Arsenic

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Article Last Updated: Dec 6, 2006

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AUTHOR AND EDITOR INFORMATION

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Author and Editor Disclosure

Synonyms and related keywords: arsine gas, heavy metal toxicity, arsenic ingestion, arsenic poisoning, arsenical pesticides, arsenic exposure

Patient Education

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INTRODUCTION

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Background

The atomic number of arsenic, an element, is 33, and its atomic weight is 74.91. A commonly found form of arsenic is gray with a metallic appearance. Yellow, brown, and black forms are also known. When arsenic is heated, it sublimes, that is, it changes directly into the gaseous form, arsine. Arsenic is considered a transitional element intermediate between metals and nonmetals, but it classically is considered a heavy metal. It has been known since ancient times and has been and continues to be used medicinally.

Arsenical pesticides are still used in some areas in agriculture. Chronic toxicity from ingestion or inhalation of arsenic may be occupational or environmental. Wells drawing from watersheds near old mines may be contaminated with dangerous amounts of arsenic. Accidental ingestion, ingestion with suicidal intent, and intentional poisoning most commonly are associated with acute toxicity. With regular and long-term exposure, some tolerance may develop. At one time, people in southern Austria reportedly found that eating arsenic had a "tonic" effect and were able to ingest without toxicity what would usually be a fatal dose.

Documented cases of arsenic poisoning have been associated with ingestion of traditional Chinese herbal balls, Korean herbal preparations used to treat hemorrhoids, and kelp supplements. Arsenic is used to treat and preserve lumber. As early as the 1890s arsenical pigments were used in wallpaper both for coloring and for its antifungal properties. The action of the fungus *Penicillium brevicaule* releases arsine. Arsenic was used to strengthen lead and in the glassmaking industry to reduce discoloration caused by trace amounts of iron. All of these applications add to the hazards of old house restorations. Arsenic was used as a poison gas called Lewisite in World War I; hence, the name of the agent used to treat arsenic intoxication is British antilewisite (BAL).

Pathophysiology

Acute exposure

Inorganic arsenicals, such as the trioxide, a by-product of smelting of ore containing copper, lead, and zinc, are more toxic than the organic. Arsenic may be inhaled in particulate form, ingested, or absorbed through skin and mucous membranes. The minimum lethal dose is 100-200 mg of arsenic trioxide.

Exposure to a toxic dose initially produces a dry burning sensation in the mouth and throat and a constricted feeling in the throat. This is followed by severe abdominal pain, cramping, diarrhea, and vomiting. The diarrhea begins with "rice water" stools progressing to a bloody discharge. Stools and breath may have a garlicky odor. Vertigo develops, followed by delirium, coma, and often convulsions. Circulatory collapse with hepatic and renal failure ensues. Myocardial toxicity involves broadening of the QRS, flattening of the T waves, and ST depression. In acute exposure to the gaseous form, inhalation of toxic amounts of arsine gas results in headache, malaise, weakness, dizziness, and dyspnea accompanied by gastrointestinal distress.

The effect is not immediate but typically is delayed by 2-24 hours. Usually, hemolysis occurs 4-6 hours after the onset of symptoms and dark red urine is noticed. Jaundice develops 24-48 hours later. Patients present to the emergency department with severe jaundice, anemia, and hemoglobinuria (ie, blackwater urine). On admission, the patient may have fever, tachycardia, and tachypnea. Acute oliguric renal failure occurs because concentration of arsenic in the proximal tubules and binding to proteins of tubular epithelium damages the tubules. Treatment involves hemodialysis and the use of BAL (Dimercaprol).

Subacute and chronic exposure

Arsine was identified in 1775. The first reported fatality from arsine inhalation was in 1815 when a German chemist died after inhaling the gas in his laboratory. Workers in the metallurgy industry are at a risk of repeated exposure to arsine gas. The action of acid on metal ore contaminated with arsenic causes release of arsine gas. Arsenic-containing dust emitted from smelters is another source.

Environmental exposure to well water containing inorganic arsenic can result in skin hyperpigmentation or an eczematous dermatitis. Peripheral vascular involvement may occur, with acrocyanosis and the appearance of a Raynaud-like picture. In addition, a sensorimotor distal neuropathy may occur that presents like Guillain-Barré syndrome, and sideroblastic anemia —a state of ineffective erythropoiesis characterized by a significant number of erythroid precursors containing mitochondria with stainable iron granules—also may be noted. Although a similar hematopoietic picture is seen in lead toxicity, the mechanism producing the anemia is not believed to be the same. Leukopenia is a common finding.

Biochemistry of arsenicals

Many enzyme systems are vulnerable to the tendency for arsenicals to react with sulfhydryl groups. The pyruvate and succinate oxidation pathways may be disrupted. The sulfhydryl cofactor dihydrolipoate appears to be the principal site of inhibition. The converting enzyme dihydrolipoate dehydrogenase is also susceptible. This inhibition effectively blocks the Krebs cycle, interrupting oxidative phosphorylation, which results in marked depletion of ATP stores. Arsenic also produces a picture of thiamine deficiency by preventing transformation of thiamine into acetyl-coenzyme A (CoA) and succinyl-CoA. Since alcohol affects the same cycle, arsenic toxicity is accentuated by alcohol ingestion. A number of other enzyme systems are susceptible, but they are of minor clinical significance.

Arsenolysis, another mechanism of toxicity, results when arsenic anions disrupt oxidative phosphorylation by replacing stable phosphoryl with less stable compounds. Unstable arsenic compounds irreversibly decompose, resulting in loss of high-energy phosphate bonds. The cell then self-destructs in an attempt to restore lost energy.

Medicinal uses of arsenicals

Inorganic arsenic has been used in medicine for over 2500 years. The most widely used form was Fowler solution containing 1% potassium arsenite, which was used for treatment of psoriasis. Arsphenamine was for many years the standard treatment for syphilis. Melarsoprol is an organoarsenic compound used to treat infections caused by *Trypanosoma brucei* or *Trypanosoma gambiense*. Retrospective studies have suggested an increase in the incidence of hepatic angiosarcoma in people previously treated with Fowler solution, but evidence is tentative. Regular, long-term arsenic exposure has been associated with various cutaneous carcinomas as well as internal malignancies including bronchogenic carcinoma and hepatocellular carcinoma.

Frequency

United States

In 1998, American Association of Poison Control Centers (APCC) reported 956 cases that were not related to pesticides. Ninety-nine cases involved exposure to arsenic-containing pesticides; 4 of the nonpesticide cases died, while no death was reported from the pesticide-related cases. Estimating the number of unreported cases is difficult. One estimate is that 900,000 people a day are exposed to arsenic.

Mortality/Morbidity

Fortunately, the known mortality rate is low—4 reported in 1998 and only sporadic cases in prior years.

Race

No racial predilection is apparent.

Sex

Industrial exposures to arsenic are more likely to involve men. The same may be said for exposure to arsenical preparations used in agriculture, construction, and forestry. Intentional poisonings involve both sexes. No hormone-related difference in the metabolism of arsenic is known.

- Most occupational exposures are in males because of the predominance of males in the mining and smelting industries.
- Accidental and environmental exposures are equal in males and females.

Age

Most cases of exposure are in adults.

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CLINICAL

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History

Acute toxicity following ingestion, inhalation, or absorption of inorganic arsenic produces a burning sensation in the mouth and throat. This is followed, usually somewhat later, by severe gastrointestinal distress with copious and severe diarrhea and vomiting. Vertigo, delirium, coma, and often convulsions are seen as the toxicity is manifest. Circulatory collapse and renal and hepatic failure ensue, and hemolysis usually occurs 4-6 hours after onset of evidence of toxicity. Acute symptoms typically develop hours after exposure to inorganic arsenic. Inhalation of arsine gas produces headache, malaise, weakness, dizziness, dyspnea, and GI distress more rapidly.

The typical picture in subacute arsenic toxicity includes the onset of gastrointestinal symptoms—nausea, vomiting, and diarrhea—which may be intermittent but in retrospect are associated with ingestion of hot or cold beverages. For a layperson's account of an experience with arsenic poisoning, read "My Husband Poisoned Me" by Ellen Harris in the March 2000 issue of *McCall's Magazine,* pages 68-73.

Chronic exposure effects should be suspected when a patient presents with a distal sensorimotor neuropathy accompanied by skin hyperpigmentation. History of drinking well water is an additional clue. Bae et al have written on the role of a rice cooking technique associated with arsenic toxicity in Bangladesh.

Physical

Heavy metal poisonings have many similarities, making clinical distinctions between them difficult at times. Arsenic is more likely than other heavy metals to produce a dramatic gastroenteric picture when ingested. Inhalation of arsine gas produces clinical features whose onset is dependent on the degree of exposure. The initial complaints may be vague, with headache, malaise, weakness, dizziness, and dyspnea. Later, the features are the same as those seen in inorganic arsenic ingestion. The cutaneous manifestations are rather different depending on the heavy metal exposure.

- Cutaneous: Hyperpigmentation of the skin of the face or extremities is in a "raindrop" distribution. The skin has a peculiar bronze tint. A patient described by Kyle and Pease had pigmentation of the buccal mucosa resembling the hyperpigmentation of Addison disease. Oral herpetiform lesions or a diffuse macular rash may be present, as may brawny, nonpruritic desquamation and patchy alopecia as well as hyperkeratosis of the palms and soles. Mees lines are transverse, 1-2 mm white striations in the fingernails, which may be deformed or fall out within 2-3 weeks of exposure. The Mees lines are actual arsenic deposits. Because of the availability of sulfhydryl groups in keratin, arsenic can be measured in hair and fingernail samples. Arsenic can be detected in hair samples as early as 30 hours after ingestion and as late as 9 years after ingestion. Thallium toxicity can be suspected in case of hair loss and fingernail loss, but thallium is more likely to produce hyperglycemia.

- Neurological: Paresthesias and numbness, usually in a symmetric stocking-glove distribution, and muscle weakness are a result of peripheral neuropathy. The onset and progression may be mistaken for Guillain-Barré syndrome. This problem may persist long after arsenic exposure stops. Fatigue and weakness are major complaints. The neuropathy is not seen acutely but develops over the weeks subsequent to exposure in acute or subacute toxicity. In regular, long-term arsenic exposure, the presenting complaint is frequently a sensory neuropathy with features that resemble an alcoholic neuropathy. Burning paresthesias in glove and stocking distribution, early loss of stretch reflexes, and later weakness are seen. In severe toxicity, flaccid paralysis may appear in the lower extremities, then the upper extremities. This is maximal about 4 weeks after acute exposure. Again, the clinical picture resembles Guillain-Barré syndrome.

- Hematologic: Anemia with leukopenia is seen frequently; splenomegaly may be apparent. Granulocytopenia and an increase in the eosinophil count often occur.

- Systemic complaints of regional subcutaneous edema are present in arsenic intoxication. The eyelids in particular, and legs less frequently, become quite edematous.

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DIFFERENTIALS

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Guillain-Barre Syndrome in Childhood

Other Problems to be Considered

Acute abdomen
Hyperemesis gravidarum
Irritable bowel syndrome
Lupus erythematosus
Thallium toxicity
Porphyria

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WORKUP

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Lab Studies

- Testing for arsenic
  - Inorganic arsenic exists in various forms. The most toxic are As-III and As-V. Detoxification occurs as As-III is oxidized in the liver to As-V and then methylated to dimethylarsine and monomethylarsine over the course of 24 hours. As-III and As-V levels in the urine peak at about 10 hours and return to normal 20-30 hours after acute ingestion; the methylated compounds peak at 40-50 hours and can be measured as long as 20 days after ingestion. Blood levels are not useful. The biological half-life of inorganic arsenic is only 2 hours so blood or serum arsenic is unlikely to be detected after 2-4 hours.
  - Organic arsenic of a nontoxic variety is present in shellfish and saltwater fish, such as haddock or cod. The arsenobetaine and arsenocholine in seafood are excreted completely in the urine within 1-2 days. The urine of a person consuming seafood within 1-2 days of testing is likely to contain 50-2000 mcg of arsenic. Actual arsenic toxicity is characterized by the excretion of 500-50,000 mcg/day. In 41 cases of arsenic-induced peripheral neuropathy, most patients had total 24-hour urine concentrations of 100-400 mcg. A method has been developed to fractionate the inorganic and organic species using a cation-exchange cartridge and then analyzing the fractions using spectrophotometry. Of historical interest, the earliest test for arsenic was developed by the English chemist James Marsh (1794-1846).
- CBC with indices and reticulocyte count: In acute arsine exposure, patients have acute hemolytic anemia; with regular, long-term exposure, patients develop microcytic, hypochromic anemia. Eosinophilia and neutropenia also may be noted.
- Urinalysis: A 24-hour urine collection for total arsenic may be done if the diagnosis is subtle. A urine spot test is helpful in acute intoxication.
- Hair analysis or fingernail analysis may be indicated in regular, long-term exposure.

- In acute exposures, renal and liver function studies should be done. Levels of potassium, magnesium, and calcium must be monitored.

Imaging Studies

- Upper GI radiography after acute ingestion may show radiopaque material in the upper GI tract, as it does in pica (ie, ingestion of inappropriate materials) involving other heavy metals. Maximal absorption of arsenic occurs in the small intestine.

- CT scans and MRIs of the brain may show the cerebral edema and hemorrhagic or ischemic changes associated with acute toxicity.

Other Tests

- Electrodiagnostic testing: Motor and sensory nerve conduction velocities, visual evoked potentials, and somatosensory evoked potentials may be helpful in monitoring the progress of treatment. The neuropathy is axonal in nature with some demyelination.
    - Electromyography shows denervation potentials and reduction in motor unit activity. High-amplitude, polyphasic motor units are seen. A myelopathy may develop and anterior horn cell abnormalities may suggest amyotrophic lateral sclerosis.
    - Following acute exposure, axonal degeneration and progressive slowing of sensory and motor conduction velocities plateaus and begins to improve after treatment. In chronic, low-level exposure, a distal, axonal, primarily sensory neuropathy develops. This is a duration-dependent sensorimotor neuropathy that affects all sensory modalities but includes severe loss of large-fiber sensation (ie, position and vibration sense).
    - Cranial nerves are spared.
- Electroencephalography may be useful in monitoring any encephalopathy or seizures associated with acute toxicity. No EEG finding is pathognomonic for arsenic toxicity.

Histologic Findings

Nerve biopsies of people who have arsenical neuropathy show degenerated fibers and reduction of myelinated fibers in particular, but axons of all sizes are absent or markedly fragmented. Spinal cord pathways and anterior horn cells may be affected. In chronic toxicity, varying degrees of nerve fiber regeneration may be observed. Acute encephalopathic changes seen in the brain include perivascular hemorrhage. The chief mechanism is cerebral edema and vascular occlusion.

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TREATMENT

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Medical Care

The patient who presents with acute exposure is usually in severe distress. Hydration is vital in managing dehydration that can rapidly lead to hypovolemic shock because of the severity of the vomiting and diarrhea. If the patient is not actively vomiting, consider lavage with warm water or (some suggest) 1% solution of sodium thiosulfate. Whole bowel irrigation with polyethylene glycol may reduce or prevent continued absorption of arsenic that has passed the stomach. Chelation therapy should be started immediately.

- In the patient with acute arsine exposure and hemolytic anemia, the renal complications must be managed promptly. Chelation and hemodialysis should be initiated as soon as possible.

- The abdominal pain associated with acute toxic ingestion is severe enough to warrant the use of morphine.

Consultations

- Nephrology and hematology consultation should be requested urgently in cases of arsine exposure even if the hemolytic anemia has not manifested itself.
- Pulmonary consultation may be necessary in cases of arsine inhalation.
- A neurologist should be consulted for management of seizures and neuropathy.
- If the arsenic was ingested as a suicidal act, a psychiatrist must be consulted.

Diet

During the acute phase, when the patient is vomiting and having diarrhea, parenteral fluids are indicated. After the patient's condition stabilizes, oral intake may be allowed as tolerated. If circumstances are suspect, the patient should not be served any food or drink from home.

Activity

Activity is dependent on the patient's level of alertness and intactness of the peripheral nervous system.

The treatment of acute toxicity from arsenic consists primarily of maintaining hydration and electrolyte balance. The use of chelating agents hastens the removal of arsenic from the system. Management of arsine toxicity generally addresses the acute hepatorenal complications. The use of chelating agents in these cases is debatable.

Drug Category: *Chelation agents*

These are substances that bind heavy metals in the plasma and render them nontoxic; they also aid in their excretion.

Drug Name	Dimercaprol (BAL in Oil)
Description	British antilewisite is agent of choice in United States. Used as chelator for other heavy metals and stocked as essential item in emergency departments and poison control centers.
Adult Dose	2.5-3 mg/kg q4h for 2 d, then qid for 1 d followed by bid for 10 d for arsenic levels over 50; larger dose may be necessary depending on severity of poisoning; maximum dose is 5 mg/kg Administered by deep IM injection
Pediatric Dose	50-75 mg/m^2 body surface area q4h for total dose as high as 450 mg/d X 5 d by deep IM injection
Contraindications	Documented hypersensitivity; hypersensitivity to peanuts (BAL is available in a suspension of peanut oil); G-6-PD deficiency; concurrent iron supplementation therapy
Interactions	Selenium, uranium, iron, or cadmium may increase toxicity
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Complications and adverse reactions include fever, tachycardia, hypertension, headache, CNS stimulation, nausea and vomiting, GI upset, burning sensation around the mouth, salivation, and urticaria Sterile abscess may develop at injection site; may be nephrotoxic; may cause hypertension; caution when administering to patients with oliguria or G-6-PD deficiency (may induce hemolysis in G-6-PD–deficient patients)

Drug Name	Succimer (Chemet)
Description	Licensed by FDA as chelating agent for lead poisoning in children; used successfully to treat arsenic intoxication as well; available as 100-mg capsule.
Adult Dose	10 mg/kg PO q8h X 5 d; 10 mg/kg PO q12h X 14 d
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Do not administer concomitantly with edetate calcium disodium or penicillamine
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Excreted via kidneys, therefore, adequate hydration must be maintained; patients with renal insufficiency should be treated with caution Probably should not be drug of choice in acute arsenic toxicity if chelator desired Thrombocytopenia, eosinophilia, and cardiac dysrhythmias reported; other adverse effects include nausea and vomiting, rash, sore throat, drowsiness, paresthesias, abdominal pain and gas, diarrhea

Drug Name	Penicillamine (Cuprimine, Depen)
Description	Metal chelator used to treat arsenic poisoning; forms soluble complexes with metals excreted in urine.
Adult Dose	25 mg/kg PO q6h to maximum 1 g/d
Pediatric Dose	Not indicated
Contraindications	Documented hypersensitivity
Interactions	Increases effects of immunosuppressants, phenylbutazone, and antimalarials; decreases digoxin effects zinc salts, antacids, and iron may decrease effects
Pregnancy	B - Usually safe but benefits must outweigh the risks.

Precautions	Adverse effects include nausea, vomiting, fever, rash, neutropenia, thrombocytopenia, eosinophilia, and Stevens-Johnson reaction

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FOLLOW-UP

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Further Outpatient Care

- The patient should be monitored regularly to observe the improvement in neuropathic features and also to assess the need for physical or occupational therapy.

In/Out Patient Meds

- Chelating agents are used during hospitalization and may be continued on an outpatient basis if the patient is discharged before the course is completed.

Transfer

- Transfer to an extended care facility or rehabilitation center may be necessary in a patient with severe neurological involvement.

Deterrence/Prevention

- The source of the arsenic poisoning should be investigated. People with chronic poisoning by well water often are reassured when testing labels their water "safe." Unfortunately, this usually means simply that the water harbors no pathogenic bacteria.
- Testing of other family members should be considered; installation of filters or even switching to bottled water may be necessary.

Complications

- Treatment with BAL sometimes produces sterile abscesses that require drainage and may necessitate home nursing care for dressing.

Prognosis

- After removal from exposure, patients generally improve over the course of time. The neuropathy and accompanying weakness may take months or years to resolve. Little is known about the effect on cognition in regularly exposed children. Lead in relatively low levels is known to sometimes produce learning delays and cognitive problems in children.
- Inorganic arsenic has been suspected as a carcinogen since 1879 when the high rates of lung cancer in German miners were thought to be caused by exposure to inhaled arsenic. Careful surveillance of patients exposed to occupational arsenic on a regular, long-term basis should include screening for cancers of the lung, liver, GI tract, kidney, and hematopoietic system.

- Arsenic exposure and smoking appear to have synergism; therefore, smoking cessation should be advised strongly.
- Regular and long-term alcohol intake also appears to contribute to the development and severity of peripheral neuropathy associated with arsenic exposure. This is another factor that can be modified and should be discussed at follow-up visits.
- The keratotic skin lesions of arsenic toxicity are considered premalignant and must be monitored. OSHA requires periodic chest x-rays and regular skin examinations in workers exposed to arsenic in a work setting.

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MISCELLANEOUS

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Medical/Legal Pitfalls

- Medicolegal advice should be sought if the poisoning appears intentional. A tip-off is that the patient improves in the hospital and has an immediate relapse at home or when a family member brings "special" food or drink from home. Cases that appear suspect should be reported to the police.
- Assessment of environmental factors causing chronic toxicity because of well-water contamination, such as toxic dump situations, also have medicolegal implications.
- In either case, or in the case of suicidal intent, the physician's records should contain careful documentation.

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Article Last Updated: Dec 6, 2006