

Arsenic Toxicity in Hawaii: A Case Report and Review

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The presence of seemingly unexplained peripheral neuropathy in a sick patient warrants persistent delving into the medical, social and especially occupational history. Bearing this in mind, we have an interesting case to present.

Case Presentation

The patient was a 36-year-old man who had been diagnosed as having peptic ulcer disease and the presence of *helicobacter pylori* in an EGD biopsy specimen 3 months earlier. He was admitted to the hospital because of an acute onset of epigastric pain that began that morning. The patient was admitted to the regular medical ward and the gastroenterologist who had been following the patient for his PUD was consulted. The gastroenterologist recommended medical therapy empirically for the ulcers. He believed the patient required a stat EGD since a follow-up EGD done 2 weeks earlier had been negative for ulcers. An H2 blocker medication for *helicobacter pylori* was started. He required 75 mgs of meperidine i.m. for his severe abdominal pain.

The abdominal pain persisted; further work-up included an upper GI series, which showed no ulcers but did show some evidence of duodenitis, and a CT scan of the abdomen that was negative. Laboratory work-up included stool cultures, pancreatic enzymes, sickle cell screen, hepatitis screen, porphyria screen, liver function tests, and ESR, all of which were negative.

The patient described his abdominal pain as being intermittent, excruciating, either localized in the epigastric region, the left lower quadrant, or sometimes everywhere; it was associated with nausea but no vomiting. On physical examination, there was no rebound or guarding but mild to moderate tenderness to palpation could be demonstrated. He continued to complain of abdominal pain throughout his hospital course, and he required a constant regimen of pain control including Demerol, Dilaudid, Darvocet, Percocet, and even a PCA pump with low-dose morphine.

The patient's abdominal pain work-up was completed without any significant findings. He was discharged to outpatient care with pain medication, an H2 blocker, and medica-

tion for *helicobacter* prophylaxis. He was instructed to return for follow-up in a clinic in a couple of days.

When he reported to the clinic, he still complained of severe abdominal pain and had taken all of the pain medicine given at discharge. During this visit, a 24-hour urine heavy-metal screen was obtained. The report came back negative for lead and mercury but was positive for arsenic at 865 mcg/liter (normal < 100). To confirm this urine arsenic finding, pubic hair analysis for arsenic was done and it also returned positive at 5.6 microgram/gram of hair (* 75% have less than 0.03 to 0.3 mcg/gm hair, 20% are between 0.3 to 3mcg/gm hair, 5 % are up to 4 mcg/gm hair.) A more detailed diet and work history was obtained. He was treated as an outpatient for arsenic toxicity with penicillamine. However, he presented himself again to the clinic with the same, severe abdominal pain before penicillamine therapy. He was again admitted to the hospital for treatment with dimercaprol or BAL (British Anti-Lewisite), which entails intramuscular injections every 4 hours. The patient improved clinically, the repeat 24-hour urine-arsenic level was < 35 mcg/liter, and the arsenic content in the hair was down to 1.3 mcg/gram of hair.

The patient continued to be followed closely as an outpatient. His abdominal pain reoccurred with a fluctuating course. Additional work-up revealed a negative colonoscopy, a negative nerve conduction test and electromyelogram and negative lab tests, including urine and hair arsenic levels. Many questions were raised: Was this definitely arsenic toxicity? If so, what was the source of the arsenic? Were the GI symptoms related to the arsenic toxicity?

The Sources of Arsenic

Arsenic is ubiquitous in nature and the 20th most common element in the earth's crust¹. Arsenic is present in saltwater and seafood. Fish and shellfish contain a relatively high concentration of arsenic; this is relatively nontoxic and is readily excreted through urine². Urinary arsenic levels may be increased as much as tenfold after eating a large seafood meal¹. Notably, arsenic also is found in well water³.

Historically arsenic has been used in medicines⁴ and currently organic arsenicals are still being used in the treatment of certain protozoan diseases. It is also an ingredient in veterinary medicine⁵. Arsenic has been used in feed for poultry, cattle and swine to improve the nutritional status of animals⁶. Furthermore, arsenic has been a constituent of drugs such as opium⁷. Industrial use of arsenic has been a major source of worker exposure. In 1973, the National Institute for Occupational Safety and Health estimated that 1.5 million

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people were potentially exposed to arsenic during the course of their work⁷. Smelter workers were at increased risk for potential arsenic exposure. A study of smelter workers indicated increased mortality—mostly secondary to lung cancer—proportional to their exposure to arsenic⁸.

Arsenic is used in many commercial products; it is used as an additive in metal alloys to increase hardening and heat resistance, in the manufacture of glass, in wood preservatives, in lead-plating, and in various types of paints including fresco, tempera, watercolor, and oil paints⁵.

Arsenic also is used in making silicon microfilm⁴, light-emitting diodes in watches⁹, and in salt-impregnated materials for fires to produce multicolored flames¹⁰. Arsenic also plays a major role in agriculture: Pesticides, herbicides, fungicides, weed/tree killers, fly killers, rodenticides all contain arsenic because of its effectiveness and low cost¹¹. The use of arsenic as a desiccant of cotton comprises 15% of the U.S. market for arsenic trioxide. Significantly in our case, arsenic trioxide is a commonly used agent in the treatment of wood against termites. The wood used in the construction industry in Hawaii often is pressure-treated with this compound.

Clinical Manifestations of Toxicity

The clinical manifestations of arsenic toxicity vary widely and are dependent on the duration of exposure, level of the dose (if ingested), whether intake is acute or chronic, and on the chemical compound of the arsenic. The 3 forms of toxic arsenic are the trivalent salt, pentavalent salts, and arsine gas¹². Elemental arsenic is not toxic¹². Pentavalent salts are found in the earth's crust and are prevalent in foods; they are less toxic than the trivalent salts which tend to accumulate in the body more readily. Arsine gas is the most toxic and is frequently fatal.

Acute toxicity can occur with arsine gas poisoning or with massive doses of ingested arsenic. The symptoms of acute arsenic intoxication are apparent within 30 to 60 minutes, but death usually does not occur until approximately 24 hours later¹³. A garlicky odor in the breath and stool may be apparent. The patient might complain of a metallic taste in the mouth¹⁴.

Arsine gas poisoning is usually overwhelming and usually leads to death. Initial symptoms include: Fever, headache, nausea, vomiting, epigastric pain, dysuria, and explosive diarrhea. Hemolytic anemia also occurs as the arsenic binds to red blood cells; cyanosis and hypoxia could ensue. Shock with intractable vascular collapse and encephalopathy can occur, and myocardial damage and bone marrow suppression.

Acute ingestion of arsenic is usually more insidious in its manifestations. Severe gastrointestinal involvement is the hallmark of acute ingestion. Symptoms can include nausea, vomiting, profuse watery diarrhea and colicky abdominal pain¹⁴. Dysphagia secondary to the toxic damage to the esophageal lining can occur, as well as dehydration and electrolyte abnormalities. Other gastrointestinal manifestations include jaundice, hepatomegaly, hepatic enzyme abnormalities and even pancreatitis.

Almost every organ system can be involved. Cardiorespiratory findings include EKG abnormalities such as QT prolongation, nonspecific ventricular arrhythmias and sagging of the ST segment^{15,16,17}. Pulmonary edema, bronchial pneumonia and pericarditis can occur. Neurological manifestations include seizures, encephalopathy, headache, vertigo, and a sensorimotor neuropathy which occurs 10 days to 3 weeks after the exposure¹³. Hematologically, anemia is the

most common (normochromic-normocytic, hemolytic). Other findings include leukopenia, aplastic anemia, leukemia, and thrombocytopenia¹⁴. Renal failure and proteinuria secondary to cortical necrosis can occur and a case of severe rhabdomyolysis with the CPK elevated to 31,350 U/L in a fatal arsenic trioxide poisoning has been reported¹³.

Chronic arsenic exposure is associated with several other abnormalities in addition to some of the features of acute arsenic poisoning. One of the most characteristic abnormalities of chronic toxicity involves the skin. Dermatologic manifestations include: Hyperpigmentation (arsenic melanosis), brawny desquamation, hyperkeratosis (especially of the palms and soles), alopecia, dermatitis, folliculitis and "rain drop" depigmentation^{12,14}. Skin cancers have been known to appear in 5% to 10% of people with chronic exposure to arsenic. The cancers can appear 5 to 25 years later and appear mostly on the trunk and upper extremities. Histologically, the lesion can be either squamous cell or basal cell¹².

The content of arsenic in nails and hair has been used for diagnosis of chronic exposure. Aldrich-Mees lines (white transverse bands across fingernails and toenails) can be seen 4 to 6 weeks after exposure^{14,19}. An elevated concentration of arsenic in the hair is a sign of chronic toxicity. The upper limit of normal content in individuals not exposed to arsenic is said to be approximately 5mg/kg but the arsenic content in hair can vary depending on environmental and nutritional factors²⁰.

Other manifestations of chronic toxicity include squamous cell carcinoma of the lung and liver abnormalities such as hepatocellular carcinoma, post necrotic cirrhosis and heman-gioendothelioma. In Taiwan, peripheral vascular (Blackfoot) disease has been associated with high exposure to arsenic in well water²¹.

Other Reported Cases in Hawaii

In the search for other cases of arsenic toxicity in Hawaii, we contacted the pathology departments of most of the major hospitals in Oahu, as well as Smith Kline Laboratory, Diagnostic Laboratory Services of Hawaii and the Hawaii Department of Health. There were several cases reported to the Department of Health, but all of the reports were dismissed as high urinary arsenic levels secondary to seafood ingestion rather than to arsenic toxicity. One patient at Kaiser Permanente Medical Center presented with peripheral neuropathy. Work-up revealed elevated urinary arsenic levels 1300 mcg/l and 372 mcg/l (normal < 100 mcgA) and an elevated hair arsenic level of 151 mcg/100 gram of hair (normal 0-65 mcg/100gram). The source of his arsenic exposure was unknown.

As a result of our investigation, there were no other reports of arsenic toxicity in Hawaii that were documented by positive urine and hair analysis.

Diagnosis and Treatment

A carefully detailed history regarding the possible source of the exposure is extremely important when considering arsenic toxicity as a diagnosis. In addition to the history and physical, laboratory tests are useful—some more than others. Serum arsenic level is often not helpful because of rapid clearance. A 24-hour urine collection is useful, especially for documenting acute arsenic intoxication. Arsenic is excreted through the kidney at a rate of 30% to 70% in a 24-hour period²¹. Toxic levels might be missed if there is a delay between

(Continued) ►

the time of exposure and the time of evaluation. In acute ingestion, abdominal radiographs might be useful because arsenic, a heavy metal, will show up radiographically²².

In chronic exposure, analysis of nails and/or hair is helpful though the arsenic content of hair is affected by nutritional and environmental factors. Arsenic is present in hair and nails 2 to 4 weeks after ingestion⁵. One paper reported analysis of arsenic in other biological fluids, such as gastric and vesicular fluids that accumulate higher levels as compared to pleural and pericardial fluids²³. There is no standardized value or a definitive test that diagnoses the arsenic toxicity absolutely, although urine arsenic levels greater than 200 mcg/l and hair arsenic levels greater than 65mcg/100 grams of hair can be used as a presumptive evidence of an increased arsenic load²¹.

Treatment should be directed in 2 ways: Chelation therapy to increase excretion of arsenic and supportive and symptomatic therapy for the organ systems involved in the toxicity. The Poisindex²⁴ at the Hawaii Poison Center recommends the following treatment: "For acute massive arsenic ingestion, cardiac and respiratory support using compressors and ventilators, as in any other critical patient is recommended. This should be followed by gastric decontamination with gastric lavage and an absorbent such as activated charcoal, or a cathartic magnesium citrate or a sorbitol solution. Alkalinization of the urine might be helpful in preventing deposition of red blood cell breakdown products in renal tubular cells when hemolysis is occurring."

Chelation therapy is recommended in symptomatic patients known to have ingested arsenic and in asymptomatic patients who have a documented urinary arsenic level greater than 200 mcg/l. Dimercaprol is the first line of treatment. The dose ranges from 3 to 5 mg/kg i.m. every 4 to 12 hours until the symptoms abate or another chelator is substituted. One author recommends tapering the dose but continuing administration of dimercaprol until the urinary excretion is less than 50mcg/24 hours¹. Dimercaprol is an effective chelator but has some disadvantages. The intramuscular injections can be painful, and there are many adverse effects such as mild systemic shock, tachycardia, hypertension, vomiting, convulsions, headache, nausea, vomiting and anorexia. A prior injection with epinephrine might alleviate some of systemic effects²⁵. D-Penicillamine is an oral chelator found to be effective. The usual dose is 25 mg/kg given 4 times a day up to one gram/day. The 3 short-term adverse effects have not been reported, but long-term effects of penicillamine have included fever, leukopenia, thrombocytopenia, eosinophilia and renal toxicity. Another agent, 2,3-dimercaptosuccinic acid (DMSA), appears to be a promising method of treatment, although currently it is approved only for use in lead-poisoning in children. DMSA for adult arsenic treatment is still under investigation and, therefore, must be obtained from the Regional Poisons Unit²⁷.

Summary

As mentioned at the beginning of this article, many questions were raised in our one particular case including the problem of verifying true arsenic toxicity and in determining the source of the exposure. In our case, there was a markedly elevated concentration of arsenic in samples of pubic hair and in the sample of urine.

While arsenic toxicity can present with GI symptoms, we felt that in this particular case the association of the abdominal pain with arsenic toxicity was unlikely. For one, the patient's symptoms persisted despite apparent adequate treatment for arsenic toxicity. Also, the usual symptom of chronic arsenic toxicity is peripheral neuropathy (which was not documented in our case) and not abdominal pain. After the exhaustive diagnostic workup, we felt that this patient had irritable bowel syndrome and that the discovery of arsenic toxicity was serendipitous.

In regards to the etiology of the toxicity, the patient's occupation involved working in the construction industry for a number of years. He indicated a definite exposure to termite-treated wood throughout that period. Wood for building houses, etc. is commonly pressure-treated with an arsenic-based compound; therefore, this source of occupational exposure appears to be a likely one.

Another remotely possible source was the ingestion of contaminated illicit drugs. Cases of the use of illicit drugs laced with various toxic agents such as cyanide and strychnine have been reported. Although our patient required analgesics not commensurate with his symptoms, he categorically denied any use of "street" drugs. The random urine drug screen for such was negative. The patient also claimed he was subjected to a series of random urine drug screens at the job and all had been negative.

In conclusion, our patient represented what appeared to be a well-documented case of arsenic toxicity. However, further investigation was needed as to whether the source might have been prolonged exposure to chemically treated wood. In that eventuality, medical practitioners need to consider arsenic toxicity in their differential diagnosis of patients presenting, in particular, with peripheral neuropathy of unknown etiology, and should obtain an appropriate occupational history.

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bone marrow assay.
Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as an *in vivo* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Pregnancy Category C (first trimester) and **D** (second and third trimesters). See WARNINGS, **Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.**

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: **Body As A Whole:** Syncope, chest pain, abdominal pain; **Cardiovascular:** Orthostatic hypotension, palpitation, tachycardia; **Digestive:** Vomiting, dyspepsia, constipation, flatulence, dry mouth; **Nervous System/Psychiatric:** Insomnia, nervousness, paresthesia, somnolence, vertigo; **Skin:** Pruritus, rash; **Other:** Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, **Cough.**

Clinical Laboratory Test Findings, Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: **Body As A Whole:** Anaphylactoid reactions (see PRECAUTIONS, **Hemodialysis Patients**); **Cardiovascular:** Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, **Hypotension**); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; **Digestive:** Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; **Hematologic:** Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported, a causal relationship to enalapril has not been established. **Nervous System/Psychiatric:** Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); **Urogenital:** Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; **Respiratory:** Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; **Skin:** Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; **Special Senses:** Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing. **Miscellaneous:** A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, **Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.**

Hydrochlorothiazide—Body as a Whole: Weakness; **Digestive:** Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; **Hematologic:** Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; **Hypersensitivity:** Purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; **Musculoskeletal:** Muscle spasm; **Nervous System/Psychiatric:** Restlessness; **Renal:** Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); **Skin:** Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; **Special Senses:** Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

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