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CASE REPORT

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A Case of Fatal Aconitine Poisoning by Monkshood Ingestion*

ABSTRACT: Accidental aconitine poisoning is extremely rare in North America. This report describes the confirmation of a case of accidental aconitine poisoning using a liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. The case involved a 25-year-old man who died suddenly following a recreational outing with friends where he consumed a number of wild berries and plants including one that was later identified as Monkshood (*Aconitum napellus*). Postmortem blood and urine samples were available for analysis. All routine urine and blood toxicology screens were negative. The LC-MS/MS method allowed sensitive quantification of aconitine, the main toxin in *A. napellus*, and showed 3.6 and 149 μg/L in blood and urine, respectively. These concentrations were similar to that reported in other aconitine-related deaths. This case illustrates the dangers of consuming unidentified plants, and documents concentrations of aconitine in blood and urine in a fatal case of *A. napallus*-related poisoning.

KEYWORDS: forensic science, toxicology, aconitine, monkshood, tandem mass spectrometry

Acontine is a diterpenoid alkaloid produced by plants of the Aconitum genus. Various species of Aconitum have been used by different populations for centuries as poisons and medicines, with certain species still being used in Chinese and Japanese herbal medicines (1). The medicinal/toxic effects of aconitine can be relatively rapid in onset, occurring within minutes, and are related to stimulatory effect on voltage-gated sodium channels which also makes it an effective neurotoxin and cardiotoxin.

In North America, aconitine is mainly found in Monkshood (*Aconitum napellus*), a plant getting its name for its blue to purple colored flowers that resemble the monastic habit (2). *Aconitum napellus* Monkshood also contains other diterpenoid alkaloids that have both neurotoxic and cardiotoxic effects. Regardless of the source, the toxidrome is similar to all with a relatively rapid onset consisting of nausea and vomiting, dizziness, hypotension, and later systemic paralysis, palpitations and cardiac arrhythmias, and finally if not treated, shock, coma, and death results (3). The use of charcoal hemoperfusion (3) and amiodarone (4) has been successful in treating the life threatening ventricular tachycardia in poisoning cases.

Very few cases of aconitine poisoning have been reported in North America, and most reports are related to users of traditional Chinese medications (3). The purpose of this report was to describe a unique case of accidental ingestion of *A. napellus* resulting in death and to describe the concentrations of aconitine found in blood and urine.

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Case History

A healthy 25-year-old man went for an afternoon walk with four friends on an uninhabited island off the coast of Newfoundland, Canada. At 2:30 PM, he picked some wild flowers with purple and pink petals along with a few blackberries (*Epetrium nigrum*) and ate them. His friends were able to get a sample of the flowers from the same site. These flowers were later identified as *A. napellus*.

At around 5 PM, he complained of nausea and abdominal pain, vomited one half hour later, and collapsed suddenly at 6:15 PM. Resuscitation was attempted but was unsuccessful. At autopsy, the nail beds were noted to be cyanosed. Internal examination showed severe congestion of all organs. Histologic examination revealed bilateral massive intrapulmonary hemorrhage and edema.

Urine and blood were collected at the time of autopsy and were sent for toxicological analyses. Urine screens for drugs of abuse including screens for cannabinoids, opiates, benzodiazepines, phencyclidine, barbiturates, amphetamines, and cocaine metabolites were negative. Analysis of the blood sample for both alcohol and digoxin was negative. The case history indicated the ingestion of *A. napellus* and the possibility of aconitine poisoning. A liquid chromatography tandem-mass spectrometry (LC-MS/MS) method was, therefore, developed for the analysis of aconitine in the blood and urine samples. These analyses confirmed the presence of aconitine which was in the postmortem femoral blood sample at a concentration of 3.6 μg/L and in the urine sample at a concentration of 149 μg/L. The cause of death was considered to be aconitinie poisoning secondary to ingestion of *A. napellus*.

Materials and Methods

Chemicals

All chemicals and reagents were of analytical grade. Aconitine was purchased from Sigma (St. Louis, MO). Prazepam was purchased from CIL (Andover, MA).

Preparation of Standards

A stock solution of aconitine was prepared by dissolving to a concentration of 2.0 mg/L in distilled water. Calibrating standards were prepared by diluting the stock solution in urine to concentrations ranging from 0 to 1000 μg/L or in whole blood from 0 to 50 μg/L. Calibrating standards were carried through the same sample preparation steps as the urine and blood samples. Calibration was linear up to 500 μg/L in blood.

Preparation of Samples

Whole blood samples were prepared as previously described (5) with minor modifications. Briefly, 1 mL of whole blood was added to 1 mL of 0.5 μg/mL prazepam (internal standard) prepared in 20 mM Na_2CO_3 solution at pH 10, and 1.75 mL of 1-chlorobutane was added. The mixture was vortexed for 3 min and then centrifuged to separate layers. The top 1-chlorobutane layer was removed and kept. Samples were extracted one more time with 1.75 mL 1-chlorobutane and the upper layer was pooled with the previous. The extract was acidified by adding 100 μL of 50 mM H_2S0_4 and back extracted by vortexing for 3 min. The layers were separated by centrifugation and the bottom aqueous phase was removed for analysis by LC-MS/MS. Urine samples were prepared in a similar manner except urine was first diluted using two volumes of drug-free plasma.

Analysis by LC-MS/MS

The concentration of aconitine in the extracts was determined using a Waters High Performance Liquid Chromatography System (2792 separator module, equipped with a temperature controller; Waters, Milford, MA) and a Micromass Quatro Ultima PT for ESI/MS/MS. Aconitine was resolved on a C18 column (Xterra MS C18 3.5 μm; 2.1 × 50 mm; Waters) using a three solvent gradient consisting of 2 mM ammonium acetate (solvent A), water (solvent B), and acetonitrile (solvent C). An extracted sample (5 μL) was injected and the column was maintained in 10% solvent A, 80% solvent B, and 10% solvent C for 0.5 min. Solvent C was then increased to 50% in exchange for solvent B from 0.5 to 1.5 min. The system was then held at 50% B for an additional 1 min and then returned to starting conditions over a 1-min period. The total run time was 5 min. The flow rate was held constant at 0.4 mL/min and the column temperature was held at 30°C. The elution of aconitine occurred at 2.9 min and was determined by monitoring the reaction 646.7 > 586.5 using a collision energy (CE) equal to 32 (Fig. 1). Prazepam was measured by monitoring 324 > 271 at CE = 20, and clomipramine, an alternate internal standard, was monitored by the reaction 315.9 > 87 at CE = 14. The two internal standards co-eluted at 3.0 min (Fig. 1). The MS used positive ion electrospray with capillary voltage held at 3.00 kV and core voltage at 65 V. The limit of detection for aconitine was less than 0.4 μg/L in blood and the imprecision of the assay for aconitine was 6.7% (n = 9 replicates) at 5 μg/L.

Discussion

The cause of death in this case was unique in that it represents an exposure to aconitine that was purely accidental and possibly due to misidentification and consuming naturally growing herbs in the wilderness. The sudden collapse and mechanism of death in this case was consistent with ventricular arrhythmias, a common finding in aconitine poisonings. These arrhythmias appear to result from aconitine-induced derangement of intracellular calcium homeostasis as recently described (6). The hemorrhagic pulmonary edema as seen in this case has also been reported (7). The 25-year-old man was symptomatic within 2.5 h and died by 4 h after ingestion. Timely medical management was not available to potentially prevent the death. The onset of symptoms due to aconitine poisoning can be relatively quick and occur as early as 10 min after ingestion (3). Most poisonings due to aconitine are due to the use of traditional oriental herbal medications. Lin et al. (3) recently reported a collection of 17 cases of nonfatal aconitine poisoning presenting from 1990 to 1999 and recorded in the National Poison Center in Taiwan. Only two of those were accidental ingestions, 13 were due to medicinal use, and the remaining two were part of a pharmacologic experiment using aconite roots. One recent North American report described a case of severe aconite poisoning in an Asian immigrant who had been consuming *A. carmichaelii* root as an herbal medicine (8).

Precise toxic and lethal doses of aconitine are not well defined, although one text estimates 2 mg of aconitine as a lethal dose (9). Furthermore, relatively few studies have provided quantitative information on blood or urine concentrations of aconitine found in toxic and lethal cases. A recent report described a homicide in which the victim was poisoned by a decoction of boiled *A. napellus* leaves and stocks that was mixed with red wine. A urine sample from the victim showed aconitine concentrations of 810 μg/L (10). A recent acute ingestion of homemade *A. napellus* capsules containing 19 μg of aconitine for medicinal purposes resulted in gastrointestinal, cardiovascular, and neurological symptoms by 5 h after ingestion and showed a plasma concentration of aconitine of 1.75 μg/L at presentation to the emergency department 7 h postingestion (11). Elliott et al. (5) described a fatality due to deliberate ingestion of self cultivated *A. napellus* and found postmortem blood and urine to contain aconitine concentrations of 10.8 and 264 μg/L, respectively. In other cases where jesaconitine was found to be the principal alkaloid, blood aconitine concentrations were 1.1 μg/L in a fatal case (12) and 1.7 μg/L in a nonfatal case (13). As highlighted by these latter two cases, aconitum alkaloids other than aconitine may collectively contribute to the toxic effect. The fatal case we report showed the presence of 3.6 μg/L aconitine in a postmortem blood sample and 149 μg/L in the postmortem urine sample. The blood concentrations are about half of that found in the fatal case of *A. napellus* poisoning (5) but about twice that found in a nonfatal case (11). Although medical management may have played a role in the survival of the nonfatal case, our results suggest that blood concentrations as low as 3.6 μg/L in *A. napellus* poisoning may be considered lethal if not treated.

A number of techniques have been used to identify and measure aconitine in overdose and fatal cases including LC-MS/MS (10,11). We adapted the sample extraction procedure previously described (5), but used LC-MS/MS to analyze the postmortem samples. While LC-MS/MS may offer some advantage with respect to specificity and shorter preparation and analytical time, none of the methods currently available are capable of providing results to allow timely management of poisoning cases. It may be prudent, however, that patient herbal medication history be taken into account when patient assessments are being carried out. It may also be important to implement screening for plant-related ingested toxins when considering patients with unknown causes of death. Prevention of cases as the one described here can only come about by educating the general public about the potential hazards of herbal medicines as well as the dangers of eating unknown plants in the wild.

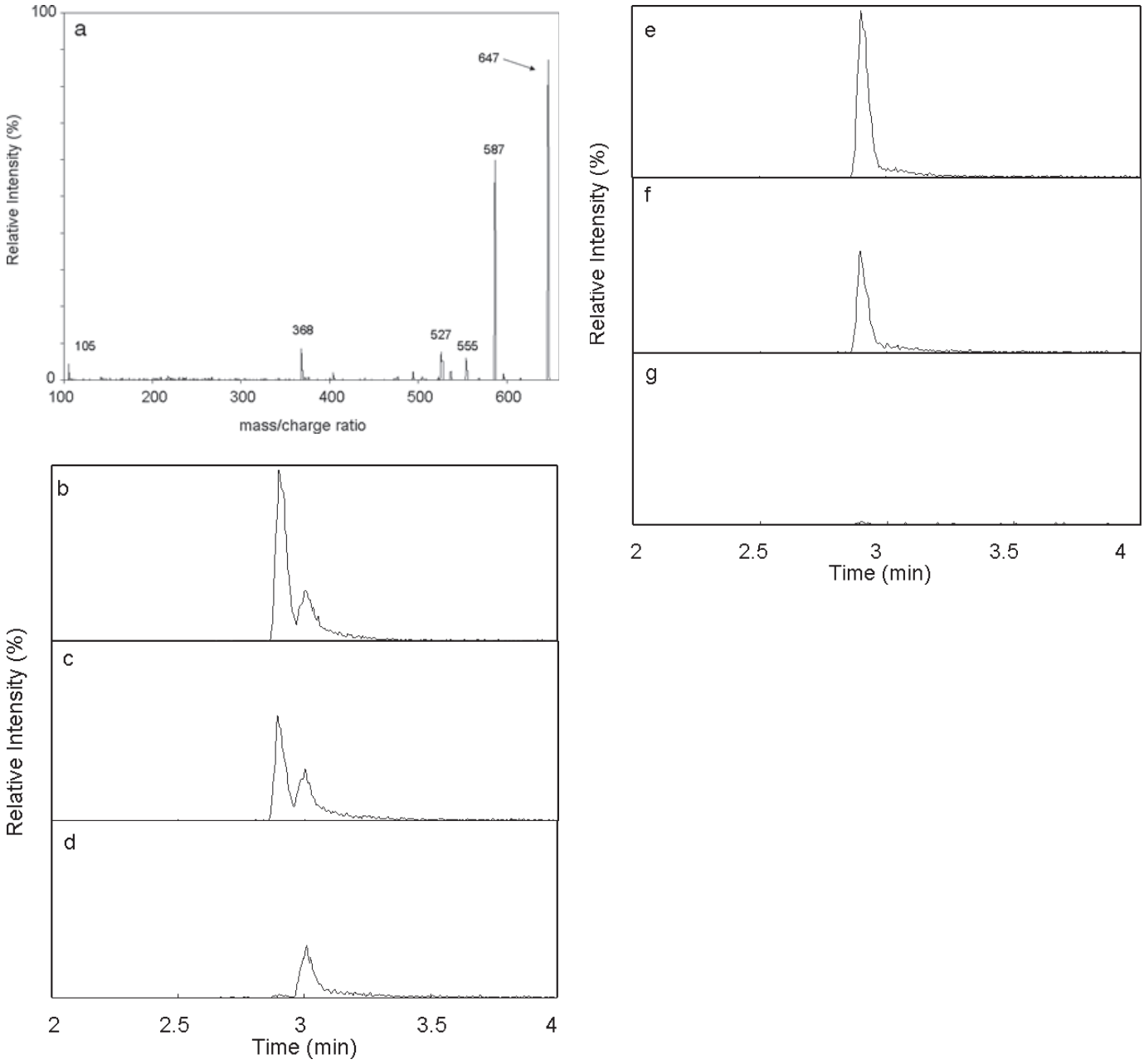

FIG. 1—*LC-MS/MS profile of aconitine. Panel a is the collision-induced dissociation profile of aconitine with collision energy of 32 eV. Panels b through to d represent total ion chormatograms for all monitored reactions in a blood sample fortified with 5 μg/L aconitine, the case blood sample, and a drug-free blood sample, respectively. Panels e through to g represent chromatograms produced by monitoring the reaction 646.7 > 586.5 for aconitine in a blood sample fortified with 5 μg/L aconitine, the case blood sample, and a drug-free blood sample, respectively.*

This report describes a very rare case of accidental aconitine poisoning due to monkshood ingestion and reports concentrations of aconitine in blood and urine. It also illustrates the importance of considering natural products when investigating unknown causes of death.

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