Acute and chronic arsenic toxicity

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Arсенічна токсичність є глобальним здоров'ям проблема, що стосується багатьох людей. Загарбництво є наслідком арсенію з природних геологічних джерел, які підносіть до акуфорів, загарб- нючи питну воду і може також відбутися із діяльності індустрії. Арсеній є різновидом, що отримується в численних традиційних лікувальній. Арсеній розчину є застосований для лікування арсенічних вимірювань і відновлення. Актуальне арсенієвого пошкодження є зв'язане зі снуєм, водою, заглахом, ацетонів кардації, а також сильними лихорадками. Енцефалопатія і периферійні невропатії є діагностічні арсенію. Арсеній є докордонно документованою людською карциногеном, що поширює дію на багато органів. Арсеній токсичність результатує в певних сістемах органів. Арсеній є однойменним документованою людською карциногеном, що поширює дію на багато органів. Арсеній токсичність результатує в певних сістемах органів.

Арсеній є одним з найбільш токсичних металів народжений від природного середовища. Найбільш вагома причина гострого арсенієвого токсичності є заселенням води від природних геологічних джерел, які не виявляються із діяльності індустрії. Арсеній є різновидом, що отримується в численних традиційних лікувальній. Арсеній розчину є застосований для лікування арсенічних вимірювань і відновлення. Актуальне арсенієвого пошкодження є зв'язане зі снуєм, водою, заглахом, ацетонів кардації, а також сильними лихорадками.

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 oxides 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 acetoarsenate 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 brevicaulis 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 the most elderly ladies use arsenic in elderberry wine to murder their male suitors.

Abbreviations: AIF, apoptosis-inducing factor; As2O3, As V, arsenate; As2O5, As III, arsenite; ppb, parts per billion; ppm, parts per million
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 Pharmacological and Therapeutic Products handbook edited by Martindale, listed the indications for Fowler’s solution as: leukaemia, 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 syphilis 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 leukaemia, 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. In chronic arsenic ingestion, arsenic accumulates in the skin. After about two weeks of ingestion, arsenic is deposited in the hair and nails. However rather than an intended ingredient, arsenic is more often a contaminant, sometimes with mercury and antimony, an analgesic, anti-inflammatory agent, and as a blood purifier. Arsenic is prescribed in herbal medicine for haemorrhoids.

**CHEMISTRY AND TOXICITY**

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

**CRYSTALLIZATION AND TOXICITY**

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 arsinocholine). Seafood, fish, and algae are the richest organic sources. These organic compounds cause raised arsenic levels in blood but are rapidly excreted unaltered 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 electrochemical 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 biotmilation 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 reported not to be 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...
Acidosis has occurred in a single patient with neuropathy that may last for as long as two years. 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 “choleraid 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 tracteventuating in severe dehydration, reduced circulating blood volume, and consequent circulatory collapse. On postmortem examination oesophagitis, gastritis, and hepatic steatosis are reported.

Haematological abnormalities reported are haemoglobinuria, intravascular coagulation, bone marrow depression, severe pancytopenia, and normocytic normochromic anaemia and basophilic stippling. Renal failure was reported in four of eight sailors exposed to arsenic. Respiratory failure and pulmonary oedema are common features of acute poisoning. The most frequent neurological manifestation is peripheral neuropathy that may last for as long as two years. The peripheral neuropathy may lead to rapid, severe ascending weakness, similar to Guillain-Barré syndrome, requiring mechanical ventilation. 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. The basis for the encephalopathy is thought to be due to haemorrhage.

Metabolic changes with acute arsenic poisoning are reported. Acidosis has occurred in a single patient and hypoglycaemia and hypocalcaemia in cattle. 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. 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. 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. 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. 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.

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

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.

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. 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. 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 inconspicuous nodules, and an unusually high incidence of variceal bleeding.

Cardiovascular system

Increased risk of cardiovascular disease is reported in smelter workers due to arsenic exposure. In a study in Millard

Clinical features manifest in virtually all body systems.

Clinicians are often faced with an acute presentation of arsenic poisoning. The most frequent neurological manifestation is peripheral neuropathy (Table 1) that may lead to rapid, severe ascending weakness, similar to Guillain-Barré syndrome, requiring mechanical ventilation. 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. The basis for the encephalopathy is thought to be due to haemorrhage.

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Cardiovascular system

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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. Peripher al vascular disease is also reported from Chile.

Neurological system
The neurological system is the major target 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 anae sthesia. 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 arsenic exposure from well water.

Genitourinary system
The Millard County study 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 fetus, and infants and children who are breast fed, are exposed to arsenic toxicity from the mother.

Respiratory system
Studies from West Bengal, India draw attention to both restrictive and obstructive lung disease. Respiratory disease was more common in patients with the characteristic skin lesions of chronic arsenic toxicity. Similar findings of an association between skin manifestations and lung disease was reported in Chilean children. 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.
Box 4: Key references


REFERENCES


Q2. In chronic arsenic poisoning the diagnostic pigmented 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.

Q6. The treatment currently used in chronic arsenic toxicity consists of vitamin and mineral supplements and antioxidant therapy that have documented objective benefits.

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QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

Q1. The main source of arsenic that contaminates drinking water is from industrial sources such as mining.

REFERENCES


ANSWERS

Q1. F
Q2. F
Q3. T
Q4. Q3
Q5. T
Q6. F