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TOXICOLOGY OBSERVATION

Good Outcomes Despite High Urinary Arsenic Concentrations from Overdose with Crabgrass Killer

Brett Roth · Evan Schwarz · Sing-Yi Feng · Amy Young

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Introduction

Monosodium methylarsonate (MSMA) is a selective pre-emergent contact herbicide considered to be significantly less toxic than inorganic arsenic. Animal studies extrapolated to humans have estimated a low order of toxicity [1], but little information is available regarding overdose in humans. Previous reports have described oral exposures with less concentrated formulations of MSMA herbicides [2] or via dermal absorption [3]. Because of the limited information in the current literature, concern exists regarding exposures to concentrated forms of organic arsenic. We describe exposures to a common crabgrass killer containing 47% MSMA.

Index Cases

Case 1 A 16-year-old female with a past medical history of depression (not on any medications) presented after intentional ingestion of crabgrass killer. The patient had an argument with her grandmother and locked herself in the garage where she drank up to 240 cc of Bonide® crabgrass killer that contained 47% MSMA. She vomited and was taken to the emergency department (ED) approximately 1 h after the exposure. In the ED, the patient was agitated. She complained of abdominal pain and generalized weakness. Her vital signs were: blood pressure 134/78 mmHg, heart rate 126 beats per minute, respirations 16 breaths per minute, and oxygen saturation 100% on room air. She received a bolus of 3 l of normal saline (NS) and was then started on NS at 500 ml/h. The patient was endotracheally intubated for gastric lavage and for transportation to the local children's hospital. Gastric lavage was done at the discretion of the treating physician, and no material was retrieved. On arrival to the children's hospital, her vital signs and physical exam were normal; she was able to follow commands. Electrolytes and complete blood count (CBC) were unremarkable. A single dose of 192 mg of British anti-Lewisite (BAL) IM was administered approximately 12 h after the ingestion; extubation occurred several hours after arrival. Urine was collected in a Foley catheter for a 24-h heavy metal measurement. Dimercaptosuccinic acid (DMSA) was then initiated at 500 mg every 8 h by mouth for 5 days followed by 500 mg every 12 h for 14 days.

In the hospital, the patient complained of generalized abdominal pain, weakness, and parasthesias. She did not have any more vomiting and never had diarrhea; mild hyperreflexia was noted on exam. She was able to eat after being extubated, and paresthesias and abdominal pain improved during her hospitalization. Initially, she had difficulty walking, but by day 5, she was walking without assistance and was discharged to a psychiatric institution. There, she was continued on DMSA for the remainder of her 19 days of treatment. After discharge, the results of her heavy metal screen returned and are noted in Table 1.

Six weeks later, the patient was followed up in the toxicology clinic where she complained of mild paresthesias in her hands and feet that developed after being transferred to the psychiatric hospital. The episodes lasted for minutes at a time, occurred in the morning, and never

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B. Roth (✉) · E. Schwarz · S.-Y. Feng · A. Young
North Texas Poison Center, Children's Medical Center Dallas,
University of Texas Southwestern,
5323 Harry Hines Blvd,
Dallas, TX 75390-8579, USA
e-mail: brett.roth@utsouthwestern.edu

Table 1 Summary of acute MSMA exposures with serum and urine levels

Patient summary	Spot blood arsenic	Spot urine arsenic	24-h urine arsenic	Fractionation of 24-h urine	Follow-up
16-year-old female drank unknown amount (up to 240 cc) 47% MSMA in a suicide attempt Treated with one dose of BAL and DMSA for 21 days	Not done	Not done	746,866.8 μg/L first hospital day	Organic As 1,245 μg/L, inorganic level 8,705 μg/L, and methylated arsenic 931,645 μg/L	1.5 months later in toxicology clinic: parasthesias in hands and feet
3-year-old male drank 5 cc 47% MSMA Treated with DMSA for 9 days	654.8 μg/L (ref range 0–62 μg/L)—8 h after ingestion on arrival	236,668 μg/L (ref range 0–35 μg/L)—8 h after arrival	3 days postingestion: 868 μg/day or 1,928 μg/L (ref range 0–50 μg/day) 4,219 μg/g Cr. 24-h Cr was 207 mg/day	Organic arsenic 7.1 μg/L, inorganic arsenic 75.9 μg/L, methylated arsenic 1,832 μg/L	10 days after; arsenic level was 10 μg/L

Methylated arsenic includes both DMA and MSMA

required any pain medication. She stated that she was having some hair loss, her nails were brittle, and she had occasional "stomach aches" and "tiredness." Physical exam at that time was normal and did not reveal alopecia, Mees lines, or objective findings of a neuropathy. Nerve conduction studies were not obtained.

Case 2 A previously healthy 14-kg, 3-year-old male drank approximately 5 ml of Green Light Crabgrass Killer which contained 47.6% MSMA. The patient had three episodes of emesis starting 1 h postingestion that resolved with ondansetron given in the ED. The patient did not have any other symptoms, including diarrhea, and his physical exam was normal. His electrolytes and CBC remained normal. Electrocardiogram showed sinus tachycardia at 114 beats per minute with normal intervals. DMSA, 140 mg, was initiated in the ED 6.5 h after exposure and continued every 8 h for 5 days, and then every 12 h for 10 additional days. Arsenic levels are described in Table 1. The patient was followed up in the clinic 10 days later where he remained entirely asymptomatic with normal physical exam.

Discussion

MSMA is believed to have low to moderate toxicity in animals. Gosselin [1] described MSMA as "moderately toxic" with an LD50 extrapolated from animal data to humans of 0.5–5 g/kg. Oral lethal doses have varied widely depending on the animal model and included 1,800 mg/kg for white mice, 1,200–1,600 mg/kg for cattle, and 346 mg/kg for snowshoe hares [4]. A possible explanation is that unlike pentavalent arsenic, MSMA(V) does not penetrate cells easily or disrupt cellular metabolism [5]. In a 2-year bioassay for bladder cancer in rats, MSMA(V) was found to be noncarcinogenic [6]. These data would seem to support the presence of high levels of organic arsenic in our patients without metabolic disturbance. The relevance of any animal data extrapolated to humans is unclear.

The human experience with MSMA consists of a few case reports summarized in Table 2. Nausea and vomiting are prominent in most cases of oral exposure including ours [7]. Unlike our cases, Shum et al. [2] described transient renal insufficiency which may have been more the result of volume depletion since recovery was rapid. Similar to our cases, no deaths occurred, and all patients seemed to have completely recovered with one exception: Hessl et al. described persistent peripheral neuropathy [3] after a prolonged dermal exposure. Our index case developed transient subjective neuropathy. In the report by Luong [8], a clinical diagnosis of an arsenical neuropathy was evidenced by the numbness, decreased sensory perception, and significant distal weakness in the extremities, after consumption of bird's nest soup. In that report, all symptoms disappeared, and there was a return to normal total urinary arsenic levels after the patient stopped eating bird's nest soup. Neuropathy has also been described as a result of treatment with melarsoprol [9]. A subjective neuropathy may not have been clinically apparent in our 3-year-old patient.

Chronic effects of MSMA have received special interest from its frequent use as an herbicide [10]. A 2006 report from the US Environmental Protection Agency [11] discussed the potential for environmental conversion to inorganic arsenic and its subsequent release into groundwater. A slow conversion of MSMA to inorganic arsenic in vivo is not believed to occur in humans, although there are few references supporting this [12]. No long-term exposure studies are available in humans, and we only followed up

Table 2 Human case reports of organic arsenic exposures

Author	Exposure	Amount/concentration	Chelation	Symptoms
Chuo, C et al.	17 patients—ferric methyl arsenic acid	Not reported; acute ingestions; suicide attempt	8 Yes 9 No	Nausea/vomiting—no long-term effects
Shum, S et al.	1 patient—MSMA	500 ml 16% in a suicide attempt	Yes	Nausea, vomiting, transient hypotension, and renal insufficiency—no follow-up
Hessl, S	MSMA dermal exposure from plane	Unknown	Yes	Prolonged peripheral neuropathy
Luong, K. et al.	Bird's nest soup: nest-cementing substance of Chinese swiftlets (*Collocalia*), a mixture of algae and mucins produced by the salivary glands	Daily consumption of bird nest soup	None	Peripheral neuropathy—resolved after discontinuation of soup
Gherardi, R. et al.	Melarsoprol	38 days of treatment with melarsoprol for sleeping sickness	None	Guillain–Barre-like syndrome, high concentration of arsenic found in spinal cord

our patients for 6 weeks. If long-term effects were to develop after a single exposure, one would think that bioaccumulation and/or in vivo conversion would be necessary. In volunteers ingesting a single oral dose of MSMA [13], the amount of arsenic excreted in urine represented 78% of the ingested dose after 4 days. This leaves 22% unaccounted for that could be metabolized or stored in vivo. With regard to the in vivo biotransformation, MSMA is slightly methylated (13%) into dimethylarsonate (DMA)—a possible carcinogen in rats. Demethylation of MSMA to more toxic inorganic arsenic is, again, not thought to occur in mammals [12].

The benefit of chelation therapy for acute MSMA exposure seems limited. The data above suggest that MSMA is rapidly excreted, not transformed to inorganic arsenic, and probably of low immediate or chronic toxicity. The prevention of peripheral neuropathy (the only persistent symptom) may be a possible rational for chelation, although there is no direct evidence that it improves outcome. The presence of inorganic arsenic in both patients' urine is also a concern and could warrant chelation itself. Known risks associated with BAL, however, would seem to make it less desirable. The chelation of our patients likely contributed to the high urinary concentrations observed.

The speciation and presence of inorganic arsenic in each of the 24-h urine samples for our cases require comment. Inorganic arsenic was reported in 3.90% of the total arsenic found in case 1 and 0.92% in case 2. Whether this was truly inorganic arsenic or a laboratory error is speculation. Given a lack of symptoms suggestive of acute inorganic arsenic toxicity (other than nausea/vomiting), laboratory error seems possible. Nausea and vomiting could be the results of irritating effects of the MSMA, or of other inert ingredients including surfactants in the preparation. Oddly, total arsenic concentrations *after* speciation were higher than total arsenic concentrations *prior* to speciation even on the same sample, again suggesting laboratory error (possibly dilution errors). If in vivo demethylation does actually occur, this finding is particularly concerning.

Summary MSMA exhibits relatively low toxicity even in the setting of extremely high urinary levels and after acute exposure with highly concentrated forms. Patients seem to do well after acute overdose. Administration of chelating agents such as DMSA may be considered, but there is no firm evidence supporting this approach. Further research is necessary to determine whether demethylation of MSMA occurs in humans and to explain the presence of inorganic arsenic in urine samples of patients with MSMA poisoning.

Conflicts of Interest The authors declare no sources of funding or conflicts of interest.

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