Glyphosate–surfactant herbicide-induced reversible encephalopathy

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ABSTRACT

Glyphosate–surfactant (GlySH) is a commonly used herbicide that has been used in attempted suicide. Most reports of GlySH toxicity in patients have followed ingestion of the commercial product “Round-up” (Monsanto Ltd; Melbourne, Victoria, Australia), which consists of a mixture of glyphosate (as a isopropylamine salt) and a surfactant (polyoxyethyleneamine), which acts as a wetting agent.1 Glyphosate contains phosphorus but does not inhibit acetylcholinesterase in humans.1 In animal studies, it has been suggested that glyphosate may uncouple mitochondrial oxidative phosphorylation, although it is more likely for the surfactant to interfere with mitochondrial function by damaging mitochondrial membranes.1,2 The mechanism of toxicity of glyphosate–surfactant (GlySH) formulations in humans is unclear, and both the herbicide and surfactant may contribute to toxicity.1 It is unknown whether mixing glyphosate with a surfactant potentiates toxicity.1

Approximately 30% of glyphosate is orally absorbed; in contrast, its dermal absorption is poor.1 The herbicide is primarily excreted unchanged in urine although aminomethylphosphonic acid (AMPA) is a recognised minor metabolite in humans.1,3 Post-mortem analysis of one patient detected glyphosate in brain tissue, which indicated transfer across the blood–brain-barrier.4,5

Ingestion of small amounts of GlySH may have mucocutaneous side-effects such as oral ulceration, oesophageal symptomatology, hypersalivation, nausea, vomiting and diarrhoea.1,5,6 Ingestion of larger amounts (usually >85 mL) causes significant toxicity including renal and hepatic impairment, acid–base disturbance, hypotension and pulmonary oedema.1,5,6 Impaired consciousness and seizures have also been reported as sequelae but there are limited data on the central nervous system (CNS) effects of GlySH toxicity.

We report a 71-year-old male who attempted suicide with GlySH and developed a prolonged but reversible encephalopathy.

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1. Introduction

N-Phosphonomethyl glycine (glyphosate) is a commonly used herbicide that has been used in attempted suicide. Most reports of glyphosate toxicity in patients have followed ingestion of the commercial product “Round-up” (Monsanto Ltd; Melbourne, Victoria, Australia), which consists of a mixture of glyphosate (as a isopropylamine salt) and a surfactant (polyoxyethyleneamine), which acts as a wetting agent.1 Glyphosate contains phosphorus but does not inhibit acetylcholinesterase in humans.1 In animal studies, it has been suggested that glyphosate may uncouple mitochondrial oxidative phosphorylation, although it is more likely for the surfactant to interfere with mitochondrial function by damaging mitochondrial membranes.1,2 The mechanism of toxicity of glyphosate–surfactant (GlySH) formulations in humans is unclear, and both the herbicide and surfactant may contribute to toxicity.1 It is unknown whether mixing glyphosate with a surfactant potentiates toxicity.1

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We report a 71-year-old male who attempted suicide with GlySH and developed a prolonged but reversible encephalopathy.

2. Case report

A 71-year-old male was found unresponsive at home with an empty bottle of herbicide. He was in cardiogenic shock with severe metabolic acidosis with a pH of 7.13, HCO3− 13.2 mmol/L (normal range: 22–30 mmol/L), base excess −15.0 (normal range: −2 to 2 mmol/L), and blood lactate 7.1 mmol/L (normal range: 0.5–1.6 mmol/L). He required ventilatory and inotropic support and continuous veno-venous haemodiafiltration. He was initially treated for organophosphorus poisoning with intravenous atropine and pralidoxime. Subsequent investigations revealed a high anion gap of 25 mmol/L (normal range: 8–14 mmol/L), high osmolality of 327 mmol/kg (normal range: 280–300 mmol/kg) and an osmolar gap of 40 mmol/L (normal: <10 mmol/L). He had a normal acetycholine esterase level of 15.9 U/mL (normal range: 8–20 U/mL). Atropine (total dose: 239 mg) and pralidoxime (total dose: 4 g) were ceased after 48 hours but supportive measures continued. The metabolic acidosis and high anion gap both normalised after 48 hours. His serum potassium was normal throughout but serum creatinine reached 134 µmol/L on day 3. A subsequent search of his home indicated GlySH as the substance ingested (which was ultimately confirmed by the patient). Over the next 72 hours his blood pressure improved but his Glasgow Coma Scale (GCS) score remained low (E1, V1, M4). Neurological investigations were performed to exclude structural pathology. CT brain scan was normal. An electroencephalogram (EEG) reading on day 8 demonstrated generalised slow wave activity with triphasic sharp and slow wave complexes consistent with an encephalopathy although non-convulsive seizures could not be excluded (Fig. 1). Subsequently, his GCS score started to improve. He was transferred from the intensive care unit on day 10 and discharged home on day 16 with full clinical recovery.

3. Discussion

This patient demonstrated prolonged clinical unresponsiveness (>7 days) following GlySH poisoning. The mechanism of CNS toxicity of GlySH is unknown but possibilities for the prolonged period of unconsciousness, as seen in our patient, include encephalopathy due to the delayed effects of reduced organ perfusion and/or a hyperosmolar state and/or metabolic acidosis and direct neuronal toxic effects of the glyphosate–surfactant combination itself. The role of glycine, a coagonist of N-methyl-D-aspartate receptors, in the CNS toxicity of GlySH is unknown, although moderate to high doses of oral glycine have reportedly been well tolerated when used therapeutically in refractory schizophrenia,8 making glycine an unlikely toxin.
The EEG demonstrated features consistent with a moderate to severe encephalopathy including potentially epileptiform periodic sharp and slow wave complexes (Fig. 1) despite significant improvements in renal and acid–base status. To our knowledge, there are no previous reports of EEG findings in patients with GlySH poisoning. The generalised sharp and slow wave discharge activity seen in the present patient also raises the possibility of altered cognition due to non-convulsive status epilepticus.

In a recent study of 2031 patients with GlySH ingestion in Taiwan, most patients experienced either mild symptoms (65%) or were asymptomatic (10%). 260 patients (13%) had moderate symptoms, 100 patients (5%) had severe effects and 146 patients (7%) died. Several other case series of glyphosate ingestion have reported mortality rates ranging from 8% to 16%. Patients who died or who lived but had a severe outcome were more likely to be older, attempted suicide more frequently, ingested a larger amount of GlySH (median 150 mL compared to 75 mL for non-severe effects), presented later after exposure (median 2.5 hours compared to 1.5 hours for non-severe effects) and received atropine more frequently. The most common causes of morbidity and/or mortality were shock and respiratory failure. The association of atropine with a poor outcome may have been explained by a more frequent use of such an agent in patients presenting with severe toxicity. In another study, respiratory distress requiring intubation, metabolic acidosis, tachycardia, elevated creatinine and hyperkalaemia were also significantly associated with a poor outcome and mortality.

Our patient had several factors associated with a poor prognosis including older age, respiratory distress requiring intubation, metabolic acidosis and elevated creatinine, although he presented early and did not manifest hyperkalaemia or tachycardia. The administration of atropine and pralidoxime in our patient is unlikely to have contributed directly to his prolonged period of unconsciousness as both agents were withdrawn within 48 hours of admission.

In conclusion, we report a patient with unique prolonged and reversible encephalopathy complicating GlySH poisoning, raising suspicion of direct cerebral toxicity. This may require additional commentary on the product information disclosure and justifies perseverance with supportive measures despite prolonged altered consciousness.

References


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