REVIEW ARTICLE

Heavy Metal - Arsenic

Nasim Karim[1], Ayesha Khan[2], Afsheen Nazar[3]

ABSTRACT:
Arsenic is detected virtually in all environmental matrices.Two forms of arsenic, reduced and oxidized can be absorbed and accumulates in tissues and body fluids causing impairment of cell respiration and subsequently diminishes ATP formation. Several million people are exposed to arsenic chronically throughout the world. Diet, for most individuals, is the largest source of exposure. It is also called as "king of poisons". Immediate symptoms of acute arsenic poisoning include vomiting, abdominal pain and diarrhea being followed by numbness, tingling of extremities, muscle cramping and death. Long-term exposure to high arsenic level usually affects skin. Blood, urine, hair, and fingernails are used for diagnosis of toxicity.This is treated by chelating agents and removal of arsenic from body. Awareness should be created among the communities. Governmental measures for provision of clean water, uncontaminated food and reduction of hazards at occupational level could play a vital role for preventing morbidity and mortality.

Keywords: Heavy metals,Arsenic, Exposure, Health hazards, Toxicity, Diagnosis, Treatment, Preventive measures

INTRODUCTION:

Heavy metals such as arsenic, lead, mercury, cadmium etc. are naturally occurring elements that have high atomic weight and a density at least 5 times greater than that of water.[1,2] Their multiple industrial, domestic, agricultural, medical and technological applications have led to their wide spread distribution in the environment; raising concerns over potential effects on human health and the environment.[3] Their toxicity depends on several factors including the dose, route of exposure, and chemical species, as well as the age, gender, genetics, and nutritional status of exposed individuals. Heavy metals are considered as systemic toxicants that can induce multiple organ damage, even at lower levels of exposure.[1,3,4]

Arsenic is a ubiquitous element that is detected at low concentrations in virtually all environmental matrices. The major inorganic forms of arsenic include the trivalent arsenite and the pentavalent arsenate. The organic forms are the methylated metabolites - monomethylarsonic acid (MMA), dimethylarsinic acid (DMA) and trimethylarsine oxide. Environmental pollution by arsenic occurs as a result of natural phenomena such as volcanic eruptions and soil erosion, and anthropogenic activities.[5] Present review aims to provide literature search including history, sources, pharmacokinetics, pharmacodynamics, uses, health hazards, toxicity, clinical features, diagnosis, treatment and preventive measures for arsenic exposure.

✉ **Dr. Nasim Karim**
Professor & Head
Department of Pharmacology
Bahria University Medical & Dental College
Karachi
E-mail: nsm_karim@yahoo.com
✉ **Dr. Ayesha Khan**
Lecturer
Department of Pharmacology
Bahria University Medical & Dental College
Karachi
✉ **Afsheen Nazar**
Demonstrator
Department of Pharmacology
Bahria University Medical & Dental College
Karachi
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METHODOLOGY:

Search engine of Google was utilized with various keywords and phrases to search articles related to arsenic from 2000-2016. Key words and phrases as heavy metal arsenic, history of arsenic, sources of arsenic, pharmacokinetic and pharmacodynamic characteristics of arsenic, hazards of arsenic, human health hazards of arsenic, clinical features and diagnosis of arsenic toxicity, treating arsenic toxicity, preventive measures for arsenic toxicity etc. were used. A total of 60 articles including reviews, original articles,WHO reports were selected. 08 articles were published before 2000 and were cited after this. They were excluded and also the remaining 03 articles that had details of arsenic at molecular level.

LITERATURE REVIEW:

(A) History: Arsenic is often referred to as the "king of poisons" and the "poison of kings" because of its potency and the discreetness, by which it could be administered, particularly with the intent of removing members of the ruling class during the Middle Ages and Renaissance.[6] For example, it is well documented that arsenic was among the poisons used by the Medici and Borgia families to eradicate rivals. Arsenic continued to enjoy its reputation as a high-profile poison and was implicated in several other prominent murder cases, most famously in the death of Napoleon Bonaparte in 1851.[7]Arsenic remained a popular poison for several reasons. Arsenic was readily available and because it is odorless and tasteless, it was undetectable in food or beverages. The most visible symptoms of acute arsenic poisoning-nausea, vomiting, diarrhea, and abdominal pain-could be easily confused with other common diseases at the time (e.g. cholera and pneumonia).[8] Also importantly, for a long time, there was no reliable analytical method for detecting, much less measuring, arsenic in tissue or other media, although early tests for arsenic were introduced in the mid-1700s. Interestingly, in the first trial ever recorded to present forensic evidence, a woman was sentenced to death because a white power recovered by a servant was "proven" to be arsenic, based on appearance, texture, behavior in water, and garlic-

like odor when burned.[9] The detection of arsenic took a leap forward in 1832 when James Marsh decided to investigate analytical methods to provide juries with more reliable evidence of "visible arsenic" His test method was first used in the trial of Marie LaFarge in France in 1840, in which Mme. LaFarge was charged with poisoning her husband with arsenic-laden cakes. Generally, the tests involved mixing the sample of interest with zinc and acid and heating the vessel with a flame, which would cause a silvery substance to accumulate on the glass vessel; this was considered diagnostic for arsenic in amounts as low as 0.02 mg.[10] Although this method would be considered primitive by today's standards, the Marsh test represented a turning point in arsenic analytics and the beginning of the end of undetected arsenic poisonings.As early as 2003, arsenic poisoning made headlines when arsenic was detected in coffee served at a church meeting in Maine.[11,12]Arsenic poisoning has been implicated in the illness and death of a number of prominent people throughout history including for example: Francesco I de' Medici, Grand Duke of Tuscany, George III of Great Britain, Theodor Ursinus, Napoleon Bonaparte,Simón Bolívar, Charles Francis Hall,Clare Boothe Luce, Guangxu Emperor,Phar Lap, King Faisal I of Iraq, Anderson Mazoka, Munir Said Thalib,Thomas Chatterton.[13,14,15,16,17,18]

(B) Sources of arsenic:

(1) Water: Arsenic found in water is almost entirely in the inorganic form and can be stable as both arsenite and arsenate, trivalent and pentavalent inorganic arsenicals, respectively.[19] The US Geological Survey estimated that the median groundwater concentration is 1 µg/l or less, although some groundwater aquifers, particularly in the western United States, can contain much higher levels For example, median levels in Nevada were about 8 µg/l.

(2) Food: Although inorganic arsenic was added to food as a preservative in the late 1800s and early 1900s, today, inorganic arsenic is not intentionally added to food. Nonetheless, because arsenic is ubiquitous in the environment, diet is the largest source of both inorganic and organic arsenic for typical individuals. Estimates of dietary inorganic arsenic intakes vary. United States, estimated an average adult intake of 3.2 µg/day, with a range of 1-20 µg/day. Estimates for children were similar.[20] The key organic arsenic compounds that can be routinely found in food (depending on food type) include monomethylarsonic acid (MMAs), DMAs, arsenobetaine, arsenocholine, arsenosugars, and arsenolipids. DMAs or MMAs can be found in various types of fin fish, crabs, and mollusks, but often at very low levels.[21]Arsenocholine, which is mainly found in shrimp, is chemically similar to arsenobetaine, and is considered to be "essentially nontoxic". Arsenosugars are detected mainly in seaweed but are also found to a lesser extent in marine. Concerns about the potential toxicity of arsenosugars have been raised because there is evidence that arsenosugars are metabolized to DMAs. Studies addressing arsenosugar toxicity, however, have largely been limited to in vitro studies, which show that arsenosugars are significantly less toxic than both inorganic arsenic and trivalent methylated arsenic metabolites .Arsenolipids, a component of fish oil, have only been recently characterized; their toxicity has not been studied.[22]

(3) Soil: The natural content of arsenic in soils globally ranges from 0.01 to over 600 mg/kg, with an average of about 2-20 mg/kg. Arsenic in soil is almost entirely in the inorganic form, except in areas with intentional organic arsenic application, where higher levels of organic compounds can be found. In soils, pentavalent arsenic predominates due to oxidation of trivalent arsenicals.[23] Exposure to arsenic in soil can occur through multiple pathways. Incidental ingestion is typically the most significant exposure pathway for soil. Compared with the intake of naturally occurring arsenic from water and the diet, soil arsenic constitutes only a small fraction of intake,[24] this is a reflection of the relatively small amounts of inorganic arsenic in soil that is typically ingested on a daily basis as well as the reduced bioavailability of arsenic in soil compared with water. Overall, a large number of studies have shown that the relative oral bioavailability of arsenic in soils to be less than 50%.[25]

(4) Air: Compared with arsenic exposure from food and water, exposure to arsenic in air, which is almost entirely as inorganic arsenic, is generally very low. The Europeal Commission (2000) has reported that levels of arsenic in air ranges 0-1 ng/m^3 in remote areas, 0.2-1.5 ng/m^3 in rural areas, 0.5-3 ng/m^3 in urban areas, and up to about 50 ng/m^3 in the vicinity of industrial sites. Based on these data, the European Commission estimated that in relation to food, cigarette smoking, water, and soil, air contributes less than 1% of total arsenic exposure, even when assuming an arsenic air exposure that is significantly above typical background (i.e 20 ng/m^3)[26].

(C) Pharmacokinetics of arsenic:

The two forms of inorganic arsenic, reduced (trivalent As (III)) and oxidized (pentavalent As(V)), can be absorbed, and accumulated in tissues and body fluids.[27] In humans inorganic arsenic is reduced nonenzymatically from pentoxide to trioxide, using glutathione (GSH) or it is mediated by enzymes. Reduction of arsenic pentoxide to arsenic trioxide increases its toxicity and bio availability, Methylation occurs through methyltransferase enzymes. Sadenosy-lmethionine (SAM) may serve as methyl donor. Various pathways are used, the principal route being dependent on the current environment of the cell.[28] Resulting metabolites are monomethylarsonous acid, MMA(III), and dimethylarsinous acid, DMA(III).The remaining unbound arsenic (= 10%) accumulates in cells, which over time may lead to skin, bladder, kidney, liver, lung, and prostate cancers. Other forms of arsenic toxicity in humans have been observed in blood, bone marrow, heart, central nervous system, gastrointestinal tract , gonads, kidney, liver, pancreatic, and skin tissues.[29]

(D) Pharmacodynamics of arsenic:

One of the mechanisms by which arsenic exerts its toxic

effect is through impairment of cellular respiration by the inhibition of various mitochondrial enzymes, and the uncoupling of oxidative phosphorylation. Most toxicity of arsenic results from its ability to interact with sulfhydryl groups of proteins and enzymes and to substitute phosphorous in a variety of biochemical reactions Arsenic in vitro reacts with protein sulfhydryl groups to inactivate enzymes, such as dihydrolipoyl dehydrogenase and thiolase, thereby producing inhibited oxidation of pyruvate and betaoxidation of fatty acids. The major metabolic pathway for inorganic arsenic in humans is methylation. Arsenic trioxide is methylated to two major metabolites via a non-enzymatic process to monomethylarsonic acid (MMA), which is further methylated enzymatically to dimethyl arsenic acid (DMA) before excretion in the urine.[30,31] It was previously thought that this methylation process is a pathway of arsenic detoxification, however, recent studies have pointed out that some methylated metabolites may be more toxic than arsenite if they contain trivalent forms of arsenic.[32] Tests for genotoxicity have indicated that arsenic compounds inhibit DNA repair, and induce chromosomal aberrations, sister-chromatid exchanges, and micronuclei formation in both human and rodent cells in culture and in cells of exposed humans.[33]

Although arsenic compounds are generally perceived as weak mutagens in bacterial and animal cells, they exhibit clastogenic properties in many cell types in vivo and in vitro.[34] In the absence of animal models, in vitro cell transformation studies become a useful means of obtaining information on the carcinogenic mechanisms of arsenic toxicity. Arsenic and arsenical compounds are cytotoxic and induce morphological transformations of Syrian Hamster Embryo (SHE) cells as well as mouse C3H10T1/2 cells and BALB/3T3 cells.[35]Arsenite inhibits not only the formation of acetyl-CoA but also the enzyme succinic dehydrogenase. Arsenate can replace phosphate in many reactions. It is able to form Glc-6-Arsenate in vitro; therefore it has been argued that hexokinase could be inhibited. Eventually this may be a mechanism leading to muscle weakness in chronic arsenic poisoning. In the reaction arsenate attacks the enzyme-bound thioester. The formed 1-arseno-3-phosphoglycerate is unstable and hydrolyzes spontaneously. Thus, ATP formation in Glycolysis is inhibited while by passing the phosphoglycerate kinase reaction. (Moreover, the formation of 2,3-bisphosphoglycerate in erythrocytes might be affected, followed by a higher oxygen affinity of hemoglobin and subsequently enhanced cyanosis) As shown by Gresser (1981), submitochondrial particles synthesize Adenosine-5'-diphosphate-arsenate from ADP and arsenate in presence of succinate. Thus, by a variety of mechanisms arsenate leads to an impairment of cell respiration and subsequently diminished ATP formation. This is consistent with observed ATP depletion of exposed cells and histopathological findings of mitochondrial and cell swelling, glycogen depletion in liver cells and fatty change in liver, heart and kidney.

(E) Uses of arsenic:

Arsenicals are used commercially and industrially as alloying agents in the manufacture of transistors, lasers and semiconductors, as well as in the processing of glass, pigments, textiles, paper, metal adhesives, wood preservatives and ammunition. They are also used in the hide tanning process. Several arsenic-containing compounds are produced industrially, and have been used to manufacture products with agricultural applications such as insecticides, herbicides, fungicides, algicides, sheep dips, wood preservatives, and dyestuffs.[36]

Arsenic is also been used in veterinary medicine for the eradication of tapeworms in sheep and cattle. Arsenic compounds have also been used in the medical field for at least a century in the treatment of syphilis, yaws, amoebic dysentery, and trypanosomaiasis.[37]Arsenic-based drugs are still used in treating certain tropical diseases such as African sleeping sickness and amoebic dysentery, and in veterinary medicine to treat parasitic diseases, including filariasis in dogs and black head in turkeys and chickens. Recently, arsenic trioxide has been approved by the Food and Drug Administration as an anticancer agent in the treatment of acute promeylocytic leukemia. Its therapeutic action has been attributed to the induction of programmed cell death (apoptosis) in leukemia cells.[38]

(F) Health hazards of arsenic:

It is estimated that several million people are exposed to arsenic chronically throughout the world, especially in countries like Bangladesh, India, Chile, Uruguay, Mexico, Taiwan, where the ground water is contaminated with high concentrations of arsenic. Exposure to arsenic occurs via the oral route (ingestion), inhalation, dermal contact, and the parenteral route to some extent.[39] Diet, for most individuals, is the largest source of exposure, with an average intake of about 50 μg per day. Intake from air, water and soil are usually much smaller, but exposure from these media may become significant in areas of arsenic contamination. Workers who produce or use arsenic compounds in such occupations as vineyards, ceramics, glass-making, smelting, refining of metallic ores, pesticide manufacturing and application, wood preservation, semiconductor manufacturing can be exposed to substantially higher levels of arsenic.[40] Arsenic has also been identified at 781 sites of the 1,300 hazardous waste sites that have been proposed by the U.S. EPA for inclusion on the national priority list. Human exposure at these sites may occur by a variety of pathways, including inhalation of dusts in air, ingestion of contaminated water or soil, or through the food chain. Interest in the toxicity of arsenic has been heightened by recent reports of large populations in West Bengal, Bangladesh, Thailand, Inner Mongolia, Taiwan, China, Mexico, Argentina, Chile, Finland and Hungary that have been exposed to high concentrations of arsenic in their drinking water and are displaying various clinicopathological conditions including cardiovascular and peripheral vascular disease, developmental anomalies, neurologic and neurobehavioural disorders, diabetes, hearing loss, portal fibrosis, hematologic disorders (anemia, leukopenia and eosinophilia) and carcinoma.[41]

Arsenic exposure affects virtually all organ systems including the cardiovascular, dermatologic, nervous, hepatobilliary, renal, gastro-intestinal, and respiratory systems.Research has also pointed to significantly higher standardized mortality rates for cancers of the bladder, kidney, skin, and liver in many areas of arsenic pollution. The severity of adverse health effects is related to the chemical form of arsenic, and is also time and dose-dependent.Although the evidence of carcinogenicity of arsenic in humans seems strong, the mechanism by which it produces tumors in humans is not completely understood [42,43].

(G) Clinical features of arsenic toxicity:

The immediate symptoms of acute arsenic poisoning include vomiting, abdominal pain and diarrhoea. These are followed by numbness and tingling of the extremities, muscle cramping and death, in extreme cases.The first symptoms of long-term exposure to high levels of inorganic arsenic (e.g. through drinking-water and food) are usually observed in the skin, and include pigmentation changes, skin lesions and hard patches on the palms and soles of the feet (hyperkeratosis). These occur after a minimum exposure of approximately five years and may be a precursor to skin cancer. In addition to skin cancer, long-term exposure to arsenic may also cause cancers of the bladder and lungs. The International Agency for Research on Cancer (IARC) has classified arsenic and arsenic compounds as carcinogenic to humans, and has also stated that arsenic in drinking-water is carcinogenic to humans.Other adverse health effects that may be associated with long-term ingestion of inorganic arsenic include developmental changes, neurotoxicity, diabetes and cardiovascular disease. In China (Province of Taiwan), arsenic exposure has been linked to "blackfoot disease", which is a severe disease of blood vessels leading to gangrene. However, this disease has not been observed in other parts of the world, and it is possible that malnutrition contributes to its development.[44]

(H) Diagnosis of arsenic toxicity:

Tests are available to diagnose poisoning by measuring arsenic in blood, urine, hair, and fingernails. The urine test is the most reliable test for arsenic exposure within the last few days. Urine testing needs to be done within 24-48 hours for an accurate analysis of an acute exposure. Tests on hair and fingernails can measure exposure to high levels of arsenic over the past 6-12 months. These tests can determine if one has been exposed to above-average levels of arsenic. They cannot predict, however, whether the arsenic levels in the body will affect health.[45]Chronic arsenic exposure can remain in the body systems for a longer period of time than a shorter term or more isolated. Hair is a potential bio-indicator for arsenic exposure due to its ability to store trace elements from blood. Incorporated elements maintain their position during growth of hair. Thus for a temporal estimation of exposure, an assay of hair composition needs to be carried out with a single hair which is not possible with older techniques requiring homogenization and dissolution of several strands of hair. This type of bio-monitoring has been achieved with newer microanalytical techniques like Synchrotron radiation based X ray fluorescence (SXRF) spectroscopy and Microparticle induced X ray emission (PIXE).[46]

(I) Treatment of arsenic toxicity:

Dimercaprol and dimercaptosuccinic acid are chelating agents that sequester the arsenic away from blood proteins and are used in treating acute arsenic poisoning. Their most important side effect is hypertension. Dimercaprol is considerably more toxic than succimer. DMSA monoesters, e.g. MiADMSA, are promising antidotes for arsenic poisoning.[47] Calcium sodium edetate is also used. Supplemental potassium has been found to decrease the risk of experiencing a life-threatening heart rhythm problem from arsenic trioxide[48] and is added to the management of arsenic poisoning.Various techniques have been evolved for arsenic removal, most frequently using absorbents such as activated carbon, aluminium oxide, co-operative with iron oxide to form sludges, adsorption onto iron-oxide-coated polymeric materials, and electrocoagulation by nanoparticle. Bacteria, yeast, fungi, and algae can also be used for remediation processes.[49]

PREVENTIVE MEASURES:

Substitute high-arsenic sources such as ground water, with low-arsenic, microbiologically safe sources such as rain water and treated surface water.

Use low-arsenic water for drinking, cooking and irrigation purposes, whereas arsenic-rich water should be used for other purposes such as bathing and washing clothes.

Install arsenic removal systems either centralized or domestic ones.

Ensure appropriate disposal of removed arsenic. Technologies for arsenic removal include oxidation, coagulation–precipitation, absorption, ion exchange and membrane techniques.

Reduce occupational exposure from industrial processes as long-term actions.

Ensure successful interventions such as education and community engagement.There is a need for community members to understand the risks of high arsenic exposure and the sources of arsenic exposure, including the intake of arsenic by crops (e.g. rice) from irrigation water and the intake of arsenic into food from cooking water.

Monitor high-risk populations for early signs of arsenic poisoning - usually skin problems.[44]

CONCLUSION:

Arsenic is a ubiquitous element that is detected at low concentrations in virtually all environmental matrices. Awareness should be created among the communities regarding its sources of exposure, features of toxicity and reporting to healthcare professionals in case of exposure and toxicity. Governmental measures for provision of clean water, uncontaminated food and reduction of hazards at occupational level could play a vital role for preventing morbidity and mortality related

to heavy metal arsenic.

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