N-Acetylcysteine In The Treatment Of Human Arsenic Poisoning

Debra S. Martin, M.D., Stephen E. Willis, M.D., and David M. Cline, M.D.

Abstract: A 32-year-old man was brought to the emergency department 5 1/2 hours after ingesting a potentially lethal dose (900 mg) of sodium arsenate ant poison in a suicide attempt. The patient deteriorated progressively for 27 hours. After intramuscular dimercaprol and supportive measures failed to improve his condition, he was given N-acetylcysteine intravenously. The patient showed remarkable clinical improvement during the following 24 hours and was discharged from the hospital several days later. (J Am Board Fam Pract 1990; 3:293-6.)

Arsenic has been used since medieval times, both as medicine and poison. Although its medicinal use has declined, arsenic can still be found as an ingredient in certain homeopathic formulas,[1] which are available in some health food stores. Arsenic also is present in high concentrations in many easily obtainable ant killers, and this source is responsible for most toxic human ingestions.[2] Other sources include insecticides, herbicides, and rodenticides. Common symptoms of arsenic poisoning are metallic taste, nausea, vomiting, abdominal pain, and diarrhea. Depending on severity, patients may experience vasodilation, circulatory collapse, seizures, and acute tubular necrosis.[3] In 1988 there were 527 reported arsenic exposures in the United States, of which 280 required treatment. Forty-three patients required hospitalization, and there were no reported deaths from arsenic exposure.[4]

Intramuscular dimercaprol (BAL) followed by oral D-penicillamine is the currently recommended treatment for acute arsenic ingestion[5]; however, both drugs have important adverse effects, and neither may be effective in severe poisonings. Animal studies have shown N-acetylcysteine (NAC) to be effective in treating arsenic ingestion. A MEDLINE literature search covering the past 15 years did not show any reported cases of NAC therapy in the treatment of human arsenic poisoning. We are reporting the first known use of intravenous NAC in a patient with arsenic poisoning.

Case Report

A 32-year-old man was brought to the emergency department by ambulance 5 hours after he ingested approximately 900 mg of sodium arsenate — five times the lethal dose[3,6] — in a suicide attempt. He was lethargic but arousable by voice and answered questions appropriately. He stated that he vomited 1 hour after the ingestion and developed diarrhea 3 hours later. His pulse rate was 145/min, respirations were 24/min, blood pressure was 74/50 mmHg, and an electrocardiographic monitor showed sinus tachycardia. In addition to lethargy and hypotension, his skin was cool but not cyanotic, and no blood was present in the mouth or nares. His neck was supple without jugular venous distention. Cardiopulmonary examination was notable only for tachycardia, and deep palpation showed mild epigastric tenderness. The genitalia were unremarkable, and the rectal examination was hemoccult negative. Pulses were equal in all extremities. There were no focal neurologic deficits.

A toxicology screen and random urine and serum arsenic levels were requested, and a 24-hour urine arsenic collection was started. Initial laboratory studies showed: sodium, 142 mEq/L (142 mmol/L); potassium, 2.7 mEq/L (2.7 mmol/L); chloride, 106 mEq/L (106 mmol/L); CO_2, 25 mEq/L (25 mmol/L); creatinine, 2.1 mg/dL (185.64 μmol/L); glucose, 163 mg/dL (9.05 mmol/L); prothrombin time, 13.2 seconds; partial thromboplastin time, 44 seconds. Blood chemistry panel, urinalysis, and complete blood count

From the Department of Family Medicine and the Department of Emergency Medicine, East Carolina University, School of Medicine, Greenville, NC. Address reprint requests to Stephen E. Willis, M.D., East Carolina University, Brody Building 4N78, Greenville, NC 27858-4354.

were normal except for phosphorus, which was 2.5 mg/dL (0.81 mmol/L).

In the emergency department, the patient received a bolus of 250 mL normal saline, saline gastric lavage (2 liters), 50 g of activated charcoal, and 5 mg/kg of intramuscular BAL. He vomited the activated charcoal shortly after transfer to the intensive care unit, and attempts at placement of a nasogastric tube were unsuccessful because of persistent vomiting. A dopamine intravenous drip was started after numerous normal saline boluses failed to bring the systolic blood pressure to 90 mmHg. The patient had a net positive fluid input of 8 liters within the first 24 hours and developed a right pleural effusion, ascites, and mild anasarca.

Urine alkalinization was initiated to prevent hemolysis; however, this was discontinued 14 hours after ingestion when the urine output decreased to less than 30 mL/hr. The patient had hemodialysis because of decreased urine output and elevated serum creatinine. After dialysis, he continued to be hypotensive, requiring dopamine for 36 hours — up to 9.3 µg/kg/min. During the first 24 hours, the patient complained of persistent nausea and vomiting, penile burning, and intermittent paresthesias of the distal extremities. His physical examination was unchanged except

for conjunctivitis, rhinorrhea, and a sterile abscess at the BAL injection site. Repeated serum glutamic-oxaloacetic transaminase (SGOT) and coagulation studies were begun 24 hours after ingesting the poison (Figure 1). The maximum elevation of the SGOT was 125 U/L at approximately 84 hours after ingestion.

Consultation with the National Capitol Poison Center, Washington, D.C., was obtained because the patient's condition remained critical despite aggressive therapy and BAL chelation every 4 hours. A physician at the poison center recommended using intravenous NAC. The first dose was a small test dose, without any adverse effects approximately 27 hours after ingestion. The dosage of NAC (4 grams every 4 hours) was based on 70 mg/kg/dose. The oral form of NAC was mixed in 250 mL of normal saline and then millipore filtered. Based on instructions from the physician at the poison center, we administered a total of 18 doses of NAC by continuous intravenous infusion.

Within 24 hours after the IV NAC was started, the prothrombin and partial thromboplastin times returned to normal. The relations between prothrombin time, partial thromboplastin time, and treatment with NAC are shown in Figure 1. The patient's clinical status also improved; dopamine was discontinued, and his blood pressure and urine output remained stable. On day 4, the patient was tolerating a clear liquid diet, and BAL was discontinued. Oral D-penicillamine therapy (500 mg every 6 hours) was started. IV NAC was discontinued, and we ordered oral NAC 4 grams every 4 hours. This treatment was discontinued after 2 doses, because he refused to ingest oral NAC. The remainder of his hospital course was unremarkable. After spending 2 days in the psychiatric unit, the patient was discharged, complaining only of a mild headache.

After discharge from the hospital, the patient was seen in follow-up at the Eastern Carolina Family Practice Center. He remained on oral D-penicillamine therapy, and serial 24-hour urine collections were continued. Urinary arsenic levels for the first 11 days of treatment are shown in Figure 2.

One month after ingestion of sodium arsenate, the patient continued to complain of a mild, persistent headache in the occipital region and intermittent paresthesias of his hands, feet, and arms. He
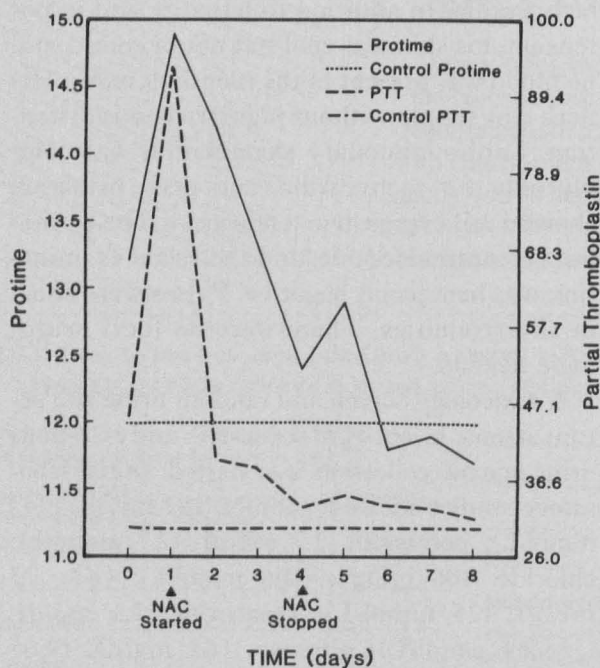

Figure 1. PT and PTT by number of days. (Note initiation and completion of NAC therapy.)
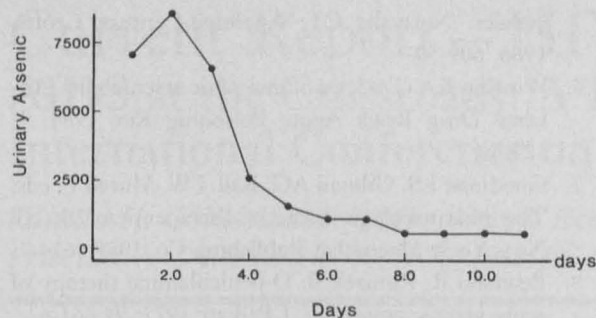
Figure 2. Urinary arsenic levels by number of days.

was referred to a neurologist because the symptoms suggested polyneuropathy. Electrodiagnostic studies were normal, and the neurologist thought that the patient may have been experiencing an acute myasthenic reaction to D-penicillamine. This drug was continued, however, because his urine arsenic levels were still elevated, and his paresthesias resolved spontaneously.

A D-penicillamine challenge test was conducted 82 days after ingestion. The patient collected a 24-hour urine specimen after D-penicillamine was discontinued. A second 24-hour urine collection was done after taking 4 500-mg doses of D-penicillamine. Because there was no increased secretion with the challenge and his urine arsenic level was within acceptable range (< 50 μg/L), D-penicillamine therapy was discontinued.

Approximately 90 days after ingesting the ant poison, the patient returned to work. At follow-up visits, he was free of signs and symptoms of arsenic toxicity. He has continued follow-up at the community mental health center and the family practice center.

Discussion

Adverse side effects make current chelation therapy for acute arsenic ingestion problematic. Up to 50 percent of patients receiving BAL chelation have one or more of the following adverse effects: hypertension, tachycardia, headache, nausea, vomiting, conjunctivitis, lacrimation, rhinorrhea, tingling of hands, penile burning, fever, and sterile abscesses.[7] D-penicillamine has been reported to cause fever, leukopenia, rash, anorexia, nausea, vomiting, syndromes resembling systemic lupus erythematosus, and nephrotoxicity.[8] It is available only in the oral form and may cause cross-reactions in penicillin-sensitive persons. Our pa-

tient experienced several toxic side effects of both the BAL and D-penicillamine.

The ideal antidote for a toxic ingestion would efficiently eliminate the agent, prevent further toxicity, have minimal adverse effects, and be easy to administer. For arsenic toxicity, a source of sulfhydryl groups could effectively prevent its inactivation of enzymes by dehydrogenation (oxidation). Arsenic dehydrogenates sulfhydryl groups of many vital enzymes, resulting in cell death.[3,6] Glutathione protects systems from oxidation by providing sulfhydryl groups. In acetaminophen overdoses, toxicity is believed to occur when glutathione fails to provide enough sulfhydryl groups. NAC prevents acetaminophen toxicity by providing a source of cysteine for glutathione synthesis.[9]

Recent studies of laboratory mice have shown increased survival time after using intraperitoneal NAC to treat lethal doses of arsenic.[10,11] However, Shum, et al. reported that there was no statistical difference in prolonging survival time when NAC was compared with D-penicillamine or BAL. The optimal time for NAC administration in arsenic toxicity has not been established. Studies in mice suggest that NAC is more effective in prolonging survival when given at 15 minutes after arsenic ingestion than at 30 minutes.[10] There are no data to predict when NAC is most effective in treating arsenic poisoning in humans.

Our patient showed remarkable improvement after the intravenous NAC was started. He received NAC according to the protocol used in the management of acute acetaminophen overdoses in Europe, where intravenous NAC is preferred to the oral form.[12] Within the next 24 hours, the patient's coagulopathy resolved (Figure 2), and during the next several days, his albumin- and liver-associated enzymes returned to normal. Dopamine was discontinued, and his blood pressure was normal during the remainder of his hospital stay.

Intravenous NAC has been used in the United Kingdom since 1979 for the treatment of acute acetaminophen overdose, with only rare cases of adverse side effects.[12] During the last 5 years, there have been only 38 cases of anaphylactoid reactions to intravenous NAC, mainly rash, angio-oedema, hypotension, and bronchospasm. In all of the cases, the symptoms subsided quickly once the infusion was discontinued.[13] Our patient did

not experience any adverse effects from his 18 doses of intravenous NAC.

We believe that this case report strongly suggests a beneficial effect of intravenous NAC in treating arsenic toxicity. NAC should be considered as an adjunct to the traditional methods of chelation with BAL and D-penicillamine. More studies are needed to establish the optimal dose, time of initiation, and duration of treatment.

References

1. Kerr HD, Saryan LA. Arsenic content of homeopathic medicines. J Toxicol Clin Toxicol 1986; 24:451-9.
2. Kersjes MP, Maurer JR, Trestrail JH, McCoy DJ. An analysis of arsenic exposures referred to the Blodgett Regional Poison Center. Vet Hum Toxicol 1987; 29:75-8.
3. Schoolmeester WL, White DR. Arsenic poisoning. South Med J 1980; 73:198-208.
4. Litovitz TL, Schmitz BF, Holm KC. 1988 annual report of the American Association of Poison Control Centers National Data Collection System. Am J Emerg Med 1989; 7:495-545.
5. Goldfrank LR, Howland MA, Kinstein RH. Arsenic. In: Goldfrank LF, ed. Goldfrank's toxicologic emergencies. Norwalk, CT: Appleton-Century Crofts, 1986; 609-50.
6. Winship KA. Toxicity of inorganic arsenic salts. Adverse Drug React Acute Poisoning Rev 1984; 3: 129-60.
7. Goodman LS, Gilman AG, Rall TW, Murad F, eds. The pharmacologic basis of therapeutics. 7th ed. New York: Macmillan Publishing Co, 1985:1614-7.
8. Peterson R, Rumack B. D-penicillamine therapy of acute arsenic poisoning. J Pediatr 1977; 91:661-6.
9. Davis M. Protective agents for acetaminophen overdose. Semin Liver Dis 1986; 6:138-47.
10. Shum S, Skarbovig J, Habersang R. Acute lethal arsenite poisoning in mice: effect of treatment with N-acetylcysteine, D-penicillamine and dimercaprol on survival time. Vet Hum Toxicol 1981; 23(Suppl 1):39-42.
11. Henderson P, Hale TW, Shum S, Habersang RW. N-acetylcysteine therapy of acute heavy metal poisoning in mice. Vet Hum Toxicol 1985; 27:522-5.
12. Prescott LF, Illingworth RN, Critchley J. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. Br Med J 1979; 2: 1097-100.
13. Mant TG, Tempowski JH, Volans GN, Talbot JC. Adverse reactions to acetylcysteine and effects of overdose. Br Med J 1984; 289:217-9.