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EFFECTS OF ARSENIC POISONING – AN OVERVIEW

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ABSTRACT

Arsenic is a recognized cause of cancer, inhalation of high level of air borne arsenic causes lung cancer. It is also implicated in many other adverse health effects, including skin lesions, diabetes, chronic bronchitis, cardiovascular disease, peripheral neuropathy, adverse reproductive outcomes and hematological effects. Our review article mainly focused on arsenic poisoning, its severity and management of toxic exposure. We developed a search strategy to find publications about arsenic poisoning and its management. So, we searched Science Direct, Medline and PubMed bibliographic databases using the key phrases causes of Arsenic poisoning, diagnosis, management of arsenic poisoning and its treatment. Our review article examines pathophysiology, clinical manifestations, toxicokinetics of arsenic, its prevention and management. In future, there is a need to create awareness about the toxicity of arsenic among the people who are routinely getting exposed to arsenic.

INTRODUCTION

Arsenic (As) occurs naturally as an element, ranks as 20th most occurring trace element in the earth's crust[1] and is widely distributed in the environment. Its association with some non-weathering resistant mineral deposits (e.g., Sulphide minerals) has contributed to its release in large amounts in to the environment.[2]

Arsenic is a metalloid with an atomic weight of 74.92. It has several oxidation states, including element (0), trivalent (-3, +3) and pentavalent (+5). The trivalent compounds are generally more toxic than pentavalent compounds.[3,4] The most toxic of them all is arsine gas 'AsH_3'.[5,6] Organic arsenical compounds exists but these are generally nontoxic.[7]

Inorganic arsenical products have been known since ancient times. Some compounds such as As_2S_2 (realgar) and As_2S_3 (orpiment) were used in ancient Greece and Rome as depilatories cosmetics, therapeutic agents and poisons. Arsenic is used in hardening of alloys and in production of semiconductors, pigments, glass manufacturing, pesticides, rodenticides and fungicides.[8] It is also used as an ingredient of the drugs for the treatment of some diseases like sleeping sickness, chronic myeloid leukemia.[9,10] Trisenox®, an Arsenic trioxide is currently available in USA for the treatment of acute rmyeloid leukemia. Because of its usefulness and exploitation, Arsenic contamination is new widespread in environment. During the Middle age and renaissance, arsenical compounds continued to be used as poisons in France and Italy until the discovery by Marsh in 1836 of a sensitive method to detect arsenic.[11,12] It is now well recognized that consumption of arsenic, even at low levels, leads to carcinogenesis.[13]

ARSENIC EXPOSURE

In recent years, there has been much interest in this element due to the contamination of drinking water in some parts of the world. Millions of people in Bangladesh and India are exposed to high levels of arsenic from contaminated ground water.[14-16] Occupational exposure to arsenic can take place through mining, copper smelting and other activities.[17] Natural exposure to arsenic can occur through consumption of seafood which contains mainly organoarsenic compounds. Whereas, drinking water is dominated by inorganic arsenic (iAs) species.[16,17] Chronic exposure to iAs through drinking water has been associated with hyperkeratosis spotted melanosis, skin pigmentation and lung cancer.[18]

Large number of persons in Taiwan, Chile, Mexico, India and Pakistan has been chronically poisoned from naturally occurring arsenic in ground water.[19-21] Arsenic containing coal used for heating homes and drying food stuffs in China has been a source of chronic exposure. Attempted homicide and deliberate long-term poisoning for maintaining invalidism have resulted in chronic toxicity.[22]

According to the American Association of Poison Control Centers' (AAPCC) National Poisoning Data System (NPDS), 1,165 human exposures related to arsenic (excluding pesticides) and 379 exposures related to arsenic-containing pesticides were reported in 2007. The bulk of the pesticide exposures occurred in children younger than 6 years of age, whereas more than 50% of the non-pesticide exposures occurred in adults.[23]

Worldwide, up to 100 million people are at risk of exposure to arsenic from excessive arsenic in drinking water. In Bangladesh, more than 95% of the water supply to over 138

million people is potentially arsenic contaminated at levels exceeding the US EPA and WHO action limits.[24]

If International efforts at elimination of the risk are unsuccessful, it is estimated that a substantial proportion of the Bangladesh population will develop arsenic-related diseases such as pulmonary and skin cancers as well as cardiovascular and renal disease. In addition to the concentration of arsenic in the water, the prevailing diet existing in the affected areas may place the citizens at increased risk for toxicity from the arsenic. The population was recently surveyed and those individuals who had diets deficient in certain vitamins and antioxidants appeared to have greater risk of arsenic dermatoses. An inverse correlation was found between consumption of B Vitamins A, C, and E, riboflavin and folic acid, and the existence of dermatological manifestations or chronic arsenic exposure.[25]

Several recent studies reported that about 6 million people of 2600 villages in 74 arsenic-affected blocks of West Bengal, India are in risk and 8500 (9.8%) out of 86,000 people examined are suffering from arsenicosis, while the source is oxidation of arsenic rich pyrite or anoxic reduction of ferric iron hydroxides in the sediments to ferrous iron and thereby releasing the adsorbed arsenic to groundwater.[26]

PATHOPHYSIOLOGY

The mechanisms arsenic toxicity is inhibition of sulfhydryl group – containing cellular enzymes and replacement of phosphate molecules in "high-energy" compounds (Arsenolysis). Trivalent arsenic compounds are more potent in inhibiting enzymes, whereas pentavalent compounds are more involved in arsenolysis.[19] The chemical forms and oxidation states of arsenic are more important as regards to toxicity. It is generally accepted that the

methylation is the principal detoxification pathway; recent studies have suggested that methylated metabolites may be partly responsible for the adverse effects associated with arsenic exposure.[27] Because ingested iAs is extensively metabolized in humans, chronic exposure to iAs results in chronic exposure to methylated and demethylated arsenicals. MMA^{III}, a biotransformant of iAs, is upto 26 times more toxic than inorganic arsenite in Chang human hepatocytes.[28] Also, in vitro studies have shown that MMA^{III} and DMA^{III}, like iAs^{III} can form GSH complexes, and that these are atleast as toxic as iAs^{III}. Another recent in vitro study concluded that high methylation capacity did not protect these cells (hepatocytes, epidermal keratinocytes and bronchial epithelial cells) from the acute toxicity of trivalent arsenicals.[29] Vega et al., 2001 reported that trivalent arsenicals induced an increase in cell proliferation, but pentavalent arsenicals did not, in an in vitro experiment with human epidermal keratinocytes.[27]

The most common toxic mode of an element is the inactivation of enzymes systems, which serves as biological catalyst. The iAs^{V} does not react directly with the active sites of enzymes. It first reduces to iAs^{III} in vivo before exerting its toxic effects.[30]

The enzymes, which generate cellular energy in citric acid cycle are adversely affected. The enzyme system comprises of several enzymes and cofactors, one protein molecule of enzyme having one lipoic acid. In the presence of iAs^{III}, it replaces the 2 hydrogen atoms from the thiol group and attaches with a sulfur molecule and forms dihydrolipoylarsenite chelate complex, which prevents the reoxidation of the dehydrolipoyl group that is necessary for continued enzymatic activity, and this pivotal enzymes steps blocked. As a result the amount of pyruvate in the blood increases energy production, is reduced and finally the cell damages slowly. The strong bond between iAs^{III}, and sulfur may be the reason why arsenic

accumulates in the keratin tissues, hair and nail. Peters proposed that trivalent arsenic form a stable ringed structure with vicinal dithiols of keratin in hairs.[31]

Arsenic inhibits enzymes, such as pyruvate oxidase, S-aminoacid oxidase, Choline oxidase and transaminase. Although iAs^{III} is regarded the more toxic form of the element, iAs^{V} as arsenate can be disruptive by completing with phosphate. The asenate produces an arsonate ester of ADP, which is unstable and undergo hydrolysis non-enzymatically. This process was termed as 'arsenolysis'. Hence the energy metabolism is inhibited and glucose-6-arsenate is produced rather than glucose-6-phosphate. Arsenate may also replace the phosphorus in DNA and this appears to inhibit the DNA repair mechanism. Such an action may explain the clastogenesity of arsenic, because an arsenodiester bond will most likely be weaker than the normal phosphodiester bond. However, no direct evidence is located to show that arsenate is incorporated in to DNA.[32]

TOXICOKINETICS

Humans are exposed to many different forms of inorganic and organic arsenic species in food, water and other environmental media. Each of the forms of arsenic has different physico – chemical properties and bioavailability and therefore the study of kinetics of arsenicals in animals and humans is the complex matter. Routes of arsenic intake in vivo considered are respiratory for dust and fumes, and oral for arsenic in water, beverages, soils and food. Few investigations of dermal absorption rates for arsenicals are undertaken. The available data sets indicate that absorption rates are generally low (<10%). However for certain forms of arsenic, higher rates may be absorbed.[33]

The bioavailability of ingested inorganic arsenic will vary depending on the matrix in which it is ingested (i.e. be it food, water, beverages or soil), the solubility of the arsenical compound itself and the presence of other food constituents and nutrients in the gastrointestinal tract. Tissue distributions of arsenic depend on blood perfusion, tissue volumes, diffusion coefficients, membrane characteristics, and tissue affinities. Arsenate is rapidly reduced to arsenite, which was afterwards partly methylated. The main site of methylation appears to be the liver, where arsenic methyltransferase enzymes mediate the methylation process with S- adenosylmethionine as the methyl donor and GSH as an essential co-factor. Studies with radioactively labeled (As^{74}) arsenate in human show that 38% of dose is excreted in urine within 48 hours and 58% of total within 5 days.[34] In the subjects who ingested 500 µg arsenic in the form of arsenite, 33% of the dose was excreted in the urine within 48 hours and 45% within 4 days. It is estimated that about 60-70% of daily ingested inorganic arsenic is excreted in the urine.[35] No studies are identified that addressed the issue of biliary excretion or other routes of elimination for organoarsenicals in humans.

Although arsenic is excreted via other routes than via urine and feces (e.g. in sweat), these routes of excretion are generally minor. Since arsenic can accumulate in keratin-containing tissues, skin, hair and nails can also be considered as potentially minor excretory routes. Both older and recent studies indicate that arsenic can be excreted in human milk, although the levels are low. The three most commonly employed biomarkers used to identify or quantify arsenic exposure are total arsenic in hair or nails, blood arsenic, and total or specific metabolites of arsenic in urine. Because arsenic (as the trivalent form) accumulated in keratin-rich tissues such as skin, hair and nails,[36] arsenic levels in hair and nails are used as indicators of past arsenic exposure.

TOXIC EFFECTS OF ARSENIC POISONING

CARDIOVASCULAR EFFECTS

Both the heart and peripheral arterial tree commonly manifest effects of arsenic toxicity such as cardiovascular abnormalities, Raynaud's disease, myocardial infarction, myocardial depolarization, cardiac arrhythmias, thickening of blood vessels and their occlusion and BFD. Studies from Taiwan was clearly demonstrated that exposure to arsenic via drinking water is associated with BFD, with significant exposure–response relationships relating both the duration and level of exposure to observed effects,[33] which is characterized by a progressive loss of circulation in the hands and feet, which ultimately leads to severely painful gangrene formation of the extremities (particularly the toes and feet), often necessitating amputation of the limb.[37-38] Rahman et al., 1999 also reported induced hypertension among arsenic affected people in Bangladesh.[39]

HEPATOLOGICAL EFFECTS

Since the liver tends to accumulate arsenic with repeated exposures, hepatic involvement is reported most commonly as a complication of chronic exposures over periods of months or years.[40] Chronic arsenic induced hepatic changes include cirrhosis, portal hypertension without cirrhosis, fatty degeneration and primary hepatic neoplasia. Patients may come to medical attention with bleeding esophageal varices, ascites, jaundice, or simply an enlarged tender liver, mitochondrial damage, impaired mitochondrial functions, and porphyrin metabolism,[41] congestion, fatty infiltration, cholangitis, cholecystitis and acute yellow atrophy , and swollen and tender liver.[42]

RENAL EFFECTS

The kidneys are the major route of arsenic excretion, as well as a major site of conversion of pentavalent arsenic. In humans, the kidneys seem to be less sensitive to arsenic than most other organ systems. The effects of organoarsenicals on the human renal system are not reported. Sites of arsenic damage in the kidney include capillaries, tubules and glomeruli, which leaded to hematuria and proteinuria, oliguria, shock and dehydration with a real risk of renal failure, cortical necrosis, and cancer.[43-44]

RESPIRATORY EFFECTS

Humans exposed to inorganic arsenic naturally and occupationally experience laryngitis, tracheae bronchitis, rhinitis, pharyngitis, shortness of breath, chest sounds (crepitations and/or rhonchi), nasal congestion and perforation of the nasal septum.[45]

GASTROINTESTINAL EFFECTS

The efficiency of absorption of inorganic arsenicals from the gastrointestinal tract depends on their water solubility. Several gastrointestinal symptoms are common and salient features of arsenic intoxication due to ingestion of heavy doses of arsenic. Sub-acute arsenic poisoning from lesser doses of arsenic may manifest as dry mouth and throat, heartburn, nausea, abdominal pains and cramps, and moderate diarrhea. Chronic low dose arsenic ingestion may be without symptomatic gastrointestinal irritation or may produce a mild esophagitis, gastritis, or colitis with respective upper and lower abdominal discomfort. Anorexia, malabsorption and weight loss may be present.[46]

NEUROLOGICAL EFFECTS

Inorganic arsenic ingestion can result in neural injury. Acute high exposure often causes encephalopathy with symptoms as headache, lethargy, mental confusion, hallucination, seizures and coma.[47]

CARCINOGENIC EFFECTS

It is observed that patients who received chronic treatment with arsenical medications have greatly increased incidence of both basal cell and squamous cell carcinomas of the skin. These arsenical skin cancers commonly occur in the presence of dermatologic manifestations of arsenicism, and some has internal neoplasms that are regarded as arsenical in origin and much of this type on the populations in the BFD-endemic parts of Taiwan,[48-49] but there are reports of elevated cancer risks at multiple sites (notably lung, skin, bladder, kidney and liver) from other parts of the world including Japan, Bangladesh, West Bengal- India, Chile and Argentina where subsets of the population are exposed to arsenic-contaminated drinking water.[50]

DERMAL EFFECTS

Exposure to arsenic either ingestion or inhalation will produce a variety of skin disorders. Hyperpigmentation may occur, particularly in body areas where the skin tends to be a little darker. The initial erythromatous flush from arsenic may phase into an actinic keratosis, a hyperkeratosis of palms and soles, papillomatosis, recurrent episodes of pruritic urticaria, or even generalized pruritis without a visible rash, basal cell carcinoma or squamous cell carcinoma, which are histologically indistinguishable from analogous non-arsenic tumors.[46]

OXIDATIVE STRESS

Studies have demonstrated that the oxidative stress generated by arsenic may disrupt the signal transduction pathway of the nuclear transcriptional factors PPAR's, AP-1, and NF-κB, as well as the pro-inflammatory cytokines IL-8 and TNF-α. The interference of oxidative stress with signal transduction pathways may affect physiological processes associated with cell growth, metabolic syndrome X, glucose homeostasis, lipid metabolism, obesity, insulin resistance, inflammation, and diabetes-2. Recent scientific evidence has elucidated the physiological roles of the PPAR's in the ω- hydroxylation of fatty acids and the inhibition of pro-inflammatory transcription factors (NF-κB and AP-1), pro-inflammatory cytokines (IL-1, -6, -8, -12, and TNF-α), cell4 adhesion molecules (ICAM-1 and VCAM-1), inducible nitric oxide synthase, proinflammatory nitric oxide (NO), and anti-apoptotic factors.[51-52]

BIOCHEMICAL EFFECTS

Epidemiological studies have suggested a correlation between chronic consumption of drinking water contaminated with arsenic and the incidence of Type 2-diabetes. The human liver after exposure to therapeutic drugs may exhibit hepatic non-cirrhotic portal hypertension, fibrosis, and cirrhosis. However, the literature provides insufficient scientific evidence to show cause and effect between arsenic and the onset of diabetes mellitus Type 2.[51]

The flowchart that describes the sources of human exposure to arsenic and various modes of arsenic toxicity is shown in Figure 1.

CLINICAL FEATURES

Acute arsenic poisoning from ingestion results in increased permeability of small blood vessels and inflammation and necrosis of the intestinal mucosa; these changes manifest as hemorrhagic gastroenteritis, fluid loss, and hypotension. Delayed cardiomyopathy accompanied by electrocardiographic abnormalities may develop. Symptoms include nausea, vomiting, diarrhea, abdominal pain, delirium, coma, and seizures. A garlicky odor may be detectable on the breath. Acute tubular necrosis and hemolysis may develop. The reported lethal dose of arsenic ranges from 120 to 200 mg in adults and is 2 mg/kg in children. Arsine gas causes severe hemolysis within 3 to 4 h of exposure and can lead to acute tubular necrosis and renal failure.

In chronic arsenic poisoning, the onset of symptoms comes at 2 to 8 weeks. Typical findings are skin and nail changes, such as hyperkeratosis, hyperpigmentation, exfoliative dermatitis, and Mees' lines (transverse white striae of the fingernails); sensory and motor polyneuritis manifesting as numbness and tingling in a "stocking-glove" distribution, distal weakness, and quadriplegia; and inflammation of the respiratory mucosa. Epidemiologic evidence has linked chronic consumption of water containing arsenic at concentrations in the range of 10 to 1820 ppb with vasospasm and peripheral vascular insufficiency culminating in "blackfoot disease," a gangrenous condition affecting the extremities. Chronic arsenic exposure has also been associated with a greatly elevated risk of skin cancer and possibly of cancers of the lung, liver (angiosarcoma), bladder, kidney, and colon.[53]

LABORATORY FINDINGS

When acute arsenic poisoning is suspected, an x-ray of the abdomen may reveal ingested arsenic, which is radiopaque. The serum arsenic level may exceed 0.9 umol/L (7 ug/dL); however, arsenic is rapidly cleared from the blood. Electrocardiographic findings may include QRS complex broadening, QT prolongation, ST-segment depression, T-wave flattening, and multifocal ventricular tachycardia. Urinary arsenic should be measured in 24-h specimens collected after 48 h of abstinence from seafood ingestion; normally, levels of total urinary arsenic excretion are less than 0.67 umol/d (50 ug/d). Arsenic may be detected in the hair and nails for months after exposure. Abnormal liver function, anemia, leukocytosis or leukopenia, proteinuria, and hematuria may be detected. Electromyography may reveal features similar to those of Guillain-Barre syndrome.[54]

TREATMENT

- Vomiting should be induced with ipecac in the alert patient with acute arsenic ingestion.
- Gastric lavage may be useful; activated charcoal with a cathartic (such as sorbitol) may be tried.
- Aggressive therapy with intravenous fluid and electrolyte replacement in an intensive-care setting may be life-saving.
- Dimercaprol is the chelating agent of choice and is administered intramuscularly at an initial dose of 3 to 5 mg/kg on the following schedule: every 4 h for 2 days, every 6 h on the third day, and every 12 h thereafter for 10 days. (An oral chelating agent may be substituted.) Succimer is sometimes an effective alternative, particularly if adverse reactions to dimercaprol develop (such as nausea, vomiting, headache, increased blood pressure, and convulsions). In cases of renal failure, doses should be adjusted

carefully, and hemodialysis may be needed to remove the chelating agent-arsenic complex. Arsine gas poisoning should be treated supportively with the goals of maintaining renal function and circulating red-cell mass.[54]

Follow-up

Further Inpatient Care: Many patients will develop profound peripheral neuropathy requiring extensive rehabilitation. Rehabilitation should be started as promptly as the clinical picture allows.

Further Outpatient Care: Perform a careful neurological evaluation in follow-up of all patients because the peripheral neuropathy, which may develop after an acute exposure, may not appear for 2-3 weeks.

Complications: Sterile abscesses after the use of dimercaprol (BAL in oil) are not unusual. They initially may appear like erythematous macules, which spread or coalesce, and may continue to drain for some time.[54]

CONCLUSION

Our review provides that effect of arsenic poisoning among person who are routinely exposed and its large enough to cause acute toxic effects would be easily recognized and the source of exposure would be found and eliminated. But the problem lies in the fact that low doses of arsenic that would be too low to cause overt acute toxicity, finally be recognized after a long time with the development of cancer. Finally, it is worth mentioning that arsenic poisoning in humans should not be considered a natural phenomenon, rather it is due to wrong policy of uncontrolled industrialization and ignorance to develop an effective water management of surface-water resources. In future, there is a need to create awareness about the toxicity of arsenic among the people who are routinely getting exposed in the community.

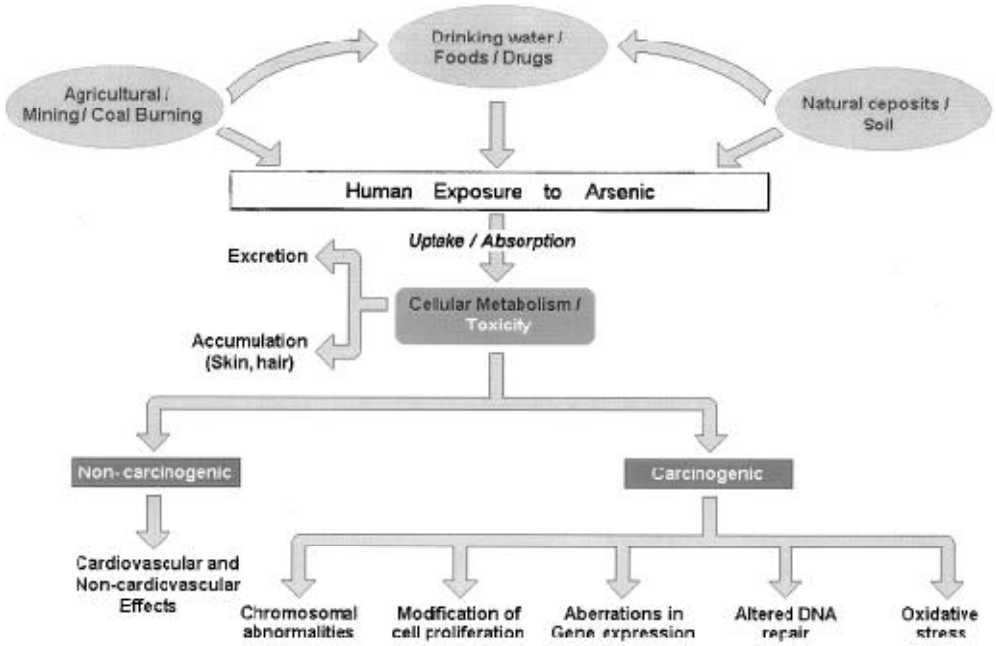

Figure 1. Sources of human exposure to arsenic and various modes of arsenic toxicity.

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