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Acute human self-poisoning with bispyribac-containing herbicide Nominee®: A prospective observational study

Indika Bandara Gawarammana^{1,2}, Darren M Roberts^{2,3}, Fahim Mohamed², Michael S Roberts⁵, Gregory Medley⁵, Shaluka Jayamanne⁴, and Andrew Dawson^{2,6}

¹Department of Medicine, Faculty of Medicine, University of Peradeniya, Sri Lanka

²South Asian Clinical Toxicology Research Collaboration, Faculty of Medicine, University of Peradeniya, Sri Lanka

³Burns, Trauma and Critical Care Research Centre, Faculty of Medicine, University of Queensland, Australia

⁴General Hospital, Polonnaruwa and Faculty of Medicine, University of Kelaniya, Sri Lanka

⁵Therapeutics Research Unit, School of Medicine, University of Queensland, Australia & School of Pharmacy & Medical Science, University of South Australia

⁶School of Medicine and Public Health, University of Newcastle, Australia

Abstract

INTRODUCTION—Self poisoning with herbicides is an important reason for hospital admission and death in Asia. Whilst some herbicides have a well described toxicity profile in humans, many of the newer compounds rely on extrapolation from animal results as no published literature on clinical outcomes of human self poisoning has been described. One example of these compounds is bispyribac, a selective herbicide used in rice and wheat cultivation that is marketed in two containers, one containing bispyribac 400g/L with a solvent and the other the surfactant, polyethylene glycol. We present the first case series of acute human self-poisoning with a herbicide product containing bispyribac.

METHODS—Clinical data for all patients who presented with acute poisoning from a bispyribac-containing herbicide (Nominee®) to two General Hospitals in Sri Lanka from June 2002 until January 2009 were collected prospectively. Admission and serial blood samples were collected from consenting patients to confirm exposure and study the toxicokinetics of bispyribac, respectively.

RESULTS—110 patients with a history of bispyribac ingestion presented after a median time of 4 hours post ingestion. There were three deaths at 15, 6 and 5 hours post-ingestion due to asystolic cardiac arrest. All three patients had reduced GCS (3, 12 and 13 respectively) of whom the former two had co-ingested ethanol and developed tonic clonic seizures. Admission blood sample was obtained from the former two of these patients but bispyribac was detected in only one of these patients. The other patient presented 2.5 hours post-ingestion with a GCS of 12 but bispyribac was not detected. Excluding the patient with undetectable bispyribac, a conservative estimate of the case fatality ratio at 1.81% (95% CI 0.32- 5.8) can be made. The majority of the remaining patients had self-limiting upper gastrointestinal symptoms and 8 patients had an abnormal Glasgow Coma Score on presentation to hospital. The overall median hospital stay was 3 days. Bispyribac was not detectable on admission in 21 patients; in the remaining patients, the median plasma concentration was 50.55µg/mL (IQR 1.28- 116.5; n=32). The peak concentration was

noted around 3 hours post-ingestion and plasma bispyribac concentration did not predict the severity of poisoning.

CONCLUSION—The majority of patients developed self-resolving symptoms and were successfully managed in rural general hospitals without transfer to larger tertiary hospitals. Patients who died developed significant poisoning within 6 hours and plasma bispyribac concentrations did not appear to predict mortality. The lack of correlation between bispyribac outcomes and available plasma concentrations may be due to exposure to non-bispyribac components or other undefined factors. Clinical outcomes from acute self-poisoning with bispyribac-containing herbicides appear to be relatively more favourable than other commonly used herbicides.

Introduction

Intentional self-poisoning with herbicides is an important public health problem in the Asia-Pacific region with an estimated 300,000 deaths occurring each year^{1,2}. Herbicides such as paraquat and propanil with case fatality ratios of over 10% and 60% respectively contribute to this mortality.³ Newer herbicide compounds are continually being developed and marketed. This almost always occurs in the absence of data on human toxicity or systems to collect data on outcomes from acute poisoning. For regulatory purposes, the potential for toxicity to humans is often extrapolated from animal studies, the precision of which is usually poorly validated. As a consequence, data reporting the clinical outcomes from human exposures to these newer herbicides is urgently required to confirm prior regulatory assessments. Such information can also assist clinicians in the risk assessment and management of patients with acute exposures. The information may also assist policy decisions by regulatory agencies in defining the relative toxicity of various herbicides. Previous restrictions on the availability of highly toxic herbicides have reduced the ingestions of these compounds and their toll in terms of deaths from poisoning and suicide in Sri Lanka⁴⁻⁶.

Bispyribac (KIH-2023, figure 1) is an inhibitor of acetolactate synthase and is used as a systemic post-emergence herbicide for control of weeds in agriculture. The commercial product is 400g/L bispyribac, formulated as the sodium salt and marketed as Nominee® in Sri Lanka. It is sold as two bottles which are mixed prior to use, one contains bispyribac and solvents and the other contains a nonionic surfactant composed of polyethylene glycol. WHO classifies bispyribac as a chemical that is unlikely to produce acute hazard on the basis of animal toxicity⁷. The acute oral LD₅₀ for male and female rats is 4111 and 2635 mg/kg, respectively, while the acute oral LD₅₀ in male and female mice is 3524 mg/kg⁸⁻¹⁰. There are no published data on the outcomes of acute human self-poisoning with this bispyribac-containing herbicide product. The objective of this study is to describe the clinical effects and toxicokinetics of bispyribac self-poisoning in humans.

Methods

Study design, setting and patients

This study was nested into an ongoing prospective observational study of all patients presenting with self-poisoning to General Hospitals in Sri Lanka. Patients presenting to Anuradhapura General Hospital between March 2002 and January 2009 and Polonnaruwa General Hospital between June 2002 and August 2008 were reviewed. We included all patients with bispyribac poisoning as indicated by the history from the patient, accompanying relatives and/or by positive identification of the herbicide container. We excluded patients who co-ingested bispyribac with other herbicides. Prospective data collection included demographic details, type and amount of the herbicide product and time

from ingestion to admission. Clinical observations and complications were recorded by on-site dedicated study doctors on purpose-built data collection forms until discharge or death and entered into a clinical database on a handheld computer.

Consent was obtained in 53 (61% of eligible patients) to obtain a blood sample on admission to confirm and quantify exposure to bispyribac. In addition, 7 of these patients provided serial blood samples at 1, 4, 12 and 24 hours post-ingestion to determine the toxicokinetics of bispyribac.

Laboratory analyses

Plasma samples were stored at -23°C and transported on dry ice (-80°C) for analysis at the Therapeutics Research Unit, University of Queensland. Samples were analysed by LC/MS/MS as follows: 50 μL of plasma and 150 μL of acetonitrile containing the internal-standard (50 ng/mL 3,5,6-trichloro-2-pyridinol) were vortex-mixed and centrifuged. 20 μL of the supernatant was injected onto a Phenomenex Luna C₁₈(2) column ($50 \times 2.0 \text{ cm } 5 \mu\text{m}$). A mobile-phase gradient at 300 $\mu\text{L}/\text{min}$ was used with the water: acetonitrile : formic acid ratio ramped from 90:10:0.001 to 5:95:0.001 over 3 min and then held at 5:95:0.001 for a further 2 min. The first 2 min of the eluent flow was diverted to waste. An API 2000 tandem mass spectrometer was used with an ESI ionisation source in negative mode. The following common instrument parameters were used: temperature= 400°C , ionspray voltage= -4200V , entrance potential= -10V . The ion-specific parameters for bispyribac were: MRM: 429 $\rightarrow$ 155, declustering potential (DP)=-41, collision energy (CE)=-32, collision cell entrance potential =-18, collision cell exit potential=-4V and for 3,5,6-trichloro-2-pyridinol MRM: 198 $\rightarrow$ 198, DP=-50, CE=-10, collision cell entrance potential =-10, collision cell exit potential=-2V. Weighted quadratic regression was used to measure the bispyribac concentration over the range 20–4000 ng/mL.

Ethics approval was obtained from the Sri Lankan Medical Association, Oxfordshire Clinical Research Ethics Committee (UK) and Australian National University.

Results

We identified 123 patients with a history of bispyribac herbicide self-poisoning. There were 13 patients excluded from further analysis because they co-ingested other products (8 patients) or surfactant alone (5 patients). None of the 5 patients who reported ingestion of surfactant alone developed any notable symptoms. Of the remaining 110 patients the age ranged from 14 to 78 years (median 28, IQR 21–38). There were 83 (75.5%) males and 27 (24.5%) females. The median time to admission post-ingestion was 4 hours (range 1 to 175 hours, IQR 2–6 hrs). 16 of these patients co-ingested ethanol. Treatment was limited to gastric decontamination when indicated and intravenous fluids only. The median duration of hospital admission was 3 days (IQR 2–3).

Symptoms and signs

Vomiting occurred in 51 (46.3%) patients soon after ingestion but only 3 patients were still vomiting at the time of admission to hospital. Epigastric pain was reported in 11 (10%) of patients which resolved within 24 hours and one patient developed diarrhea.

One survivor had a systolic blood pressure of 88mmHg on admission which increased with intravenous fluids. All other survivors had a normal cardiovascular status on admission, with a median mean arterial pressure (MAP) of 87mmHg (IQR 83–93) and median pulse of 82 beats per minute (IQR 74–92). There were no adverse cardiovascular events during their hospital stay.

The median Glasgow Coma Score (GCS) was 15 but in 11 patients the GCS was low on arrival at hospital (14,14,13,13,13,12,12,11,9,7,3). Two patients who co-ingested ethanol had a low GCS (3 and 12) and developed generalized tonic clonic seizures around the time of admission and subsequently died.

Plasma concentration and toxicokinetics of bispyribac

Bispyribac was quantified in admission blood samples from 53 patients. It was not detected in 21 patients at the time of admission (median time post-ingestion 3.5 hours (IQR 2.68-5.25) while in the remaining 32 patients the median bispyribac concentration was 50.55 µg/mL (IQR 1.28- 116.5), figure 2. Bispyribac was only detected in 3 of the 7 patients who provided serial samples (figure 3). The peak plasma concentration was observed at the time of admission or soon after, around 3 hours post-ingestion. In two patients this was followed by a very slow decrease in concentration until around 6 hours post-ingestion. In the third patient in whom concentrations were generally lower, there was a more pronounced decrease in concentration. A log-linear decay in the concentration-time curve was not noted in any of the three patients so the apparent elimination half-life could not be confirmed. However, from the available data the apparent elimination half-life approximated 13 and 16 hours in Patient 2 and Patient 3, respectively (figure 3).

Abnormal GCS and bispyribac concentrations

Excluding death, a depressed GCS was the most prominent sign of poisoning in this series and was noted in only 11 (10%) of patients. In these patients there was no apparent correlation ($r = 0.01$) between the GCS and admission plasma concentration of bispyribac. For example, a patient with a plasma concentration of 218 µg/mL had a GCS of 3 while the patient with the highest concentration (568 µg/mL) remained asymptomatic until discharge (figure 2).

Case fatality

There were three deaths at 15, 6 and 5 hours post-ingestion due to asystolic cardiac arrest. All three patients had reduced GCS (3, 12 and 13 respectively) of whom the former two had co-ingested ethanol and developed tonic clonic seizures. Admission blood sample was obtained from the former two of these patients but bispyribac was detected in only one of these patients (see case report below). The other patient presented 2.5 hours post-ingestion with a GCS of 12 but bispyribac was not detected and there was no history or signs convincing of an alternative exposure. Excluding the patient with undetectable bispyribac, a conservative estimate of the case fatality ratio at 1.81% (95% CI 0.32- 5.8) can be made.

Case report

A 32 year-old male with a history of childhood epilepsy was admitted 2 hours after ingesting 375ml of bispyribac and 400ml of alcohol. Generalized tonic clonic seizures were noted during transfer to hospital. On admission his GCS was 3, pupils 2mm, pulse 84 beats/min, blood pressure 100/70mmHg, respiratory rate 16 breaths/min and peripheral oxygen saturations of 98% on room air. The blood glucose concentration was 3.1mmol/L and plasma concentration of bispyribac was later measured to be 218 µg/mL. Intravenous crystalloid solutions were administered and the GCS improved to 6 transiently. He died 15 hours after ingestion of an asystolic arrest.

Discussion

This is the first case series reporting clinical outcomes of acute human self-poisoning with a bispyribac-containing herbicide product. Our study establishes that bispyribac is a relatively

safe herbicide in acute human self poisoning. The simple statistical estimate of the upper end of the 95% confidence interval for the case-fatality indicates that the case fatality is less than 5.8 %. The relative safety of bispyribac in acute poisoning in this series is further supported by animal data that indicate low toxicity. The peak bispyribac plasma concentration was observed around 3 hours post ingestion and the admission concentration did not appear to correlate with GCS or death.

Toxicokinetic studies of bispyribac in the rat demonstrated a peak plasma concentration 1-2 hours following enteral administration followed by an apparent elimination half-life of 5-7 hours¹¹. More than 60% of the dose administered to rats is eliminated unchanged, mostly in the faeces following biliary excretion. Of the three patients for which toxicokinetic data were available, the plasma bispyribac concentration also peaked within a couple of hours post-ingestion. In two of these patients it remained elevated until around 6 hours post-ingestion, suggesting ongoing absorption. Elimination was not first order which may occur due to prolonged absorption, including enterohepatic recirculation, or distribution kinetics. Bispyribac was not detected in some patients at the time of admission. These patients may have ingested small volumes of the bispyribac solution so that the concentration was below the level of quantification, or surfactant only.

There were three deaths in this series but bispyribac was not detected in one patient. In another patient the admission bispyribac concentration was 218 µg/mL which is similar or less than concentrations in others who remained asymptomatic. Therefore, the importance of the bispyribac component for predicting fatal outcomes was not confirmed. Plasma bispyribac concentration peaks soon after ingestion but death occurred many hours afterwards which may occur due to downstream effects following herbicide exposure. Acetolactate synthase catalyses the first step in the biosynthesis of isoleucine and valine in plants, bacteria and fungi¹² as well as leucine in humans ¹³. While inhibition of acetolactate synthase may inhibit amino acid synthesis this is unlikely to cause death or seizures within 24 hours. Potentially, some patients may have an uncharacterized metabolic disorder which predisposes them to toxicity from inhibition of acetolactate synthase. Other possible factors contributing to death in these patients include complications of pre-admission clinical effects, such as hypoxic brain injury or aspiration pneumonia from inadequate airway management during seizures. Potentially, seizures and death may have occurred in these patients due to ingestion of another herbicide not reported to study doctors. However, on the basis of previous studies by our group in Sri Lanka, it is rare for deaths to occur in patients with a history of ingestion of a particular herbicide that was not subsequently identified¹⁴⁻¹⁷. This supports the importance of confirming the presence of a herbicide in studies of outcomes from self-poisoning.

Co-formulants and undisclosed ethanol intoxication may have contributed to the clinical outcomes noted in these patients with acute poisoning. We can not exclude that the lack of a correlation between bispyribac concentrations and GCS is due to generation of a toxic metabolite or undisclosed ethanol intoxication. Surfactants and solvents are included in most herbicide formulations and appear to contribute significantly to poisoning severity and mortality¹⁸⁻²⁰. The Sri Lankan distributor would not provide details of the solvent components in Nominee for commercial reasons so we were not able to consider their influence completely. The surfactant used in this formulation is Tergitol® NP-10 (polyethylene glycol, nonoxyl-9), a nonionic surfactant that is a gastrointestinal irritant.²¹ Polyethylene glycols are minimally absorbed and there were no deaths in the group who reported ingesting only the surfactant, so it is less likely to contribute to severe outcomes from poisoning with bispyribac-containing herbicides. Resource limitations prevented analysis for surfactants and other herbicides in these patients.

Compared to other herbicides available in Sri Lanka that we have prospectively collected data on (figure 4) the mortality from bispyribac-containing herbicides is less (this is a conservative case fatality estimate given that bispyribac was not identified in one of the deaths).¹⁷ Therefore, there may be public health benefits if herbicide regulators encourage the marketing and use of this herbicide in place of more toxic herbicide products, in particular the selective herbicide propanil.³

Clinical management of bispyribac self-poisoning consists mainly of supportive care and reassurance. Gastric decontamination, especially with forced emesis or gastric lavage should be discouraged as the herbicide itself is of relatively low toxicity and the procedure may cause more harm than benefit²². Because all patients with a normal GCS who did not develop seizures within 6 hours of poisoning had an uncomplicated admission, treatment consists largely of reassurance and basic supportive care. These patients can be managed safely in primary care hospitals. Those patients who have low GCS should be managed with special attention to protect the airway. This simple observation is an important outcome of this study because, at present, transferring patients is one of the leading costs encountered in the care of poisoned patients in the North central province in Sri Lanka²³. Educating medical officers working in primary care hospitals of the clinical outcomes of bispyribac self poisoning can reduce unnecessary inter-hospital transfers and, therefore, the economic burden of managing poisoned patients in Sri Lanka.

Conclusion

Bispyribac has favourable human toxicity compared with other herbicides used for the same indication. The most significant manifestation of poisoning was a decreased GCS on admission. The lack of correlation of bispyribac concentration with GCS and death suggests that toxicity may be due to a co-formulant or an undefined individual susceptibility.

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Figure 1.
bispyribac molecular structure

Figure 2. Admission bispyribac concentrations in patients presenting with acute self poisoning

Figure 3. Concentration-time profile for three patients with acute bispyribac self-poisoning who provided serial blood samples

Figure 4.

The case fatality (95% CI) of self-poisoning with the most common herbicides used in Sri Lanka, [adapted from Zavahir S et al. Acute intentional self-poisoning with a herbicide product containing fenoxaprop-P-ethyl, ethoxysulfuron, and isoxadifen ethyl: a prospective observational study. *Clin Toxicol (Phila)*. 2009 Sep;47(8):792-7].