Acute and chronic arsenic toxicity

R N Ratnaike

Arsenic toxicity is a global health problem affecting many millions of people. Contamination is caused by arsenic from natural geological sources leaching into aquifers, contaminating drinking water and may also occur from mining and other industrial processes. Arsenic is present as a contaminant in many traditional remedies. Arsenic trioxide is now used to treat acute promyelocytic leukaemia. Absorption occurs predominantly from ingestion from the small intestine, though minimal absorption occurs from skin contact and inhalation. Arsenic exerts its toxicity by inactivating up to 200 enzymes, especially those involved in cellular energy pathways and DNA synthesis and repair. Acute arsenic poisoning is associated initially with nausea, vomiting, abdominal pain, and severe diarrhoea. Encephalopathy and peripheral neuropathy are reported. Chronic arsenic toxicity results in multisystem disease. Arsenic is a well documented human carcinogen affecting numerous organs. There are no evidence based treatment regimens to treat chronic arsenic poisoning but antioxidants have been advocated, though benefit is not proven. The focus of management is to reduce arsenic ingestion from drinking water and there is increasing emphasis on using alternative supplies of water.

Arsenic toxicity is one of the most toxic metals derived from the natural environment. The major cause of human arsenic toxicity is from contamination of drinking water from natural geological sources rather than from mining, smelting, or agricultural sources (pesticides or fertilisers). Many industrialised and less industrialised countries have drinking water contaminated with arsenic. The problem is of major concern in the USA—for example, the arsenic content of drinking water from public and private sources in Millard County ranges from 14 parts per billion (ppb) to 166 ppb. The Environment Protection Agency lowered the permissible level of arsenic in drinking water in the USA in 2001 from 50 ppb to 10 ppb. Prolonged ingestion of water contaminated with arsenic may result in the manifestations of toxicity in practically all systems of the body as subsequently discussed. The most serious concern is the potential of arsenic to act as a carcinogen.

The two worst affected areas in the world are Bangladesh and West Bengal, India. In 42 districts in southern Bangladesh and in nine adjacent districts in West Bengal, 79.9 million and 42.7 million people respectively are exposed to groundwater arsenic concentrations that are above the World Health Organisation maximum permissible limit of 50 µg/l. In both these areas, the source of arsenic is geological in origin, contaminating aquifers which provide water for over one million tube wells. In West Bengal the arsenic concentration in some tube wells is as high as 3400 µg/l.

The mechanism of arsenic accumulation in the Bengal Delta Plain is thought to have occurred during the late Quaternary age (Holocene age) with arsenic-containing alluvial sediments deposited by the Ganges, Brahmaputra, Meghna, and other smaller rivers that flow across the Bengal Delta Plain into the Bay of Bengal. In the Bengal Delta Plain, the arsenic is adsorbed as arsenic oxanions onto oxyhydroxides of iron, aluminium, and manganese and then mobilised in the alluvial aquifers where, due to the reducing environment, the oxyhydroxides are dissolved by biogeochemical processes, releasing the arsenic into the groundwater.

Over the centuries, arsenic has been used for a variety of purposes. Arsenic was a constituent in cosmetics, and used more extensively than at present in agriculture to protect crops from pests. Arsenic as copper acetarsenite was a pigment in paints, the best known being “Paris green”. Before electricity was used for illumination, hydrogen liberated from coal fires and from gas for lighting combined with arsenic in the Paris green used in wallpaper to form arsine, a toxic gas. A fungus Scopulariopsis breviculis present in damp wallpaper also metabolised the arsenic in Paris green to arsine.

In industry, arsenic is used to manufacture paints, fungicides, insecticides, pesticides, herbicides, wood preservatives, and cotton desiccants. As it is an essential trace element for some animals, arsenic is an additive in animal feed. Gallium arsenide or aluminium gallium arsenide crystals are components of semiconductors, light emitting diodes, lasers, and a variety of transistors.

Arsenic is a popular murder weapon. Many arsenic compounds resemble white sugar and this apparent innocuousness is enhanced by being tasteless and odourless and was publicised by Frank Capra’s film Arsenic and Old Lace, in which two elderly ladies use arsenic in elderberry wine to murder their male suitors.

Correspondence to: Professor Ranjit N Ratnaike, Queen Elizabeth Hospital, Woodville, South Australia 5011, Australia; ranjit.ratnaike@adelaide.edu.au
Submitted 14 November 2002
Accepted 31 March 2003

Abbreviations: AIF, apoptosis-inducing factor; \( \text{As}_2\text{O}_3/\text{As}_2\text{O}_5, \text{arsenite/arsenate); As}_2\text{O}_3/\text{As}_3\text{, arsenite/ppb, parts per billion; ppm, parts per million.

Postgrad Med J 2003;79:391–396

Postgrad Med J: first published as 10.1136/pmj.79.933.391 on 1 July 2003. Downloaded from http://pmj.bmj.com/ on December 15, 2021 by guest. Protected by copyright.
HISTORICAL THERAPEUTIC USES OF ARSENIC
Arsenic was used as a healing agent after Greek physicians such as Hippocrates and Galen popularised its use. Arsenic compounds became available as solutions, tablets, pastes, and in injectable forms. Fowler’s solution, a 1% arsenic trioxide preparation, was widely used during the 19th century. As recently as 1958, the British Pharmaceutical and Therapeutic Products handbook edited by Martinrdale, listed the indications for Fowler’s solution as: leukemia, skin conditions (psoriasis, dermatitis herpetiformis, and eczema), stomatitis and gingivitis in infants, and Vincent’s angina. Fowler’s solution was also prescribed as a health tonic. Chronic arsenic intoxication from the long term use of Fowler’s solution caused haemangiosarcoma, angiosarcoma of the liver, and nasopharyngeal carcinoma. Arsenic was the primary treatment for syphils until World War II. Arsenphenamine (neoarsphenamine), a light yellow compound containing 30% arsenic was used intravenously to treat syphilis, yaws, and some protozoan infections.

CURRENT THERAPEUTIC USES OF ARSENIC
Arsenic trioxide (As$_2$O$_3$) is now widely used to induce remission in patients with acute promyelocytic leukemia, based on its mechanism as an inducer of apoptosis (programmed cell death). Arsenic induces apoptosis by releasing an apoptosis-inducing factor (AIF) from the mitochondrial intermembrane space from where it translocates to the cell nucleus. AIF then effects apoptosis, resulting in altered nuclear biochemistry, chromatin condensation, DNA fragmentation, and cell death. AIF has been isolated and cloned and is a flavoprotein with a molecular weight of 57 000.

Arsenic continues to be an essential constituent of many non-western traditional medicine products. Some Chinese traditional medications contain realgar (arsenic sulphide) and are available as pills, tablets, and other preparations. They are used for psoriasis, syphilis, asthma, rheumatism, haemorrhoids, cough and pruritus, and are also prescribed as a health tonic, an analgesic, anti-inflammatory agent, and as a treatment for some malignant tumours. In India, herbal medicines containing arsenic are used in some homeopathic preparations and haematological malignancies. In Korea arsenic is prescribed in herbal medicine for haemorrhoids.

However rather than an intended ingredient, arsenic is more often a contaminant, sometimes with mercury and lead. The Department of Health Services of California screened 251 products in retail herbal stores and detected arsenic in 36 products (14%) in concentrations from 20.4 to 114 000 parts per million (ppm) with a mean of 145.53 ppm and the median 180.5 ppm. A study in Singapore identified 17 patients during a five year period with cutaneous lesions and haematological malignancies. In Korea arsenic is prescribed in herbal medicine for haemorrhoids.

CHEMISTRY AND TOXICITY
Arsenic occurs in two oxidation states: a trivalent form, arsenite (As$_3$O$_3$; As III) and a pentavalent form, arsenate (As$_5$O$_3$; As V). As III is 60 times more toxic than As V. Organic arsenic is non-toxic whereas inorganic arsenic is toxic.

Arsenic toxicity inactivates up to 200 enzymes, most notably those involved in cellular energy pathways and DNA replication and repair, and is substituted for phosphate in high energy compounds such as ATP.

Unbound arsenic also exerts its toxicity by generating reactive oxygen intermediates during their redox cycling and metabolic activation processes that cause lipid peroxidation and DNA damage. As III, especially, binds thiol or sulphydryl groups in tissue proteins of the liver, lungs, kidney, spleen, gastrointestinal mucosa, and keratin-rich tissues (skin, hair, and nails).

Many other toxic effects due to arsenic are being determined and are detailed by Abernathy et al in 1999.

ARSENIC EXPOSURE
Arsenic exposure occurs from inhalation, absorption through the skin and, primarily, by ingestion of, for example, contaminated drinking water. Arsenic in food occurs as relatively nontoxic organic compounds (arsenobetaine and arsenocholine). Seafood, fish, and algae are the richest organic sources. These organic compounds cause raised arsenic levels in blood but are rapidly excreted unchanged in urine. Arsenic intake is higher from solid foods than from liquids including drinking water. Organic and inorganic arsenic compounds may enter the plant food chain from agricultural products or from soil irrigated with arsenic contaminated water.

ABSORPTION
The major site of absorption is the small intestine by an electrogenic process involving a proton (H+) gradient. The optimal pH for arsenic absorption is 5.0, though in the milieu of the small bowel the pH is approximately 7.0 due to pancreatic bicarbonate secretion.

METABOLISM
The absorbed arsenic undergoes hepatic biomethylation to form monomethylarsonic acid and dimethylarsinic acid that are less toxic but not completely innocuous. About 50% of the ingested dose may be eliminated in the urine in three to five days. Dimethylarsinic acid is the dominant urinary metabolite (60%–70%) compared with monomethylarsonic acid. A small amount of inorganic arsenic is also excreted unchanged. After acute poisoning electrothermal atomic absorption spectrometry studies show that the highest concentration of arsenic is in the kidneys and liver. In chronic arsenic ingestion, arsenic accumulates in the liver, kidneys, heart, and lungs and smaller amounts in the muscles, nervous system, gastrointestinal tract, and spleen. Though most arsenic is cleared from these sites, residual amounts remain in the keratin-rich tissues, nails, hair, and skin. After about two weeks of ingestion, arsenic is deposited in the hair and nails.

CLINICAL FEATURES
Acute poisoning
Most cases of acute arsenic poisoning occur from accidental ingestion of insecticides or pesticides and less commonly from attempted suicide. Small amounts (<5 mg) result in vomiting and diarrhoea but resolve in 12 hours and treatment is not necessary. The lethal dose of arsenic in acute poisoning ranges from 100 mg to 300 mg. The Risk Assessment Information System database states “The acute lethal dose of inorganic arsenic to humans has been estimated to be about 0.6 mg/kg/day.” A 23 year old male who ingested 8 g of arsenic survived for eight days. A student who consumed 30 g of arsenic sought help after 15 hours and survived 48 hours but died despite gastric lavage and treatment with British anti-lewisite (an arsenic antidote) and haemodialysis. Depending on the quantity consumed, death usually occurs within 24 hours to four days.

The clinical features initially invariably relate to the gastrointestinal system and are nausea, vomiting, colicky abdominal pain, and diarrhoea. These gastrointestinal symptoms are followed by typical signs and symptoms of acute arsenic poisoning. Hypertension, hypereosinophilia, and lymphadenopathy are common. Cardiovascular abnormalities include tachycardia, hypotension, peripheral vasospasm, and cardiac arrest. Renal failure is common and is often irreversible.

The most common symptoms are headache, malaise, nausea, vomiting, colicky abdominal pain, diarrhea, and anorexia. Other symptoms include hypertension, hypereosinophilia, and lymphadenopathy. There are cardiovascular abnormalities including tachycardia, hypotension, peripheral vasospasm, and cardiac arrest. Renal failure is common and is often irreversible. Hematological abnormalities include anemia, thrombocytopenia, and leukopenia. Hepatic abnormalities include jaundice, hepatomegaly, and ascites.

Nervous system toxicity includes tremors, fits, and permanent neurological damage. Renal abnormalities include proteinuria, hematuria, and renal failure. Pulmonary abnormalities include pulmonary edema, pneumonia, and respiratory failure.

Other symptoms include vomiting, diarrhea, and anorexia. There are gastrointestinal abnormalities including anemia, thrombocytopenia, and leukopenia. Hematological abnormalities include anemia, thrombocytopenia, and leukopenia. Hepatic abnormalities include jaundice, hepatomegaly, and ascites.

Nervous system toxicity includes tremors, fits, and permanent neurological damage. Renal abnormalities include proteinuria, hematuria, and renal failure. Pulmonary abnormalities include pulmonary edema, pneumonia, and respiratory failure.

The most common symptoms are headache, malaise, nausea, vomiting, colicky abdominal pain, diarrhea, and anorexia. Other symptoms include hypertension, hypereosinophilia, and lymphadenopathy. There are cardiovascular abnormalities including tachycardia, hypotension, peripheral vasospasm, and cardiac arrest. Renal failure is common and is often irreversible.
Box 2: Acute arsenic poisoning

- Clinical features manifest in virtually all body systems.
- Prominent features are nausea, vomiting, colicky abdominal pain, profuse watery diarrhoea, and excessive salivation.
- Other clinical features are acute psychosis, a diffuse skin rash, toxic cardiomyopathy, and seizures.
- Haematological abnormalities occur and renal failure, respiratory failure, and pulmonary oedema are common.
- Neurological manifestations include peripheral neuropathy or encephalopathy.
- Urinary arsenic concentration is the best indicator of recent poisoning (1–2 days).

Diarrhoea attributed to increased permeability of the blood vessels is a dominant feature. The voluminous watery stools are described as “choloidal diarrhoea”. In cholera the stools are described as “rice water”, but in acute arsenic poisoning, because of blood in the gastrointestinal tract, the term “bloody rice water” diarrhoea is used. The cause of death is massive fluid loss due to secretion from the gastrointestinal tract eventuating in severe dehydration, reduced circulating blood volume, and consequent circulatory collapse. On postmortem examination oesophagitis, gastritis, and hepatic steatosis are reported.46

Haematological abnormalities reported are haemaglobinuria, intravascular coagulation, bone marrow depression, severe pancytopenia, and normocytic-normochromic anaemia and basophilic stippling.51–54 Renal failure was reported in four of eight sailors exposed to arsenic.55 Respiratory failure and pulmonary oedema are common features of acute poisoning.56

The most frequent neurological manifestation is peripheral neuropathy that may last for as long as two years.57–60 The peripheral neuropathy may lead to rapid, severe ascending weakness, similar to Guillain-Barré syndrome, requiring mechanical ventilation.56 Encephalopathy is a common manifestation and the possibility of arsenic toxicity must be considered if the aetiology of encephalopathy is uncertain. Encephalopathy has occurred after intravenous administration of arsphenamines.57 The basis for the encephalopathy is thought to be due to haemorrhage.56

Metabolic changes with acute arsenic poisoning are reported. Acidosis has occurred in a single patient58 and hypoglycaemia and hypocalcaemia in cattle.61 In acute poisoning the best indicator of recent ingestion (1–2 days) is urinary arsenic concentration.

Chronic poisoning

Long term arsenic toxicity leads to multisystem disease and the most serious consequence is malignancy. The clinical features of arsenic toxicity vary between individuals, population groups, and geographic areas. It is unclear what factors determine the occurrence of a particular clinical manifestation or which body system is targeted. Thus in persons exposed to chronic arsenic poisoning, a wide range of clinical features are common. The onset is insidious with non-specific symptoms of abdominal pain, diarrhoea, and sore throat.

Skin

Numerous skin changes occur with long term exposure.62 Dermatological changes are a common feature and the initial clinical diagnosis is often based on hyperpigmentation, palmar and solar keratosis. The keratosis may appear as a uniform thickening or as discrete nodules.44 It is emphasised that both palmar and solar keratosis are a significant diagnostic criterion. Hyperpigmentation occurs as diffuse dark brown spots, or less discrete diffuse darkening of the skin, or has a characteristic “rain drop” appearance.48 Arsenic associated skin cancer, Bowen’s disease, is an uncommon manifestation in Asians and may be due to the high skin melanin content and increased exposure to ultraviolet radiation. Arsenic may cause a basal cell carcinoma in a non-melanin pigmented skin.59 The latent period after exposure may be as long as 60 years and has been reported in patients treated with Fowler’s solution, in sheep dip workers, in vineyard workers using arsenical pesticides, and from drinking contaminated wine.62

Another manifestation due to arsenic deposition in keratin-rich areas are prominent transverse white lines in the fingernails and toenails called Mee’s lines.63

Large population based studies from West Bengal in India show a relationship between arsenic concentration in tube well water, dose per body weight, and hyperpigmentation and keratosis, and that persons with a poor nutritional status were more susceptible. However the study by Smith et al reports that arsenic induced skin lesions occur among Atacameño people in northern Chile, despite a good nutritional status.64 These subjects in Chiu Chiu village were from an area “famous” for its cultivation of carrots and other vegetables. The arsenic content of the food consumed was not measured to determine if arsenic in the food chain perhaps “nullified” the nutritional benefits of the foods consumed.

Gastrointestinal system

Though diarrhoea is a major and early onset symptom in acute arsenic poisoning, in chronic toxicity diarrhoea occurs in recurrent bouts and may be associated with vomiting. Suspicion of arsenic ingestion should be aroused if other manifestations such as skin changes and a neuropathy are also present.65 In 248 patients with evidence of chronic arsenic toxicity from West Bengal, India who consumed arsenic-contaminated drinking water for one to 15 years, hepatomegaly occurred in 76.6%, and of the 69 who were biopsied, 63 (91.3%) showed non-cirrhotic portal fibrosis.65 In another study, arsenic was considered the aetiologic agent in five of 42 patients with incomplete septal cirrhosis, an inactive form of macronodular cirrhosis, characterised by slender, incomplete septa that demarcate incompitosic nodules, and an unusually high incidence of varical bleeding.66

Cardiovascular system

Increased risk of cardiovascular disease is reported in smelter workers due to arsenic exposure.67 In a study in Millard
County, USA, based on a matrix for cumulative arsenic exposure, a significant increase in mortality in both males and females from hypertensive heart disease occurred. In Bangladesh, Rahman et al in 1999 reported an increased incidence of hypertension in a large study of 1481 subjects exposed to arsenic in well water. Seventy four Taiwanese patients with ischaemic heart disease in “arseniasis-hyperendemic villages” were studied and a link between ischaemic heart disease and long term arsenic exposure was suggested. Arsenic causes direct myocardial injury, cardiac arrhythmias, and cardiomyopathy. Black foot disease is a unique peripheral vascular disease, causing gangrene of the foot unique to a limited area on the south western coast of Taiwan, due to long term exposure to high arsenic in artesian well water. Periipheral vascular disease is also reported from Chile.

Neurological system
The neurological system is the most important for the toxic effects of a number of metals, especially the heavy metals such as mercury, lead, and arsenic. The neurological effects are many and varied. The most frequent finding is a peripheral neuropathy mimicking Guillain-Barré syndrome with similar electromyographic findings. The neuropathy is initially sensory with a glove and stocking anaesthesia. The effects of toxicity also include changes in behaviour, confusion, and memory loss. Cognitive impairment was reported in two workers from 14–18 months of exposure and mental function returned to normal after withdrawal from the source of arsenic. An increased prevalence of cerebrovascular disease, especially cerebral infarction, was observed in a large study of 8102 men and women who experienced long term exposure to high arsenic from drinking water.

Genitourinary system
The Millard County study group also reported an increased mortality from nephritis and prostate cancer. Guo et al in 1997 analysed cancer registry data (1980–87) of tumours of the bladder and kidney in Taiwan and reported that high arsenic levels in drinking water from wells were associated with transitional cell carcinomas of the bladder, kidney, ureter and all urethral cancers in both males and females, and adenocarcinomas of the bladder in males. The authors suggest that the carcinogenicity of arsenic may be cell-type specific. In contrast, a study from Finland found an association with bladder cancer risk but not kidney cancer, despite very low arsenic concentrations in the drilled wells.

The results of studies by Concha and colleagues in the Andes in Argentina add another dimension to this problem. The possibility of increased deposition of arsenic in the lung, although the reason is not known, is supported by necropsy studies in a limited number of patients. An increased incidence of bronchitis occurs in a study on patients with black foot disease in Taiwan.

Endocrine and haematological systems
Exposure to high concentrations of arsenic is associated with an increased risk of diabetes mellitus. In chronic arsenic toxicity neutropenia occurs.

Malignant disease
The relationship between arsenic and malignancy is of growing concern as many millions of people are potential victims. In Bangladesh and India arsenic is associated with skin, lung, liver, kidney, and bladder cancers. There is evidence from other countries that arsenic exposure causes malignancies of the skin, lung, liver, kidney, and bladder. Data from Taiwan also documents malignancies of the bladder, kidney, skin, lung, nasal cavity, bone, liver, larynx, colon, and stomach as well as lymphoma.

The mechanisms, though not fully determined, are possibly an adverse effect on DNA repair, methylation of DNA, and increased free radical formation and activation of the protooncogene c-myc. Arsenic may act as a co-carcinogen, tumour promoter, or tumour suppressor under certain circumstances. High levels of arsenic are teratogenic in animals. Structural chromosome aberrations were studied in a group of individuals who consumed arsenic from well water in Finland and the association was stronger in current users than in the 10 subjects who had stopped using the contaminated well water for 2–4 months before sampling.

DIAGNOSIS
Analyses of blood, urine, and hair samples are used to quantify and monitor exposure. Levels between 0.1 and 0.5 mg/kg on a hair sample indicate chronic poisoning while 1.0 to 3.0 mg/kg indicates acute poisoning.

ARSENIC DEFICIENCY
In animals deficiency is manifest as increased mortality, reduced fertility, increased spontaneous abortion rate, low birth weight in offspring, and damage to red blood cells.

ECONOMIC COSTS OF CONTAMINATION
The economic significance of arsenic toxicity includes medical expenses, income loss, and reduced crop productivity and quality due to soil and water contamination. The current health, economic, and nutritional problems would be greatly compounded when information regarding arsenic contamination of the food chain is better known and if agricultural products and livestock are found to be contaminated. These issues are of serious concern particularly in Bangladesh where 97% of the rural population relies on ground water for drinking, cooking, and irrigation.

PREVENTION, MANAGEMENT, AND FUTURE DIRECTIONS
The human tragedy due to arsenic toxicity is most acute in the developing world where in countries such as Bangladesh the lives of millions of people are affected.

In solving the increasing problem of arsenic contamination and ill health, many issues need to be clarified. Information is required to determine if there is a threshold for carcinogenic effects to manifest and also to define the dose and duration of exposure. Studies are required to link toxic manifestations with possible genetic polymorphism, age, gender, nutritional status, and the protective role of vitamins, minerals, and antioxidants. There is a marked variation in clinical features among individuals in the same household as is commonly seen in Bangladesh. This may be due to “slow” or “fast” methy- lators of arsenic similar to patients with inflammatory bowel disease who are “slow” or “fast” acetylators who therefore respond differently to treatment with salicylate.

The provision of safe drinking water is a priority. A variety of methods of diverse complexity are available to remove arsenic from drinking water. The methodology, especially in
Box 4: Key references


REFERENCES


Q2. In chronic arsenic poisoning the diagnostic pigmentary changes occur only in the palms and not the soles of the feet.

Q3. The central nervous system manifestations of chronic arsenic toxicity include cerebral infarction, changes in behaviour, confusion, and memory loss.

Q4. In regard to cardiovascular system manifestations, arsenic may cause direct myocardial injury, cardiac arrhythmias, cardiomyopathy, and invariably peripheral vascular disease.

Q5. Arsenic induces apoptosis by releasing an apoptosis-inducing factor from the mitochondrial intermembrane space.

The treatment currently used in chronic arsenic toxicity consists of vitamin and mineral supplements and antioxidant therapy that have documented objective benefits.


