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What is This?
Intentional Self-Poisoning with Glyphosate-Containing Herbicides

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Four cases of self-poisoning with 'Roundup' herbicide are described, one of them fatal. One of the survivors had a protracted hospital stay and considerable clinical and laboratory detail is presented. Serious self-poisoning is associated with massive gastrointestinal fluid loss and renal failure. The management of such cases and the role of surfactant toxicity are discussed.

Introduction

Although cases of 'Roundup' poisoning have been reported in the Japanese and Taiwanese literature, experience of it elsewhere is limited. Glyphosate is the active ingredient in several widely used herbicides (e.g. 'Roundup', 'Network'). Glyphosate is inactivated by exposure to soil, and, while less toxic than some other herbicides, has been used with variable success as a means of suicide. Questions have been raised about the contribution to fatal outcome of the surfactants used in herbicide preparations as well as any concomitant drugs taken, including alcohol. This report presents several cases of deliberate self-poisoning and considers the toxic contributions of both glyphosate and the surfactants.

Case one

In a planned suicide attempt, a 27-year-old single white male accountant swallowed 235 ml of 'Roundup' concentrate, containing approximately 85 g glyphosate. This act followed 5-6 months of depressive symptoms (low mood, difficulty falling asleep plus early morning waking, irritability, lethargy, constriction of interests and social activity) and consistent consumption of beer 2-3 litres d⁻¹, equivalent to 100-130 g ethanol, which continued up to the time of poisoning. A suicide note with prominent self-criticism was found later.

Relevant background information includes the fact that he had lost his left leg below the knee after a motor vehicle accident at age 17. Four years later, persistent problems with his stump led to an above knee amputation. At age 23 he had donated a kidney to an elder brother with advanced glomerulonephritis. He was otherwise healthy, taking no medication, smoking 30-40 cigarettes per day, with moderate to heavy alcohol intake (above).

After the poisoning he developed diarrhoea, vomiting and lethargy, but deceived his concerned family by ascribing these to the 'flu' and, after being seen by a doctor the following day, was admitted to a rural hospital some 36 h after ingestion. At this time the first suggestion of 'Roundup' toxicity emerged when he mentioned spraying this compound in his garden 2 d previously.

He continued to vomit foul-smelling material and the watery bowel motions had some blood staining. He was anuric and reported not passing any urine since the night following ingestion. On admission he was afebrile and markedly dehydrated, with hypotension (80/60), tachycardia (130), reduced skin turgor, dry mouth and cold extremities. Bowel sounds were absent and his abdomen non-tender. A first set of laboratory values (Table 1) showed haemoconcentration, hyperkalaemia and early azotaemia.

Over 18 h he received 7.5 l of intravenous fluid, mostly normal saline; catheterization obtained 500 ml of concentrated urine (specific gravity 1.030) with 1+ protein. He was pyrexial (38.5°C). With rehydration, his blood pressure rose to 130/80 but vomiting continued and was treated by nasogastric intubation. Urine output fell below 100 ml over 8 h, now with 2+ protein,
Despite continued intravenous fluid and normal blood pressure. Because of evidence of incipient renal failure, transfer to a University teaching hospital was arranged some 60 h post-ingestion.

Re-assessment after transfer confirmed the findings of early pre-renal failure apparently consequent to massive gastrointestinal fluid and electrolyte loss (Table 1). Drug and alcohol screen at this time (3 d post-ingestion) was negative. Shortly after transfer he acknowledged deliberate self-poisoning with approximately 235 ml of 'Roundup' concentrate. A sample from the same source (father's shed) was spectroscopically identical to authentic 'Roundup' concentrate. He was kept in the ICU for 11 d: daily blood sampling showed the development and resolution of marked azotaemia over this time and the subsequent 2 weeks in a general ward (Table 1). Daily haemodialysis was initiated on transfer and continued for 2 weeks. Intravenous fluid replacement and total parenteral nutrition was also required during this time as his diarrhoea and emesis gradually settled.

At no stage was respiratory function significantly impaired, although daily arterial blood gases showed a persistent, mild metabolic acidosis during his 11 d in ICU (Table 1). Oxygen saturation remained above 96% throughout the period of monitoring. Hepatic function showed some impairment with borderline hypoalbuminaemia and transient elevation of alkaline phosphatase. His γ-GTP was elevated when sampled 15 and 20 d after poisoning (100 and 50 U l⁻¹, respectively). Prothrombin ratio was normal on admission but rose to 1.58 d after ingestion, prompting the administration of Vitamin K; within a week this value had dropped to 1.2. Toxic changes were noted in the neutrophils a week after the poisoning, but the blood count remained otherwise normal until 12 d after ingestion, when a neutrophil leukocytosis developed and continued for 3 weeks. No infective origin of this leukocytosis was established, despite multiple attempts to culture blood, urine and catheter tips. Also arguing against infection was the observation that his temperature, elevated to 38–38.5°C during the first 10 d, was settling by the time the leukocytosis became evident.

Mental state remained clear throughout, although a transient period of irritability and aggressiveness was observed in the ICU when he wished to leave against advice. Intravenous chlormethiazole was used to aid sleep on several occasions during his first week in the ICU. Liaison psychiatric opinion confirmed the diagnosis of major depression and he was treated with amitriptyline (later switched to nortriptyline) 100 mg d⁻¹ starting a week after admission. Because amitriptyline and its metabolite, nortriptyline, are extensively inactivated in the liver (less than 5% of either is excreted unchanged), standard dosage is appropriate in renal failure. Following resolution of his renal failure 4 weeks after self-poisoning, he was transferred to an inpatient psychiatric facility for a further 6

| Table 1 Vital signs and laboratory measures from case one. |
|-----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Post-ingestion** | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 11 | 13 | 15 | 20 | 25 | 210 |
| Temperature | 38.7 | 38.5 | 37.8 | 37.7 | 38.1 | 37.0 | 37.0 | 37.7 | 36.9 | 36.8 | 37.0 | 36.8 |
| BP, supine | 80/60 | 120/70 | 160/75 | 175/70 | 170/80 | 160/70 | 170/70 | 180/80 | 170/80 | 130/75 | 130/80 | 118/64 |
| Pulse | 130 | 120 | 88 | 82 | 75 | 80 | 80 | 96 | 90 | 80 | 74 | 90 |
| Urine output (litres 24 h⁻¹) | 0.5 | 0.2 | <0.1 | <0.1 | 0.1 | <0.1 | <0.1 | 0.1 | 0.8 | 2.8 | 2.4 | 1.4 |
| Haematology: | | | | | | | | | | | | |
| PCV (0.4–0.5) | 0.60 | 0.44 | 0.37 | 0.38 | 0.42 | 0.36 | 0.34 | 0.31 | 0.28 | 0.27 | 0.32 | 0.34 | 0.42 |
| WBC (4–11) | 11.3 | 9.1 | 10.6 | 9.0 | 8.9 | 7.5 | 11.3 | 12.1 | 18.8 | 11.0 | 14.0 | 12.4 | 9.0 |
| Blood chemistry | | | | | | | | | | | | |
| Urea (2.6–6.8) | 14.0 | 26.0 | 27.0 | 21.0 | 16.0 | 16.0 | 13.0 | 11.0 | 13.0 | 18.0 | 11.0 | 9.1 | 5.1 |
| Creatinine (50–100) | 530 | 754 | 899 | 826 | 727 | 777 | 564 | 468 | 472 | 508 | 279 | 150 | 84 |
| Potassium (3.5–5.0) | 6.6 | 5.0 | 3.9 | 3.2 | 3.3 | 3.1 | 3.8 | 3.6 | 4.3 | 4.4 | 4.4 | 4.1 | 4.1 |
| Albumin (30–50) | 29.0 | 25.0 | 28.0 | 28.0 | 28.0 | 29.0 | 26.0 | 29.0 | 41.0 | 39.0 |
| Alkaline phosphatase (30–90) | 77.0 | 82.0 | 143.0 | 121.0 | 98.0 | 91.0 | 83.0 | 83.0 | 59.0 |
| Arterial blood gases: | | | | | | | | | | | | |
| CO₂ (35–45) | 32.0 | 26.0 | 35.0 | 32.0 | 35.0 | 38.0 | 40.0 | 33.0 |
| HCO₃⁻ (23–28) | 17.0 | 13.0 | 19.0 | 19.0 | 17.0 | 21.0 | 21.0 | 19.0 |
| pH (7.37–7.42) | 7.34 | 7.31 | 7.40 | 7.38 | 7.31 | 7.36 | 7.33 | 7.37 |

Blood chemistry values reported are those prior to daily haemodialysis (3rd to 15th days).
weeks. Follow-up 6 and 11 months later showed normal renal function and blood screen, and stable mood.

Case two

A 15-year-old girl with numerous psychosocial problems impulsively swallowed 50-100 ml of 'Roundup' concentrate (approx. 18-36 g glyphosate). Forty-five minutes later she was vomiting and complaining of abdominal pain. Fifteen minutes later she was assessed at the local emergency room, noted to be drowsy but cooperative, and given gastric lavage with a good result. Vomiting continued over the next 10 h, producing approximately 1 l of fluid. She received IV fluids overnight but the abdominal pain and vomiting settled and she was able to take fluids the next day.

Initially afebrile, she developed a mild pyrexia 24 h after ingestion, along with clinical and radiographic signs of a right aspiration pneumonia. Yellow sputum grew Haemophilus influenzae and treatment with amoxycillin was associated with the resolution of pyrexia and X-ray findings over 3 d.

Case three

A 38-year-old man drank a large volume (thought to be up to 1 l) of 'Roundup' solution, together with alcohol, and vomited almost immediately. (The patient concerned was in an emotionally labile state and was noted to be not very forthcoming with a clinical history.) He presented himself to the local emergency room complaining of nausea and was given syrup of ipecac 80 ml in two doses. After further emesis, activated charcoal was given and he was admitted to the medical ward for 6 d. There were no further complaints or physical signs; liver function tests, urea and electrolytes remained normal at days 2 and 4.

Case four

A 43-year-old woman with a history of depression and a recent marital separation swallowed 200-250 ml 'Roundup' concentrate (approx. 72-91 g glyphosate) in a successful suicide attempt. She was found semi-conscious and covered with vomitus 2-3 h after ingestion. There was no evidence of other substances being ingested (no other chemicals in her body were detected post-mortem, including alcohol).

She was semi-rousable on admission to hospital and confirmed what she had taken. Abnormal findings on admission included dilated pupils, hypotension (systolic 95 mmHg), metabolic acidosis (pH 7.14, pCO₂ 40, pO₂ 104 mmHg) and hyperkalaemia (7.8 mmol l⁻¹).

Treatment with intravenous bicarbonate, dextrose/saline, and insulin improved her condition temporarily; 10 h after admission she was awake, with normal pupils, BP 120/80, pH 7.25, potassium 5.4 mmol l⁻¹. Urine output was 500-600 ml over 10 h.

Over the next 10 h she deteriorated markedly. Urine output essentially ceased and her BP fell despite intravenous fluid and inotropic support. Her acidosis remained constant (pH 7.23) but potassium rose again to 7 mmol l⁻¹. Her mental state deteriorated progressively to a coma, and, with an unrecordable BP, she had a respiratory and cardiac arrest. Post-mortem examination showed an ulcerated oropharynx, acute pulmonary oedema, and acute renal tubular necrosis. Tissue samples, analysed using ion exchange clean-up followed by HPLC/PCR, confirmed glyphosate poisoning with concentrations ranging (in ppm) from brain 100, blood 550, liver 600, kidney 3650.

Comment

The clinical management of 'Roundup' poisoning is largely based on experiences gained from overdoses in Japan and Taiwan. This report of cases of glyphosate-containing herbicide poisoning confirms the pronounced gastrointestinal irritant effects of these preparations. Massive fluid and electrolyte loss through this mechanism appear to have triggered acute tubular necrosis in cases 1 and 4; as noted in the literature and in our experience, renal failure is usually associated with severe poisoning and death following 'Roundup' poisoning. Other causes of acute tubular necrosis may also have played a role, including haemolysis or direct nephrotoxicity of the product (see below). As noted in Case 4, renal concentrations of glyphosate may be considerably higher than in other tissues.

Case 1 also emphasizes the importance of intensive supportive care in the management of such poisonings. Both vigorous intravenous fluid replacement and haemodialysis were critical in this man's survival. It needs to be stressed that glyphosate, despite being a phosphorus-containing organic compound, does not inhibit cholinesterase; thus anticholinergics have no role in the management of such cases. 

'Roundup' is formulated in water from the isopropylamine salt of glyphosate with 15% surfactant, the latter to achieve emulsification of insoluble glyphosate.
and wetting of target plants. The resultant solution is acid at pH 4.8. This formulation of 'Roundup' by Monsanto (glyphosate 360 g l⁻¹ equivalent to 41%) has an oral LD₅₀ of 5400 mg kg⁻¹ in rats which is generally regarded as a low toxicity. This is similar to pure glyphosate’s acute oral LD₅₀ in rats of 4300–5600 mg kg⁻¹. The acute oral LD₅₀ of the pure polyoxyethylene surfactants is lower, ranging from 1000–4000 mg kg⁻¹ in rats and mice.³,⁴ According to some authors have ascribed the toxicity of 'Roundup' to the surfactant in the formulation,³,⁴ even though this constitutes only 15% of the formulation.

Glyphosate acts on the plant shikimic acid pathway, blocking the formation of chlorismic acid and inhibiting formation of aromatic amino acids, carotenoid and chlorophyll. This seems to indicate a good deal of specificity for glyphosate to damage plant and not human metabolism, since there is no shikimic acid pathway in animals. Moreover, the human and experimental experience of surfactant toxicity includes vomiting and diarrhoea at high doses and haemolysis due to damage to erythrocyte cell membranes⁵ and hypovolaemia, pulmonary oedema and impaired consciousness⁶. On the other hand, the extreme diarrhoea and hypovolaemia was not commented upon in the earlier animal studies of Grubb et al.¹⁰ and Berberian et al.⁸, nor was renal damage seen on histology following acute LD₅₀ experiments. It must also be noted that the concentration of glyphosate in 'Roundup' is more than three times the concentration of surfactant and, despite being poorly absorbed, some systemic effects are observed with glyphosate. This compound may interfere with mitochondrial oxidative phosphorylation;¹¹,¹² it is possible that such a mechanism could contribute to the pyrexia (Cases one and two), metabolic acidosis with renal damage (Cases one and four) and early central nervous system depression (Cases one, two and four) observed in this survey. In these cases, of course, marked hypotension with acute renal failure could also have contributed to acidosis.

In considering all of the toxicological data available, together with the relative concentration of glyphosate and surfactant in 'Roundup', it seems unlikely that toxicity can be ascribed solely to the surfactant. The role of concomitant alcohol or other drug intake always needs to be considered, as inhibition of the cough reflex and general obtundation by CNS depressants have been linked to aspiration of vomitus after 'Roundup' poisoning,⁵ as may have occurred in Case two. Case one was a known alcohol abuser and was probably drinking at the time of the poisoning. He has not had further complications arising from this, though alcohol may have been at least partly responsible for the hepatic abnormalities recorded during his hospitalization.

A final interesting aspect of Case one arises from the fact that the individual concerned had only one kidney, having donated the other some years previously. His good pre-morbid renal function and good recovery emphasize the reversibility of pre-renal failure with acute tubular necrosis consequent to 'Roundup' poisoning, provided vigorous monitoring and dialysis are available.

Unfortunately the cases described here do not provide enough data to evaluate a dose response relationship in glyphosate poisoning, particularly given the severe emesis generally seen after ingestion. Toxicological analysis in future cases will clearly be required to assess the relationship between tissue levels, toxic effects and clinical outcome.

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