Arsenic is a semi-metallic naturally occurring element widely distributed in the universe and earth’s crust. The atomic number is 33 and its atomic weight is 74.91. Arsenic is considered a transitional element intermediate between metals and nonmetals. In nature arsenic exists in three allotropic forms (alpha or yellow, beta or black, gamma or grey) and several ionic forms. When arsenic is heated, it sublimes into the gaseous form arsine. Arsenic occurs naturally in soil and minerals and it therefore may enter the air, water, and land from wind-blown dust and may get into water from runoff and leaching.\(^1,^5\)

Arsenic has a long, rich and nefarious history in Medicine and Toxicology. Arsenic has been used medicinally for centuries to treat syphilis in the pre-penicillin era, as an ingredient in many Asiatic pills, herbal balls, solutions (Donovan’s, Fowler’s) and homeopathic tonics. Arsenicals were used until 1965 to treat leukemia, asthma, pemphigus, psoriasis, puerperal fever, and are currently used in the treatment of trypanosomiasis and acute myelogenous leukemia.\(^3-10\) Arsenic is also used in numerous products including insect, rodent, pesticides and weed killers, but also in certain paints, fertilizers, wallpaper, semiconductors and ceramics. Arsenic had also been used to whiten the skin and to prevent ageing in the Victorian era but especially as an infamous poison for political assassinations in the 15th and 16th centuries. We are all exposed to small doses on a regular basis. Exposure is usually occupational, therapeutic, malicious, homicidal, accidental or suicidal.\(^1-12\)

Arsenic is difficult to detect as it is generally odorless and flavorless. Inorganic forms are more toxic than organic forms. Exposure to arsenic is usually the result of an occupational accident. It may occur through industrial exposure, from unintentional poisoning via contaminated well or ground water, through contaminated moonshine or because of malicious intent. Arsenic poisoning in humans most often results from the ingestion or inhalation of insecticides containing arsenical trioxide.\(^4,5,6,15\)

In this review, I shall include a brief report of two cases of arsenic intoxication recently diagnosed and treated in our city, the clinical presentation, causes, pathophysiology, diagnosis, treatment, plus a brief review of Arsenicosis and of El Paso’s arsenic status.

**Case Reports:**

**Case 1.** 79-year-old Hispanic female admitted with uncontrollable diabetes mellitus, right lower lobe pneumonia, acute exacerbation of COPD, and coagulopathy. The patient was referred to the renal service for evaluation of BUN 141 mg% and Creatinine of 4.3mg%. The PT was 100 and INR 11.3. The serum arsenic level was 48 mcg/L (normal 2-23 mcg/L). The random urine level was 104 mcg/ml (normal 0 to 50mcg/ml). The patient wanted to leave the facility against medical advice but after extensive and multiple counseling she agreed to our recommendations and required two hemodialysis treatments with gradual improvement of her symptoms and renal failure.

**Case 2.** 45-year-old hydrologist admitted for evaluation and treatment of chronic bacterial prostatitis resistant to oral quinolones, doxycycline, gentamycin and sulfa drugs. He was referred to the renal service for impaired renal function (Creatinine 1.5 mg %) and history of abnormal urine arsenic levels of 113 mcg/L (reference range for the unexposed population is less than 20 mcg/L) or an arsenic/creatinine ratio of 3 mcg/g of creatinine. He was treated with IV antibiotics for the prostatitis and given mannitol and advised to refrain from additional arsenic field exposure. Thereafter, the prostatitis, urinalysis and renal tests improved and repeated arsenic levels five weeks later were non detectable. The limit of detection with the assay is 10 mcg/L.

**CLINICAL PRESENTATIONS:**

Arsenic poisoning can occur acutely, subacutely or following chronic exposure. Arsenic itself is not very poisonous but arsenic oxide is extremely poisonous. The initial clinical presentation of acute arsenic poisoning may resemble cholera and certain bacterial or viral gastroenteritis, or poisoning by staphylococcal enterotoxins and even poisoning by colchicine and thalium and all of them need to be considered in the differential diagnosis.

Arsenic can kill humans quickly if consumed in large amounts and symptoms will appear within 30 minutes of exposure. The Lethal Dose 50 for pure arsenic is 763 mg/kg (by ingestion). For an 80 kg individual, this correspond to 61 grams (less than 2 ounces). However other compound containing arsenic can be significantly more toxic.\(^4,5,12,15\)

**ACUTE INORGANIC ARSENIC INTOXICATION:** the symptoms following a single acute ingestion of several hundred milligrams or more of a soluble arsenic compound (sodium arsenite or sodium trioxide) includes multi-systemic findings. The classic description includes three phases that relies on reports of suicidal or homicidal arsenic ingestion. The organs affected are usually the lungs, intestines, skin, kidney and liver progressing to death in extreme cases. Frequently patients exposed to arsenic have a garlic smell, but the signs and symptoms may vary on an individual basis.

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Arsenic Intoxication: The Good, the Bad and the Ugly

(Continued)

vidual basis for each patient.

The first phase typically begin 30 minutes to several hours post ingestion with prominent cholera-like gastrointestinal symptoms (vomiting, diarrhea, cramping muscles, severe stomach pain) often associated with hypotension and metabolic acidosis. Headaches and lightheadedness can occur and if untreated will progress to confusion, sleepiness, and even convulsion and coma. In severe cases death may occur from shock or ventricular arrhythmias. If the patient survives the initial phase, a second phase of cardiovascular symptoms ensues in 1 to 7 days (CHF, pulmonary edema and arrhythmias). If the patient survives, the third phase appears 1 to 4 weeks and includes pancytopenia and sensorimotor peripheral neuropathy.4-8,15

I devised the following mnemonic which summarizes the typical findings of acute intoxication:

A bdominal pain and tenderness
R etching and vomiting
S mell of garlic
E yes red and sparkling
N europathy
I nability of Speech
C holera like symptoms

Acute arsenic gas exposure due to inhalation of arsenic gas (AsH3) is now quite rare but has no known antidote. It is very toxic to the lungs and kidneys and is often fatal. Initial symptoms may include headache, abdominal pain, and hematuria. It manifest with rapid and severe hemolytic anemia, hematuria, shaking chills. Hemoglobinuria causes the plasma and urine to appear black. Before hemodialysis all cases were fatal.4,12-15,17

SUBACUTE ARSENIC INTOXICATION: Accidental exposure to arsenic from the environment may occur by three routes, inhalation of dust from smelters, ingestion of contaminated water or therapeutic administration. The symptoms may start with a metallic taste in the mouth, sialorrhea and problems swallowing. It may be seen in patients undergoing treatment of refractory or relapsed acute promyelocytic leukemia and other malignancies wherein 10 to 20 mg of IV arsenic trioxide daily for two month courses are given and may show cardiotoxicity effects including prolongation of the QTc interval and malignant ventricular arrhythmias, plus peripheral neuropathy and GI and hepatic toxicity.4,12,15

CHRONIC ARSENIC INTOXICATION: Environmental exposure usually leads to chronic arsenic poisoning. It is more insidious and occurs particularly from naturally occurring arsenic in drinking water (vide infra: Arsenicosis) and may manifest as non malignant cutaneous changes such as hyperpigmentation and hyperkeratosis, hair loss, “blackfoot disease” (a form of peripheral vascular insufficiency leading to gangrene). Hyperpigmentation and hyperkeratosis are delayed hallmarks of chronic arsenic exposure. If the patient survives initial problems the sequela observed includes peripheral neuropathy (stocking-glove distribution) Mee’s lines on nails to a broad spectrum of serious chronic illnesses. Arsenic poisoning can lead to a variety of problems ranging from skin keratoses of the feet and predisposition to skin, lung and bladder cancer.1,6,9,10-15

CAUSES: Children may encounter arsenic trioxide as a rodenticide or herbi-

cide. Adults may be exposed through work in metal foundry, copper smelting, mining, sheep dipping, semiconductor, glass industry and metallurgic industries or in a job that produces or sprays any kind of pesticide or agricultural insecticide or if somebody is trying to poison you. Arsenic may contaminate wine, grapes, paints and pigments.1,6,12-15

PATHOPHYSIOLOGY:

In the environment arsenic is usually found in combination with other element and can be classified into three groups: 1) inorganic arsenic compounds, 2) organic arsenic compounds, and 3) arsine gas. In nature, arsenic is most often found in group 1, as inorganic (trivalent form) which is formed when arsenic is combined with oxygen, chlorine and sulfur. The organic (pentavalent forms) result when arsenic combines with carbon and hydrogen to form arsonic compounds, which are less toxic than the inorganic forms. Fish and shellfish can accumulate arsenic, most of this arsenic in an organic form called arsenobetaine or arsenocholine that is much more harmful. Seafood meals may markedly elevate arsenic levels and patient or family should be questioned about food ingestion within the past two days. Inorganic arsenic compounds are mainly used to preserve wood. Organic arsenic compounds are used in pesticides, primarily on cotton plants.1,6-12-15

The average intake of arsenic is estimated at 1mg per day, mainly from food, but this is not toxic arsenic and is well tolerated. Most organic and inorganic arsenic leaves the body in urine within a few days of exposure, although some remains in the body for months or longer. On the average, there is about 10-20 mg of arsenic in the human body, higher levels may provoke problems. Arsenic is present in small amount in soil and therefore is present in our food. It is present in the ocean, so there is some arsenic in most seafood’s, especially in the filtering mollusks, such as clams and oysters.4,12,15

Analysis of the toxic effect of inorganic arsenic soil is complicated, but it is generally agreed that over 90 percent of both inorganic and organic arsenic compound in water are well absorbed but the bioavailability of arsenic in soil that is absorbed is about 40%. Its metabolism includes oxidative/reduction reactions and methylation reactions that are beyond the scope of this review.4,5,12,15,16

The inorganic trivalent forms are more toxic than the organic forms and react with thiol groups. Arsenic trioxide is used industrially and is the strongest poison of the arsenics, while pentavalent organic forms are less toxic but uncouple oxidative phosphorylation. Trivalent inorganic arsenic inhibits conversion of pyruvate to acetyl coenzyme A, the citric acid activity cycle is decreased and production of cellular ATP is decreased and the production of glutathione is blocked. The effects of pentavalent inorganic arsenic forms include formation of ADP arsenate instead of ATP, and the high energy phosphate bonds of ATP are lost.1,2,12-15,18,20

DIAGNOSIS:

The diagnosis is based on the history, clinical findings, laboratory studies and may be confirmed by quantitation of urinary arsenic in acute cases and hair arsenic in chronic cases. The patient’s urine should be screened for arsenic and heavy metals using either a 24-hour urine collection or a first void morning specimen.

There are tests available to measure arsenic in blood, urine, hair and fingernails. The half life of ingested inorganic arsenic is brief-

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probably less than a day. Blood arsenic levels should not exceed 50 mcg/L. In acute intoxications the level may go up to hundreds or even thousands mcg/L. The urine test is the most reliable test for arsenic exposure within the last few days. A urine spot test for arsenic can be helpful, but the 24 hour urine collection for arsenic excretion is diagnostic. Urine Arsenic (As) levels are normally less than 5 mcg/day. Because nutritional sources of arsenic are not unusual (seafood), the laboratory should report include organic and inorganic moieties. The latter is the one than provokes most toxicity. Once arsenic distribute into the tissues, treatment may be unsuccessful. Nerve conduction studies confirm the peripheral neuropathy. Cardiac arrhythmias and cardiac failure may occur. Tests on hair and fingernails can measure exposure to high levels of arsenic over the past year and can determine if there is an above-average level but can not predict how it will affect your health. Arsenic poisoning is usually determined by a hair analysis. One way to check for arsenic poisoning is by checking hair follicles. Below 7-10 ppm or arsenic in hair is relatively safe level. If arsenic is within the bloodstream, it will enter hair and remain there for many years and can be used in forensic studies.

TREATMENT:
Treatment of acute arsenic toxicity is supportive. It is extremely important to seek medical advice immediately if arsenic poisoning is suspected. Prehospital care provides support to airway, breathing and circulation. Persons with acute arsenic poisoning usually die from hypovolemic shock. Hemodynamic support, volume repletion and stabilization are of paramount importance, because of significant GI losses (i.e. vomiting and diarrhea). Remove and double-bag contaminated clothing and all personal belongings. The use of gastrointestinal decontamination is controversial. A toxicologist, pulmonologist and nephrologist should be consulted. Chelating therapy with Dimercaprol, Succimer or Penicillamine is imperative but the use of chelators in patients exposed to arsenic gas is controversial.

Chelating agents given within hours of arsenic absorption can prevent arsenic toxicity. Arsenic blood levels (normally less than 7 mcg/dl) are less useful than urine arsenic in following the clinical course of acute poisoning because of the rapid clearance of arsenic from the blood (the initial half-life in blood is 1 to 2 hours). Thus the 24-hour urine arsenic level is recommended for monitoring affected patients. The normal level is less than 50 mcg/l in the absence of consumption of seafood in the past 48 hours. (Human volunteers given lobster tail may excrete more than 1000 mcg/l of arsenic but return to pretest values within 48 hours). A urinary arsenic level of more than 100 mcg/l is considered abnormal. In asymptomatic patients a urinary level of more than 200 mcg/l is indication for chelation therapy. Chelation therapy should be continued until the 24 hour urine arsenic level is less than 50 mcg/l. Patients with significant history and symptoms may require chelation therapy before laboratory confirmation.

**Dimercaprol** (British Anti-Lewisite or BAL in oil) is the first line agent for arsenic poisoning. Dimercaprol (2,3-dimercapto-1-propanol) chelates arsenic by producing an insoluble complex that is excreted by the kidneys. The adult dose is 2.5-3 mg/kg (maximum of 5mg/kg) IM every four hours for the first two days, followed by every twelve hours for 7 to 10 days. The pediatric dose is 50-75 mg/m2 IM q4h not to exceed 450 mg/d. for 5 days. The main contraindications include hypersensitivity, G 6PD deficiency, pregnancy, concurrent use of medicinal iron or hypersensitivity to peanut oil. The most important side effect is hypertension.

**Succimer** (DMSA) is also efficacious in treating arsenic intoxication. It has been used successfully in acute poisoning in children. The dose for children and adults is 10 mg/kg PO q8h for 5 days, then q 12h for 14 days. DMSA has a safety ratio of 20 times greater than BAL. It should not be given concomitantly with edetate calcium disodium or Penicillamine.

**Penicillamine** is administered at a dose of 100 mg/kg/d PO in four divided doses for 5 days. The maximum dose should not exceed 1 g/d.

**Hemodialysis** removes arsenic 24-100 mg in 24 hours, with a clearance of 80-90 ml/min and is indicated if renal failure occurs. When this is done in conjunction with dimercaprol it may limit arsenic distribution and enhances clearance of free and complexed arsenic.

**Exchange transfusion** and **hemodialysis**, if renal failure develops, are the preferred treatment for arsenic gas poisoning.

If you suspect that you are being exposed to arsenic your diet needs to include lots of sulfur. The foods that contain sulfur are: eggs, onions, legumes and garlic. Fiber (whole grains and cereals, fruits and vegetables) can also help eliminate arsenic from your system.

**ARSENICOSIS:**
Arsenicosis results from drinking water with high levels of arsenic over a long period of time. This occurs in third world countries, especially Bangladesh, where contaminated ground water supplies are called by villagers the “Devil’s Water”.

Exchange of a population in history” (Editorial, The Daily Star, 22 June 2003). The concentration in these wells can exceed 1 part per thousand whereas the WHO recommends a limit of 0.01 mg/L of arsenic in drinking water.

Arsenosis provokes changes in the skin color and texture (hard patches), skin cancer, lung cancer, cancer of the kidney and bladder and even gangrene. Current evidence does not support routine use of chelation therapy in patients with an established arsenic neuropathy.

**EL PASO ARSENIC STATUS:**
El Paso has two main drinking groundwater water sources: the Mesilla Bolson aquifer on the west side and the Hueco Bolson aquifer on the east side. About half of the water supply comes from the Rio Grande River, except during times of drought. Arsenic occurs naturally in deep volcanic formation in El Paso affecting 46 of the city 175 wells. In October 2002 the Environmental Protection Agency (EPA) proposed a new standard for drinking water of 10 ppm arsenic. This new standard is expected to be implemented in 2006.

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parts per billion (ppb) of arsenic at the entry point to a distribution center. The El Paso Water Utilities Service acted accordingly and constructed a 60 million-gallon-per-day (mgd) arsenic removal plant, the largest such plant in the country, located in the upper valley. There are also two additional plants in which raw water is treated with chlorine and carbon dioxide to acidify and oxidize the water prior to contact with Bayoxide E33 which is the arsenic removal media. Sodium hydroxide is added after the blending of the two waters. Upon exiting the media the blended water is essentially arsenic free and achieves a 5-8 ppb arsenic concentration, which is within the EPA guidelines and it is the water we drink.20-23

There are standards and regulations for Inorganic Arsenic. The occupational Safety and Health Administration (OSHA) mandates the limits for occupational exposure. The permissible exposure limit (PEL) for air at the workplace is set at 10 micrograms per cubic meter of air, averaged for any 8-hour period for a 40-hour workweek. The EPA standard for water is 10 ppb (parts per billion). The Food and Drug Administration (FDA) regulation for food is 0.5-2.2 ppb (parts per million). There are three known sources of arsenic emission: primary copper smelters24; glass-manufacturing plants and arsenic plant.25 However there is no ambient air standard for arsenic.20

There is growing concern about levels of arsenic in the environment, both from natural occurrence and from pollution from copper smelter. The EPA has also set limits on the amount of arsenic that industrial sources can release to the environment and has restricted or cancelled many of the uses of arsenic in pesticides. The Agency for Toxic Substances and Diseases Registry (ATSDR) can provide information on occupational and environmental health clinics and may be contacted by e-mail at ATSDR.CIRT@cdc.gov, by phone at 1-888-232-6348 or by fax (770-488-4178). The CDC Contact Center is 1-800-CDC-INFO. Background concentrations of arsenic in soil range from 1 to 40/kg with an average value of about 5 mg/kg.20

The EPA declared El Paso a time critical emergency Superfund site in 2002, based on 35 residential sites sampled in West and Central El Paso neighborhoods that contained lead and arsenic levels above screening levels. The EPA notified Asarco as potentially responsible for elevated metals in soils in residential areas near its El Paso copper smelter. Asarco called EPA's assumption “premature” but later performed a residential clean up of homes where arsenic or lead level exceeded EPA's screening levels. On August 17, 2005, ASARCO filed for Chapter 11 bankruptcy in Corpus Christi. One reason was more than 100 civil environmental pending lawsuits! Prior to the bankruptcy Asarco transferred much of its assets to a shell company set up by Grupo Mexico, which began as one of its subsidiary in 1965. For additional information the reader is referred to Asarco corporate web site (http://www.asarco.com)

CONCLUSIONS:
Arsenic is the king of poisons and has been implicated in the illness and death of famous victims including: Francesco I de Medic, Grand Duke of Tuscani, George III of Great Britain, Napoleon Bonaparte, Charles Francis Hall, Clare Booth Luce, impressionist painters, members and enemies of the Borgia’s family and millions of people in Bangladesh.3,4,20

In The US in 2004 there were 989 non-pesticide-related arsenic exposures with 2 fatalities and 344 arsenic-containing pesticide exposures with no fatalities, according to the American Associa-

tion of Poison Control Center (AAPCC) and the Exposure Surveillance System (TESS)4

The source of exposure is identified in fewer than 50% of arsenic poisoning.20 Our two patients, one with acute intoxication and the other with subacute intoxication, tolerated well the treatment given. The first one was reported to adult protective services and apparently she had exposure to insecticide at home. She required two hemodialyses and the renal failure resolved and she recovered. The second patient had mildly increased level from occupational exposure as hydrologist, and removal from potential additional exposure was recommended. The repeat level was undetectable five weeks later.

The good news is that El Paso’s water is safe and within EPA standards. Our environment is relatively well known to us but we must remain vigilant to possible acute arsenic toxicity by remembering the ARSENIC mnemonic suggested and by performing a heavy metal toxicology screen when hepatic or renal abnormalities are detected or unexplained and by immediate and proper referral when indicated. Chelation therapy and dialysis can save lives.

The bad news is that we do not have any current data on El Paso’s soil contamination. Environmental studies should be required before and after ASARCO is granted a permit to work again. Senator Shapleigh has also noted that ASARCO has $24 billion in liabilities in 17 western states and before they get another permit, ASARCO has to have the financial capacity to do the cleanups, since they tend to shift this responsibility to the US taxpayers. Nonetheless, we need to keep a high index of suspicion in many cases of arsenic intoxication since it could be lethal and easily missed.

The ugly news is that more study, research, investment in water infrastructure are needed to prevent Arsenicosis in third world countries near the Indian Ocean and Bay of Bengal and Bangladesh where millions are suffering from arsenic contaminated drinking water. In acute cases, medicolegal advice should be sought if the poisoning appears intentional.

REFERENCES

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