the cohort. This was performed by nonlinear regression with global fitting of the rate constant in a monoexponential decay model [$C_t = C_i \times \exp(-kt)$]. Here, C_i is the initial concentration and C_t is the concentration after time t when elimination occurs with a rate constant of k . Data following an apparent C_{\max} were included in this regression if patients had two or more samples with concentrations greater than the limit of quantification (LOQ) (1.5 µg/mL). Concentrations below the LOQ were included in the analysis using the method of Beal³¹ by fixing the first value lesser than the LOQ to 0.75 µg/mL (LOQ/2) and excluding subsequent values.

The dose–response relationship was demonstrated graphically by plotting the available glyphosate concentration–time points relative to the clinical outcome (survival or death) for each patient.

Statistical analyses

Statistical analysis compared baseline clinical and demographic characteristics for patients in four groups: asymptomatic, mild, moderate to severe, and fatal poisoning, as defined in Table 1. The χ^2 test was used for categorical variables and continuous nonparametric variables were compared using the Kruskal–Wallis test. Receiver–operator characteristic (ROC) curves were constructed to demonstrate the practical prognostic utility of three variables from Table 1 that were most strongly associated with death. We also present the likelihood ratio, sensitivity, and specificity at the best threshold (as determined by Youden’s index). Sensitivity is defined as the proportion of people who died that were predicted to die, and specificity as the proportion of people who survived that were predicted to survive. All analyses were conducted using GraphPad Prism version 4.03 for Windows, GraphPad Software, San Diego, CA, USA (www.graphpad.com), and $p < 0.05$ was considered statistically significant.

Ethical approval

Ethics approval for each of the above studies was obtained from the relevant institutions in Sri Lanka (the Universities of Colombo, Peradeniya and/or Sri Lankan Medical Association) and the lead researcher's university [Oxfordshire Clinical Research Ethics Committee (UK) or Australian National University].

Results

Over 5 years, there were 601 presentations with a history of ingestion of glyphosate-containing herbicides that were eligible for inclusion, see Table 2. Of these, 27.7% patients were also enrolled in the previously mentioned randomized controlled trial assessing the efficacy of activated charcoal in the treatment of acute poisoning.²⁷ Nearly all the exposures were because of intentional self-poisoning. A patient who died following an acute myocardial infarction in whom glyphosate was not detected in the plasma was excluded following data extraction.

The majority of patients presented with ingestion of the concentrated formulation (29 of 30 brands in Sri Lanka are 36%, w/v and one is 12%, w/v of glyphosate acid equivalent; no patient specifically reported ingesting a nonconcentrated solution). No patients were transferred from the study hospital to another hospital for further management and so follow-up to discharge was complete for all patients. The time to presentation was not significantly longer in more severe poisonings (Table 2).

Blood samples from 216 patients, representing 77.4% of patients who presented during this period, were analyzed for glyphosate, including serial samples in 26 patients.

Clinical outcomes

About 27.6% of patients remained asymptomatic from presentation until discharge. The majority of patients (64%) developed signs of minor poisoning only. Gastrointestinal manifestations were documented in 83% of patients with minor poisoning at the time of arrival, mostly nausea, vomiting, diarrhea, and abdominal pain. Other toxicities in minor poisonings included transient hypotension (5% of patients, mean arterial blood pressure < 70 mmHg), bradycardia (heart rate < 60 beats/min) or tachycardia (heart rate > 100 beats/min), and tachypnea (respiratory rate > 25). Respiratory crackles were noted on auscultation in 8% of patients who were diagnosed with aspiration pneumonitis and treated with intravenous antibiotics. The mainstay of treatment for these patients was intravenous fluids and clinical observation.

Moderate to severe poisoning occurred in 5.5% of patients (33 patients) and led to longer admissions (Table 2). Gastrointestinal symptoms, similar to those with minor poisoning, were still the most common manifestation of toxicity. Bilateral respiratory crackles were noted in six patients, four patients were tachypneic (respiratory rate > 25/min) and one patient required intubation and ventilation for respiratory failure. Hypotension (mean arterial blood pressure < 70 mmHg) was noted during hospitalization in 48% of these 33 patients, most commonly at the time of admission. Other markers of moderate to severe poisoning included seizures (two patients) and/or a depressed level of consciousness (12 patients).

There were 19 deaths, giving a case fatality of 3.2%. The median time to death was 20 h (interquartile ranges 12–53 h) and most deaths occurred within 72 h of poisoning (Fig. 1). Most deaths occurred in medical wards because of very

Table 2. Clinical outcomes, demographics, and clinical features at the time of presentation to hospital

| Severity of poisoning | Asymptomatic | Minor | Moderate to severe | Fatal | Statistical significance |
|---|-------------------------|----------------------------|----------------------------|-------------------------------|--------------------------|
| N (%) | 166 (27.6) | 383 (63.7) | 33 (5.5) | 19 (3.2) | |
| Gender (M:F) | 101:65 | 228:155 | 25:8 | 18:1 | p = 0.0062 |
| Age (years) | 24 (18–32) | 25 (20–33) | 25 (21–34) | 46 (35–52) | p < 0.0001 |
| Reported volume ingested (mL) | 50 (25–90; n = 75) | 58 (25–100; n = 242) | 53 (25–125; n = 10) | 200 (75–350; n = 12) | p = 0.0072 |
| Time to present ^a (h) | 4.9 (3.2–8.3) | 4.7 (3.0–8.6) | 4.3 (2.4–6.0) | 5.0 (3.1–8.5) | p = 0.4048 |
| Glasgow coma score | 15 (15–15) | 15 (15–15) | 15 (9–15) | 15 (14–15) | p < 0.0001 |
| Mean arterial blood pressure (mmHg) | 90 (83–93) | 90 (83–93) | 83 (67–93) | 87 (73–93) | p = 0.0024 |
| Gastrointestinal symptoms (%) | 0 | 83 | 67 | 79 | |
| Time to discharge or death ^{a,b} (h) | 39 (29–47) | 44 (35–53) | 47 (40–73) | 20 (12–53) | p < 0.0001 |
| Glyphosate plasma concentration (µg/mL) | 2.9 (0.0–46.5) (n = 69) | 40.8 (1.6–139.4) (n = 129) | 72.4 (18.9–104.2) (n = 13) | 1373.0 (820.7–1929.0) (n = 5) | p < 0.0001 |

Median values and interquartile ranges presented.

^aThe time of poisoning was not recorded or unknown for two asymptomatic patients, four patients with minor poisoning, two patients with moderate-severe poisoning, and one patient who died.

^bTime to discharge or death is from the time after poisoning.

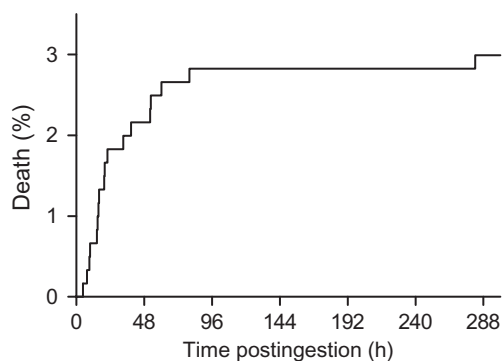


Fig. 1. Survival curve showing the time to death after poisoning. Time of poisoning unknown for one patient, so the median value of the others was used to construct the curve.

limited intensive care beds. Observations at the time of admission did not accurately reflect the much more severe poisoning (Table 2). Similar to the survivors, gastrointestinal signs and symptoms were commonly reported, including ileus and a distended and painful abdomen in three patients. An altered level of consciousness was noted in some patients and seizures were reported in one patient at the time of a cardiorespiratory arrest. Oliguria was also noted in five patients. This was not necessarily in the context of hypotension and generally did not respond to fluids, inotropes, and diuretics.

Respiratory crackles were noted in 11/19 patients (58%) who died and were usually associated with respiratory distress suggesting pulmonary edema. Three patients also had hypotension and a fever suggesting possible aspiration pneumonia and sepsis. They were administered intravenous antibiotics, fluids, and a dopamine infusion.

Death occurred because of progressive hypotension associated with tachycardia or bradycardia despite inotropic support with dopamine infusions and adrenaline boluses in three patients. This was associated with respiratory distress and hypoxia (pulse oximetry < 90% on room air). Hypotension was noted in two other patients on admission, but this early hypotension improved and did not appear to contribute to death.

Compared with patients with less severe poisoning, those who died were more likely to be older, male, and to present with decreased consciousness (Table 2). ROC curves demonstrated moderate predictive utility for age, amount ingested, and concentration (see Fig. 2) but not Glasgow coma score (area under the curve = 0.60 and $p = 0.132$, ROC plot not shown).

Dose–response and toxicokinetics of glyphosate

Patients who died ingested significantly larger amounts (Table 2), but reported volumes were highly variable within each group and the best cut-point of >190 mL of the concentrated formulation had a specificity of 86% and sensitivity of only 58% for predicting death (Fig. 2). Glyphosate plasma concentrations were also significantly higher in patients who

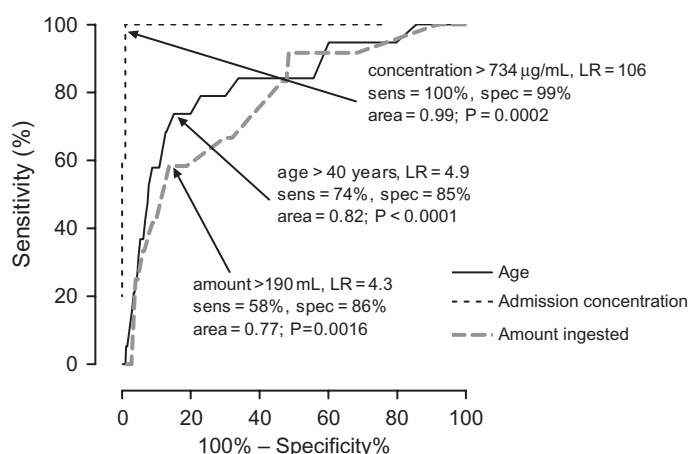


Fig. 2. Receiver operator characteristic curves demonstrating the prognostic utility of age, amount ingested, and admission concentration to predict death. LR is likelihood ratio, sens is sensitivity, and spec is specificity.

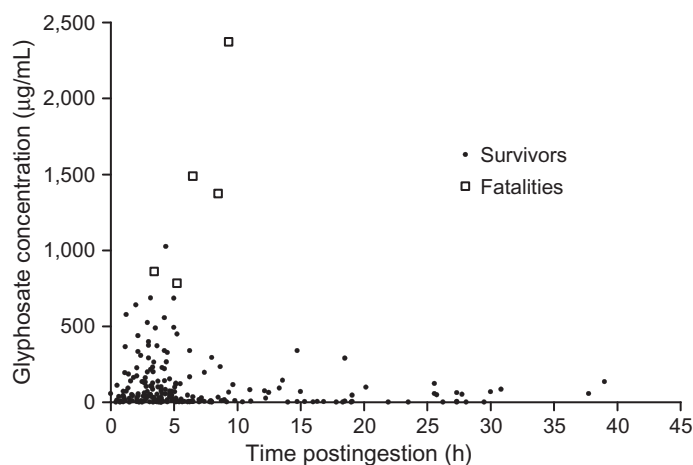


Fig. 3. Dose–response relationship, demonstrating an approximate separation between survivors and fatalities.

died as shown in Table 2 and Figs 2 and 3. A glyphosate plasma concentration greater than 734 $\mu\text{g/mL}$ was the best predictor of death with a likelihood ratio of 106 (Fig. 2). However, this simply reflects the lowest peak value observed among fatal cases (Fig. 3; $n = 5$) and requires independent validation in a larger new data set.

Glyphosate plasma concentration–time profiles were available in 21 patients who experienced only mild poisoning; glyphosate was not detected in five asymptomatic patients. In most patients, the initial plasma sample was the maximum concentration, suggesting rapid absorption of glyphosate. This was followed by an elimination phase with log linear decline in plasma concentration, suggesting first-order elimination (data not shown). In three patients, the changes in concentration were bizarre, suggesting mislabeling of the

date or time on the sample. These results were excluded from the regression analysis. The best-fit apparent elimination half-life of glyphosate was 3.1 h with a fairly narrow 95% CI of 2.7–3.6 h. In a sensitivity analysis including the data from the three patients with bizarre changes in concentration, the estimates of elimination half-life only increased by 2.6%.

Discussion

This is the largest reported prospective series of patients with acute intentional self-poisoning with herbicides containing glyphosate. Most patients demonstrated mild clinical effects and settled with routine supportive care. Mortality was 3.2% and deaths occurred following increasing cardiorespiratory toxicity over many hours, the pathophysiology of which is poorly defined. It is not known whether improved access to intensive care facilities or laboratory services would have improved these outcomes. The mortality in this series is lower than other studies of glyphosate poisoning and is likely to be more representative of the true outcome from self-poisoning given the study design. Patients with a history of ingestion of a large volume of glyphosate-containing herbicides in Sri Lanka or a high glyphosate plasma concentration on admission are more likely to die.

Gastrointestinal symptoms were the most common manifestations of acute poisoning, including abdominal pain with nausea, vomiting, and/or diarrhea. Similar to previous studies,^{15,16,18,22,25,32} these symptoms were usually mild and self-resolving. However, in severe poisoning gastrointestinal symptoms were recurrent, leading to dehydration and possibly contributing to hypotension. Other markers of severe poisoning included pulmonary edema or pneumonitis, oliguria, and altered level of consciousness. These are also reported in previous studies, in addition to hepatic dysfunction, hyperkalemia, dysrhythmias, and acidosis which may be transient or severe. In previously reported fatal cases, these multi-system effects progress over 12–72 h to shock and death despite supportive care,^{15,16,18,20–22,25,33,34} a time course of clinical symptoms and death similar to this study (Fig. 1).

It has not been determined whether these clinical features reflect primary (direct) or secondary (indirect) toxic effects of these herbicide formulations. Further research is required including cases of acute poisoning with detailed and specific investigations into the mechanism of toxicity. Proposed mechanisms include disruption of cellular membranes (including mitochondrial) and uncoupling of oxidative phosphorylation, which may be interrelated.^{25,35} Better understanding of mechanisms might lead to rational antidote development and specific treatments to improve outcomes, but until then only general supportive care can be recommended.

Worldwide variations in brands of glyphosate-containing herbicide formulations over the last 20 years may influence regional differences in case fatality. Surfactants are considered the most toxic component in glyphosate (and other herbicide)

formulations but other co-formulants may also contribute.^{25,26} There are various brands of glyphosate-containing herbicides that have different formulations. Differences involve the glyphosate salt (most commonly potassium or isopropylamine; trimesium is no longer available), type and amount of surfactant, and, in a few products, solvents other than water. Historically, the most commonly used surfactant in these products is polyoxyethyleneamine (POEA or tallow amine). The concentration of POEA varies from 7 to 15%. The composition of glyphosate-containing products in Sri Lanka is likely to be similarly varied although the formulations are not publicly available because of commercial interests. At least two brands marketed in Sri Lanka are based on the original Monsanto formulation that consists of 41% glyphosate isopropylamine (equivalent to 36% of the glyphosate acid) and 15% POEA surfactant.

Previous series have proposed markers of poisoning for predicting clinical outcomes. Patients developing the following clinical effects appear to be more likely to die: acute kidney injury, hyperkalemia, pulmonary edema, and metabolic acidosis.^{18,19} Furthermore, patients with extensive erosions of the upper gastrointestinal tract are more likely to develop severe systemic poisoning and require prolonged admission.³² Unfortunately, these features could not be evaluated in our study because resources for biochemical and endoscopic investigations were not available. Ingestion of larger volumes of concentrated formulations causes increasing severity of poisoning.^{16,18,20–22} This may reflect either the total dose ingested or the direct effects of co-formulants.^{16,32} In our study, poisoning severity also related to the reported amount ingested (Fig. 2 and Table 2) supporting other studies.^{15,16,18,20,22} Other studies also support our observation that death is more likely with increasing age.^{15,16,20}

The importance of measuring the plasma concentration of glyphosate has not been fully assessed. It can obviously confirm exposure for forensic purposes but it might also have a role with quantifying or predicting the severity of poisoning.³⁶ Glyphosate is considered to be of low toxicity, so the rationale for quantification is that it is a reasonable surrogate measure of exposure to unmeasured co-formulants. A previous study reported concentrations greater than 1,000 µg/mL in patients with severe poisoning,³⁷ however, in our data, death occurred with a concentration as low as 734 µg/mL (Figs 2 and 3). It is tempting to suggest that this could be used to predict individuals at risk of death. However, as it is a surrogate for the more toxic co-formulants, this may only relate to exposures with formulations similar to those used in Sri Lanka. Globally, glyphosate formulations vary widely in the ratio of glyphosate to surfactant (including a few without surfactant at all) and the surfactant used. Therefore, more research is required to confirm the utility of quantification of glyphosate in patients with self-poisoning.

There are limited human data on the kinetics of glyphosate. It undergoes minimal metabolism *in vivo* and is renally eliminated.^{3,38} Data from a previous report³⁷ and our study suggest that glyphosate is rapidly absorbed with a peak concentration

generally within 4–6 h, followed by an apparent elimination half-life of 3–4 h. In one case, glyphosate was still present in serum up to 5 days postingestion in a patient with renal failure who was also treated with hemodialysis.³⁹

Based on our experience and the kinetics, we make the following suggestions for the management of acute poisoning with glyphosate-containing herbicides. Patients with a history of intentional ingestion (particularly if greater than 190 mL of a concentrated formulation) and with gastrointestinal symptoms should be observed for at least 24 h. All patients should receive routine clinical observations, resuscitation, and supportive care. The role of hemodialysis in improving outcomes is debated but would require accurate identification of those at high risk.^{15,18,33,34,40,41}

Limitations

The patients described were treated in hospitals where staffing, resources, and investigations are extremely limited. For example, chest X-rays and routine biochemistry were not available to guide clinical management and clarify the etiology of clinical observations such as respiratory crackles, oliguria, and hypotension. However, these results are likely to be an accurate reflection of the clinical outcomes from acute intentional self-poisoning with glyphosate-containing herbicides in developing countries.

Blood samples were obtained from 77.4% of the 279 patients (including only five deaths) who presented during the period from which we analyzed admission samples, and no samples were analyzed from the later years of the cohort. Clinical priorities did not allow collection in every patient and we believe the samples are likely to be representative. Following glyphosate quantification, the remaining plasma was unfortunately discarded. This prevented the analysis of biomarkers of toxicity or other chemicals such as isopropylamine.

Conclusion

In this large prospective case series, 91.3% of patients demonstrated minimal symptoms, 5.5% moderate to severe poisoning, and the case fatality was 3.2%. The median time to death was 20 h and predictors of death were increasing age, amount ingested, and plasma concentration of glyphosate on admission. This case fatality is lower than previously reported despite limited resources for treatment.

Acknowledgments

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Declaration of interest statement

DAG, AM, and MSB are employees of Monsanto Company that produces and distributes glyphosate-containing herbicides. AM and MSB were blinded to clinical details of the plasma samples. By prior arrangement, employees of Monsanto Company were provided with the opportunity to comment on the manuscript but the final decision regarding its contents and the decision to submit rested with the South Asian Clinical Toxicology Research Collaboration.

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