Survival after a massive overdose of arsenic trioxide

Lawrence H C Kim and Simon J C Abel

ABSTRACT

Arsenic poisoning remains a therapeutic challenge, and outcomes are often poor. An 18-year-old man deliberately ingested termiticide containing a massive dose of arsenic trioxide. Arsenic concentration was 6.3 µmol/L in serum on ICU Day 1, and 253 µmol/L in the first 24-hour urine sample, with a urinary arsenic/creatinine ratio of 84 200 µmol/mol. He was treated with the chelating agent meso-2,3-dimercaptosuccinic acid (DMSA) (replaced by dimercaprol on Days 2–5) and required intensive support for multisystem organ failure, but recovered slowly. Nine weeks after the ingestion the only ongoing clinical issue was persistent but slowly improving peripheral neuropathy.

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Arsenic is a naturally occurring metalloid element that has long been used as a preservative and pesticide. Arsenic poisoning remains a therapeutic challenge, and outcomes are often poor.[1] We describe a patient who survived after ingesting a massive dose of arsenic trioxide.

Clinical record

An 18-year-old man deliberately ingested an unknown quantity of white arsenic (arsenic trioxide) while under the influence of alcohol. The source was a tin of termiticide, which was at least 40 years old. He immediately developed characteristic features of arsenic intoxication, including profuse vomiting, diarrhoea and abdominal pain. He was transferred to a tertiary institution from a country centre and arrived 12 hours after the ingestion.

On arrival, he had sinus tachycardia (heart rate, 136 beats/min) and mean arterial pressure (MAP) of 68 mmHg. Oxygen saturation was 96% when breathing room air, and score on the Glasgow Coma Scale was 15. Gastrointestinal decontamination was not attempted because of the time elapsed since ingestion: charcoal was deemed unlikely to be of benefit, and polyethylene glycol to increase gastrointestinal clearance was considered unnecessary as the patient had profuse diarrhoea.

Arterial blood gas analysis on admission revealed a compensated metabolic acidosis: pH, 7.41; $Paco_2$, 28 mmHg; Pao_2 79 mmHg; HCO_3, 18 mmol/L; and base excess, –5. Blood biochemical testing revealed serum concentrations of sodium, 147 mmol/L (reference range [RR], 135–145 mmol/L); potassium, 3.5 mmol/L (RR, 3.2–4.5 mmol/L); glucose, 6 mmol/L (RR, 3.0–7.8 mmol/L); creatinine, 131 µmol/L (RR, 50–100 µmol/L); and urea, 5.2 mmol/L (RR, 3.0–8.0 mmol/L). Liver function was normal, apart from a bilirubin concentration of 40 µmol/L (RR, < 20 µmol/L).

Arterial monitoring and central venous access were secured, and treatment was begun with the chelating agent, meso-2,3-dimercaptosuccinic acid (DMSA) (500 mg, three times daily), on the recommendation of a toxicologist. Another chelating agent, 2,3-dimercapto-1-propanesulfonic acid (DMPS), was considered but is not available in Australia, and delivery from Europe would have involved a comparatively long wait. A combination of total parenteral nutrition and nasogastric feeding was begun within the first 24 hours.

The patient's arsenic concentration in serum was 6.3 µmol/L and in the first 24-hour urine sample was 253 µmol/L, with a urinary arsenic/creatinine ratio of 84 200 µmol/mol. Subsequent urinary arsenic/creatinine ratios during the course of the patient's stay in the intensive care unit are shown in Table 1.

On Day 1, the patient's condition deteriorated, with progressive multisystem organ failure, decreasing level of consciousness, and increasing respiratory distress and hypoxia, with bilateral pulmonary infiltrates, consistent with acute respiratory distress syndrome. He was intubated and ventilated. Haemodynamic instability required vasopressor support, and continuous veno–venous haemodiafiltration (CVVHDF) was begun for acute renal failure (serum creatinine concentration, 157 µmol/L on Day 1).

He developed coagulopathy, and liver function progressively deteriorated (international normalised ratio, 3.1; concentration of aspartate aminotransferase, 845 mmol/L; and alanine aminotransferase, 1126 mmol/L on Day 3). Myelosuppression and rhabdomyolysis also became evident (haemoglobin, 81 g/L; and white cell concentration, 2.5×10^9/L on Day 5; platelet count, 14×10^9/L on Day 6; and creatine kinase, 22 127 U/L on Day 5).

Table 1. Patient's urinary arsenic/creatinine ratio over time in the ICU

	Day in ICU						
	1	2	4	8	10	16	20
Ratio (µmol/mol)	84 200	12 390	8394	9258	8636	2200	1644

The patient did not tolerate nasogastric feeding, and another chelating agent, dimercaprol in its intramuscular form, was substituted for DMSA from Day 2 to Day 5 in the ICU (400 mg every 4 hours for the first 48 hours, and every 6 hours thereafter). Total parenteral nutrition was continued.

The patient developed hyperthermia (temperatures up to 40.2° C). A "septic work-up" was performed: preliminary blood cultures showed α-haemolytic streptococci, methicillin-sensitive *Staphylococcus aureus*, and presumptive *Clostridium perfringens.* He was treated empirically with vancomycin and meropenem, but subsequently developed a generalised urticarial, erythematous rash. The most likely cause was considered to be meropenem, and the antibiotic regimen was changed to ciprofloxacin, vancomycin and metronidazole.

A tracheostomy was performed on Day 10. The patient's level of consciousness improved, but he remained confused. Neuropathic limb pain, paraesthesia and weakness, with near-absent reflexes, became significant problems. On Day 16, scores for power were 3/5 and 2/5 for the proximal upper and lower limbs, respectively, and 0–1/5 for the distal upper and lower limbs. These neurological features were considered secondary to arsenic-induced polyneuropathy. Nerve conduction studies were not performed as the diagnosis was considered clinically highly probable.

CVVHDF was ceased on Day 11. By 9 weeks after the ingestion, the patient's urine arsenic level had returned to the reference range, and DMSA was withdrawn. The features of multisystem organ failure had also resolved, and the only ongoing clinical issue was persistent but slowly improving peripheral neuropathy.

Discussion

Acute arsenic toxicity typically presents with gastrointestinal symptoms, including nausea, vomiting, diarrhoea and abdominal pain. There may be a garlic odour of breath and stool.[2] These symptoms are soon followed by dehydration, hypotension, cardiac instability and, in severe cases, rhabdomyolysis, multisystem organ failure, and sometimes death.[3,4] The condition may be misdiagnosed as gastroenteritis.

Sensorimotor polyneuropathy is one of the most prominent features of arsenic poisoning, usually developing 1–3 weeks after acute exposure. It usually manifests with sensory symptoms, such as paraesthesia and neuropathic pain in a stocking and glove distribution with symmetrically decreased tendon reflexes, reflecting distal motor and sensory axonopathy.[5] Electrophysiological studies reveal decreased nerve conduction velocity, consistent with axonal degeneration.[6]

In the acute phase, an abdominal x-ray may show radioopaque material. Arsenic levels are measured preferentially in urine rather than blood, as blood arsenic is cleared rapidly. In the emergent situation, a spot test for urine arsenic can be performed before beginning chelation therapy. Creatinine concentration should be measured in the same spot sample to correct for urine concentration. Ongoing measurement of arsenic in 24-hour urine samples is usual during treatment to monitor arsenic excretion.

In patients with acute symptoms, urine arsenic levels are usually in the order of thousands of micrograms per litre. Because urine arsenic excretion can be intermittent, a definitive diagnosis is usually supported by the finding of a concentration $\geqslant$ 50 µg/L, or 100 µg arsenic per gram creatinine. Our patient excreted 253 µmol/L arsenic in urine during the first 24 hours, with a urinary arsenic/creatinine ratio of 84 200 µmol/mol at initial presentation. This equates to a urine arsenic concentration of about 19 000 µg/L (74.9216 g arsenic per mole) and 745 µmol (55 800 µg) arsenic per gram creatinine (113 g creatinine per mole). His blood arsenic concentration at presentation was 6.3 µmol/L, equivalent to 470 µg/L. Considering these values, our patient's recovery was better than expected.

For instance, a patient with a urinary arsenic concentration of 6700 µg/L died within several hours despite aggressive ICU measures.[7] Another patient who ingested 10 g of arsenic and had a urinary arsenic concentration of 9000 µg/L also died despite treatment with dimercaprol, DMSA and CVVHDF.[8] A 39-year-old woman with a urinary arsenic level of 2000 µg/L was reported to have chronic peripheral neuropathy.[9] A 27-year-old woman developed chronic polyneuropathy after ingesting 9 g of arsenic trioxide. Her urinary arsenic concentration at the first 24 hours was about 10 000 µg/L.[10]

Others have reported better outcomes. A 44-year-old man attempted suicide by drinking 54 g of arsenic trioxide. His urine arsenic level was 67 500 µg/L, and blood arsenic level was 132 µg/L. He was discharged from hospital after 55 days, albeit with severe polyneuropathy, after aggressive resuscitative measures, including laparotomy, gastrotomy and colonoscopies to remove arsenic.[11] A 22-year-old woman in the 20th week of pregnancy had a urine arsenic concentration of 3030 µg/L, but recovered completely with an ensuing normal pregnancy and delivery.[12] Two men aged about 30 years presented with arsenic/creatinine ratios of about 1300 µmol/mol and 9000 µmol/mol, respectively, but both recovered with no evidence of peripheral neuropathy.[13] However, these levels were much lower than that in our patient (84 200 µmol/mol).

Management of acute arsenic poisoning involves eliminating further exposure, and care should be taken to avoid contamination of medical personnel.[14] Skin decontamination is particularly important in patients poisoned by arsenical pesticides. Patients should be treated in a centre where advanced life support and chelation therapy can be pro-

vided. Consultation with a regional poison centre or clinical toxicologist is recommended. Patients should have continuous cardiac monitoring and intravenous fluids to maintain adequate urine flow, with careful monitoring of fluid and electrolyte balance.

Gastrointestinal decontamination with activated charcoal and nasogastric suction can be considered in cases of recent ingestion (typically within an hour), although there is no good evidence of benefit. Cathartics are not indicated as arsenic typically causes diarrhoea. A review of the effectiveness of whole-bowel irrigation did not find any significant benefit.[15] A case report also found decontamination to be minimally effective.[13]

The decision to use a chelating agent depends on the clinical condition of the patient, the history of arsenic exposure and laboratory results. Two chelating agents are available in the United States and Australia: dimercaprol (British anti-Lewisite, BAL) and DMSA. BAL is administered intramuscularly, and has a low therapeutic : toxic ratio and a high rate of side effects. It helps speed excretion of arsenic, but it is not clear if it prevents peripheral neuropathy. The recommended dosage is 3 mg/kg intramuscularly every 4 hours for the first 2 days, then four times a day for 1 day, and twice a day for the remaining period. It should be ceased when the patient recovers, when 24-hour arsenic excretion falls below 50 µg or after 10 days. DMSA is an oral hydrophilic analogue of BAL and is the chelating agent of choice. Its safety ratio is 20 times higher than that of BAL. The recommended dosage is 10 mg/kg (maximum, 500 mg per dose) every 8 hours with food for the first 5 days, and then every 12 hours for a further 14 days.

Another chelating agent, DMPS, has been used widely in Europe, and several studies have shown it is potentially superior to conventional agents such as BAL and DMSA. Two brothers aged 19 and 21 years who ingested 1 g and 4 g of arsenic, respectively, made a full recovery with no evidence of morbidity after treatment with DMPS.[16] A patient with multisystem failure that progressed to quadriplegia and respiratory failure despite DMSA treatment made a dramatic neurological recovery after treatment with DMPS.[17] The authors speculated that the intracellular penetration and bioavailability of intravenous DMPS may have favoured redistribution of arsenic away from the nervous system. In another patient, a 1000-fold reduction in total urinary arsenic concentration was seen after 8 days of DMPS therapy.[18] A striking finding was the almost complete inhibition of the second methylation step in arsenic metabolism. The authors considered the high dose of DMPS to be the most likely explanation.

Several studies have highlighted arsenic-induced oxidative stress leading to the formation of free radicals. The authors suggested that antioxidants could be of benefit, along with a chelating agent. A review of in-vivo studies in animals and fetal cell cultures exposed to arsenic showed that antioxidants, particularly N-acetylcysteine, glutathione, selenium, zinc, vitamin E, and vitamin C, given in conjunction with DMSA, reduced damage secondary to oxidative stress.[19] Another recent review further supported the role of antioxidants and emphasised the limited therapeutic effect of currently approved chelating agents as they are not able to remove arsenic from intracellular sites, where most of the heavy metal is firmly bound. The authors suggested the use of structurally different chelating agents or a combination of adjuvant/antioxidant and a chelating agent to improve clinical and biochemical recovery.[20,21] In our patient, the early introduction of optimal nutritional support with total parenteral nutrition (within 24 hours of ICU admission) may have had a role in the favourable outcome, as it is proven to contain antioxidants.

Haemodialysis and haemofiltration have been suggested to have a role in patients with early renal failure.[22,23] Other studies have argued that the enhanced clearance of arsenic by haemodialysis and CVVHDF is negligible in comparison with the ingested dose.[8,24] Additional studies are needed to evaluate the safety and efficacy of CVVHDF.

Current evidence suggests that arsenic-induced distal polyneuropathy improves little over time, remaining a therapeutic challenge. Several studies strongly advocate the use of DMPS over other chelating agents, specifically for its effectiveness in treating polyneuropathy; further study is warranted.

Author details

Lawrence H C Kim, Registrar[1]
Simon J C Abel, Senior Staff Specialist[2]
1 Intensive Care Unit, Royal Prince Alfred Hospital, Sydney, NSW.
2 Intensive Care, Manly Hospital, Sydney, NSW.
Correspondence: lawrence.h.c.kim@gmail.com

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