

D-Penicillamine therapy of acute arsenic poisoning

Severe poisoning resulting from single ingestions of rodenticides, herbicides, or insecticides containing arsenic have been frequently recognized.¹⁻¹⁰ We record three cases of solubilized arsenic trioxide poisoning in Navajo Indian children and one case of sodium arsenate ingestion in an infant. One fatality occurred during dimercaprol therapy prior to initiation of therapy with D-penicillamine. Three survivors were treated with 2,3-dimercaprol intramuscularly and with oral D-penicillamine. The use of D-penicillamine in arsenic poisoning has not been generally appreciated. Excretion data from the three children are presented which document the effectiveness of D-penicillamine, administered orally in four daily doses of 25 mg/kg/dose, in the therapy of arsenic intoxication. Excretion data for the trace metals, zinc and copper, during D-penicillamine chelation therapy are also reported.

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D-PENICILLAMINE has been effectively used in the treatment of Wilson disease and cystinuria. It has been advocated in the therapy of lead¹¹⁻¹³ and mercury intoxication^{14, 15} and has been suggested as useful in rheumatoid arthritis.¹⁶ We report here the successful chelation of three children with D-penicillamine, administered orally, following ingestion of soluble arsenicals. Measurement of urinary excretion patterns of arsenic during chelation revealed D-penicillamine to be at least as effective as intramuscular dimercaprol. No relapse in symptoms was observed following a five-day course of D-penicillamine and no further arsenic could be mobilized by giving intramuscular dimercaprol or additional oral D-penicillamine. Plasma homeostasis of zinc, copper, calcium, and magnesium was maintained without supplementation during D-penicillamine therapy.

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CASE REPORTS

Three children were found with an empty bottle of Cowley's Rat and Mouse Poison (arsenic trioxide 1.75%, inert ingredients 98.25%; elemental arsenic 1.32%). The bottle had been recently purchased and had contained 6 fluid ounces. They were taken immediately to an outpost clinic and received ipecac syrup within 20 minutes of the ingestion. Patient 1 produced a small amount of emesis, while Patients 2 and 3 each produced large volume emesis. They were then given castor oil which was retained in all but Patient 2. Patient 1 suffered a grand mal convulsion following which all three children were transferred to the Shiprock Public Health Service Indian Hospital at Shiprock, New Mexico.

Abbreviation used BUN: blood urea nitrogen

Patient 1 (UCMC No. 479313-9) was a 2 5/12 year-old, 10 kg, Navajo Indian boy with no previous history of illness. On arrival at the referring hospital, pulse was 108/minute, respirations were 48/minute, and the patient was markedly lethargic. The hematocrit was 45 and the BUN was 30 mg/dl. He was given 5 mg/kg dimercaprol intramuscularly four hours following the ingestion. His pulse increased over the next 3½ hours to 172/minute with a blood pressure of 102/52, respirations of 60/minute, and arterial blood gases revealed a pH of 7.31, a Po₂ of 44.4, and a Pco₂ of 27. During air transfer to the University of Colorado Medical Center the patient developed uncontrollable convulsions which did not respond to a total of 2.4 mg intravenous diazepam in divided doses over 2½ hours. Continuous cardiac monitoring revealed an abrupt change from a sinus tachycardia of 180/minute to

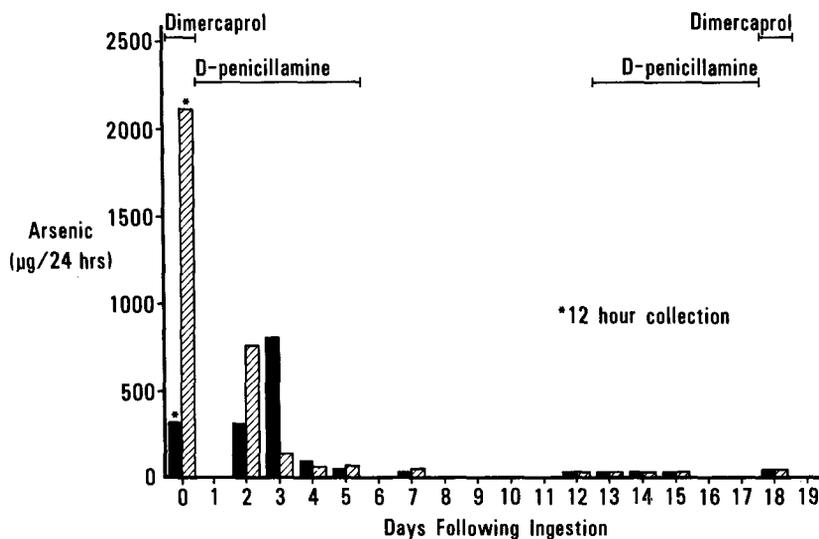


Fig. 1. Urinary arsenic excretion in Patients 2 (▨) and 3 (■) per 24-hour collection. Normal range is less than 50 µg/24 hours. Administration of chelating agents indicated by horizontal bars at dosages stated in text.

ventricular fibrillation and finally asystole. Resuscitative efforts over the following 1½ hours were unsuccessful. Blood drawn just prior to death revealed a whole blood arsenic value of 26 µg/dl (normal value is less than 7 µg/dl).

Patient 2 was a 4½ year-old, 10 kg, Navajo boy (UCMC No. 479314-7) who at the time of transfer had a pulse of 156/minute, blood pressure 112/50, respirations of 28/minute, temperature of 99.2°, a hematocrit of 40, and slight lethargy. Cardiac monitoring revealed a sinus tachycardia. He received dimercaprol, 5 mg/kg, intramuscularly four hours following the ingestion and this dose was repeated every four hours for a total of four doses. D-Penicillamine was begun 16 hours after ingestion with an oral dose of 25 mg/kg every six hours and this was continued for five days. Urinary excretion of arsenic was measured and these values are given in Fig. 1. Alkaline diuresis was performed for the first 24 hours to prevent deposition of hemoglobin breakdown products. Plasma hemoglobin on admission was 6.5 mg/dl, rose to 68.5 mg/dl three hours after admission, but by eight hours had dropped back to 6.3 mg/dl. The hematocrit on admission was 40.4 and dropped to 35 twelve hours later, where it stabilized. Charcoal adsorption and catharsis were performed with 15 mg of charcoal and 10 gm of magnesium sulfate orally. He developed an urticarial rash over the lower extremities while receiving dimercaprol, which subsided after discontinuation. The blood arsenic was 16 µg/dl whole blood and the first 12-hour urine collection contained 2,120 µg of arsenic. The urinary content of arsenic decreased gradually during the five days of D-penicillamine therapy. Following a seven-day rest, a second course of D-penicillamine was begun on day 12 with only a small increase in urine arsenic output. Liver enzymes remained normal throughout his entire hospital stay. At the completion of the second D-penicillamine course, six doses of dimercaprol at 5 mg/kg/dose were given with no increase in urinary arsenic.

Patient 3 was a 4 8/12 year-old, 16.7 kg, Navajo Indian boy (UCMC No. 47315-4) who on arrival at the referring hospital had

a pulse of 110, a temperature of 99.8°, an hematocrit of 40, a BUN of 19 mg/dl, and was alert and oriented. He received 50 mg of dimercaprol intramuscularly, 15 gm charcoal, and 10 gm magnesium sulfate orally. Forced alkaline diuresis was begun to prevent deposition of possible hemoglobin breakdown products. Physical examination at the time of transfer was normal except for a right conjunctivitis. Dimercaprol was continued at 5 mg/kg/dose intramuscularly every four hours for four doses. Concurrently, oral D-penicillamine was begun at 250 mg every six hours, and this was continued for five days. The blood arsenic level at the start of therapy was 12 µg/dl and his urine arsenic levels were given in Fig. 1. Plasma hemoglobin on admission was 4.4 mg/dl with a hematocrit of 34. The plasma hemoglobin did not rise above 4.4 mg/dl and was 1.2 mg/dl after eight hours. BUN was 14 mg/dl and liver enzymes were normal. He had several diarrheal stools during his first five hours in the hospital. An initial 12-hour urine collection revealed 306 µg of arsenic early in his course of chelation. Following a seven-day rest, a second course of D-penicillamine resulted in no additional excretion of arsenic. In addition, a 24-hour course of dimercaprol did not elicit further arsenic excretion (Fig. 1).

Patient 4 was a 12½-month-old white female who ingested approximately 15 to 20 mg of sodium arsenate in the form of "Terro" ant poison. The ingestion occurred at 10:30 AM with spontaneous and copious emesis at 12:10 PM. The child presented in the local emergency room with slight lethargy and mild perioral cyanosis. She received 25 mg dimercaprol intramuscularly (2.5 mg/kg) and transport to this medical center was arranged. Her vital signs during this period were: a pulse of 160/minute and regular, respirations 44/minute, blood pressure 118 mm Hg systolic, and temperature 101.2. She received a second intramuscular dose of 2.5 mg/kg of dimercaprol immediately prior to transport. Physical examination at this hospital six hours following the ingestion was normal except for a sinus tachycardia. The child had normal laboratory values for BUN, serum

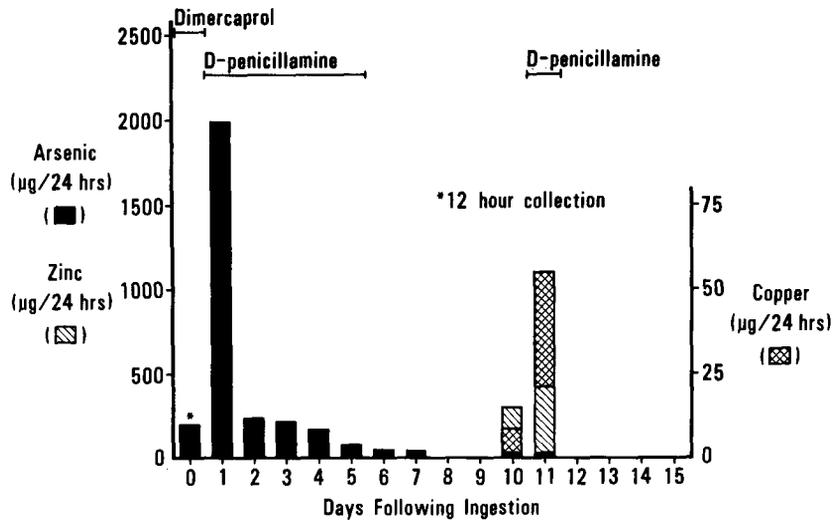


Fig 2. Urinary excretion of arsenic (■), zinc (▨), and copper (▩) in Patient 4. Normal range for copper excretion is less than 30 µg/24 hours. Normal range for zinc excretion at this age is less than 500 µg/24 hours. Administration of chelating agents indicated by horizontal bars at dosages stated in text.

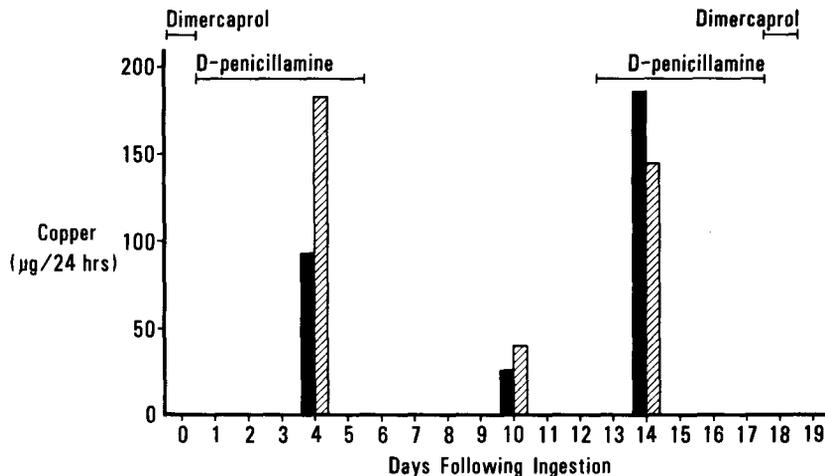


Fig. 3. Copper excretion in Patients 2 (▨) and 3 (■) per 24 hours. Normal range is less than 30 µg/24 hours. Administration of chelating agents indicated by horizontal bars at dosages stated in text.

creatinine, electrolytes, serum glutamic oxalacetic transaminase, and a normal complete blood count. D-Penicillamine at 100 mg/kg/day divided in four doses was begun and she received no further dimercaprol. Her first 12-hour urine collection contained 192 µg of arsenic. Subsequent urinary levels during chelation are shown in Fig. 2. Following a five-day course of oral D-penicillamine and a three-day period of observation, a 24-hour course of D-penicillamine resulted in no further mobilization of arsenic.

Plasma measurements of zinc and copper were performed in Case 2 and Case 3 and were all greater than 85 µg/dl during therapy. Normal values in this laboratory are 68 to 110 µg/dl for zinc and 25 to 150 µg/dl for copper. The urinary excretion of copper and zinc was measured during chelation therapy in all three children who survived. The results of these determinations

are given in Figs. 2 to 4. Serum calcium and magnesium determinations were within the normal range in these children during and following chelation therapy.

DISCUSSION

Clinical manifestations of acute arsenic poisoning usually occur within the first few hours following exposure. In addition to abdominal pain, vomiting, and diarrhea, common presenting signs may include hematuria, albuminuria, glycosuria, and elevation of liver enzymes.¹⁻¹⁰ Cardiac toxicities include sinus tachycardia, prolonged QT interval, abnormal T waves, and ventricular arrhythmias.^{1, 17, 18} Neurologic manifestations include pain in the extremities, headache, muscular weak-

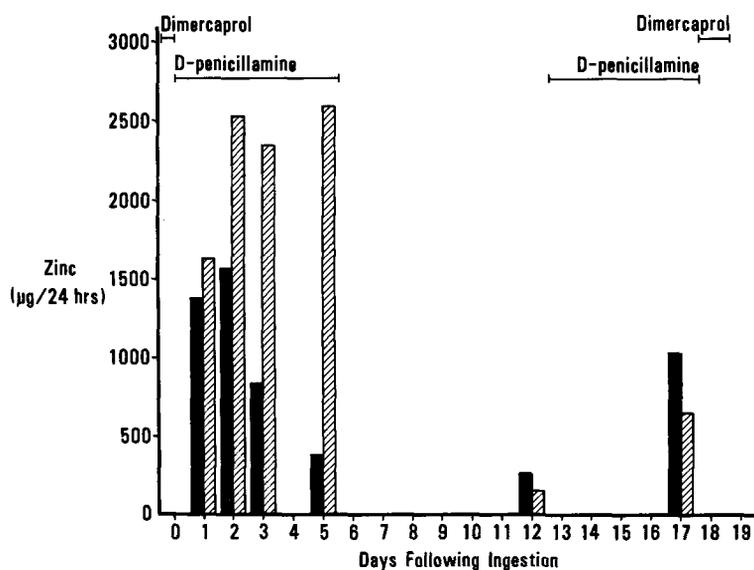


Fig. 4. Zinc excretion in Patients 2 (▨) and 3 (■) per 24 hours. Normal range at this age is less than 500 $\mu\text{g}/24$ hours. Administration of chelating substances indicated by horizontal bars at dosages stated in text.

ness, central nervous system depression with coma, and polyneuropathies, usually as a later finding.^{1-10, 19, 20} Increased skin pigmentation is considered a common characteristic of acute arsenic poisoning⁵ and of chronic arsenic exposure.

The child (Case 1) most seriously affected of the four, died approximately 12 hours after the arsenic ingestion. Tachycardia was noted in this child as well as in the other three children. This preceded sudden cardiac arrest and unsuccessful resuscitation associated with ventricular fibrillation and irreversible asystole.

The three remaining children were treated with an initial course of dimercaprol and simultaneous administration of D-penicillamine. Dimercaprol therapy was terminated in Patients 2 and 3 after four doses, owing to the development of a rash in one child. D-Penicillamine was continued for a five-day course. Because the efficacy of D-penicillamine therapy had previously been documented by urinary arsenic levels in only one patient,²¹ a 24-hour course of dimercaprol was given to two of the patients to attempt further mobilization of arsenic after D-penicillamine therapy. No increase in urinary arsenic was observed in either of the children following administration of dimercaprol.

Kjeldsberg and Ward²¹ reported chelation with D-penicillamine in a thrombocytopenic patient chronically exposed to arsenic. An initial urine arsenic measurement in that patient revealed 7,840 $\mu\text{g}/\text{l}$. With the institution of D-penicillamine therapy as much as 20,246 $\mu\text{g}/\text{l}$ was excreted. Repeat chelation in that patient following further arsenic exposure several months later gave a base

line value of 194 $\mu\text{g}/\text{l}$ but, upon chelation, the excretion rose to 86,000 $\mu\text{g}/\text{l}$; thus providing a clear demonstration of the effectiveness of D-penicillamine in mobilizing arsenic.

Kuruwilla and associates⁴ recently reported the use of D-penicillamine as an adjunct to therapy following recurrence of symptoms after chelation with dimercaprol. The children were reported to have had complete disappearance of all signs of arsenic poisoning while receiving D-penicillamine, although these authors did not measure the urinary excretion of arsenic.

Although dimercaprol has been considered to be the standard therapy for arsenic poisoning and has been used with great success since 1946, the use of D-penicillamine has several advantages. In chronic as well as in acute arsenic poisoning, D-penicillamine can be given orally, whereas dimercaprol must be given intramuscularly. D-Penicillamine is associated with rare toxicity, although there has been severe toxicity when L-penicillamine or the mixture with DL-penicillamine has been employed.²² D-Penicillamine has been implicated as cause of maculopapular rash accompanied by fever, leukopenia, thrombocytopenia, eosinophilia, arthralgias, lymphadenopathy, nephrotic syndrome, thrombophlebitis, cheliosis, mild angioneurotic edema, and fatal agranulocytosis. The more serious complications have been associated with chronic administration in Wilson disease.^{22, 23} Optic neuritis, reversible by the administration of pyridoxine, has been reported following DL-penicillamine but has not been reported with the use of D-penicillamine.²² Penicillin sensitivity may also indicate potential cross-reactivity to

D-penicillamine.^{22, 24} Mild iron deficiency has been reported following prolonged use of D-penicillamine²⁵ and a lupuslike syndrome has been reported in one patient while receiving D-penicillamine for cystinuria.²⁶

Excretion of trace metals by patients receiving chelation has been reported by McCall and associates,¹⁵ specifically with reference to the effects of EDTA and D-penicillamine. Their studies in patients who received D-penicillamine for lead or mercury poisoning revealed a significant increase in the urinary excretion of trace metals during therapy. Zinc, copper, magnesium, and calcium all exceeded normal excretion values. They also observed that as excretion of that metal poison for which chelation had been instituted decreased, there was an increase in the excretion of the less well-chelated metals, such as calcium and magnesium. Balance studies in man were not performed during D-penicillamine administration except in the case of zinc. While the urinary excretion of zinc increased with D-penicillamine therapy, the absorption of zinc from the intestine also increased and there remained a positive zinc balance. Recently, however, a report of skin lesions responsive to zinc therapy has appeared after prolonged D-penicillamine administration in Wilson disease.²⁷ In contrast to these findings was the observation of no significant increased absorption of dietary copper in Wilson disease during D-penicillamine therapy.²⁸

Plasma levels of zinc and copper during chelation remained within the range of normal for the two children (Patients 2 and 3) in whom they were measured. Urinary excretion of these metals was, nevertheless, elevated in both children. Whether increased absorption of dietary zinc and copper or mobilization of body stores was responsible for maintaining plasma homeostasis is not known; but no clinical symptoms of trace metal deficiency such as skin lesions, altered hair texture, or anemia was observed.

Serum determinations of calcium and magnesium were within the range of normal for the three surviving children during their entire hospitalization.

In summary, we propose the following therapy for arsenic poisoning: administration of D-penicillamine, 100 mg/kg/day orally in four divided doses, preceding meals, to a maximum dose of 1 gm/day for five days. Three to five days of observation should follow with reinstitution of therapy, if symptoms recur. A "mobilization" course prior to discharge, as utilized in Patient 4, is strongly recommended to ascertain the completeness of chelation. Measurement of the urinary excretion of the metal is important. When the 24-hour urinary arsenic excretion has fallen below 50 $\mu\text{g}/24$ hours, further chelation therapy has not been necessary. Adult therapy with D-penicillamine has been successful at 500 mg every six hours.¹⁶

While there has been some suggestion that D-penicillamine can be absorbed from the stomach as rapidly as dimercaprol is from muscle, in instances of coma or shock, consideration should be given to the safety of any oral agents. In such circumstances it is probably well to initiate dimercaprol therapy and change to therapy with D-penicillamine as early as possible. D-Penicillamine should be considered an effective agent in the therapy of acute arsenic intoxication.

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