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A Long-Lasting "Emergency": Arsenic Poisoning in the Developing World

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Abstract

Arsenic is among the heavy metals metallic elements most commonly associated with disease states in primary care medicine. Arsenic trioxide, sodium arsenite, and arsenic trichloride are among the forms most easily found in the environment. There is a strong link between exposure to inorganic Arsenic (iAs) in drinking water and the prevalence of cancer and the risk of cardiovascular disease, hypertension and diabetes. The acute lethal dose of iAs has been estimated to be about 0.6 mg/kg/day.

A patient with as intoxication can present with metabolic, cardiorespiratory, hematological, gastrointestinal, and neurological abnormalities. Skin manifestations are evaluated to be among initial and reliable diagnostic criteria for acute and chronic exposure to As compounds. Massive fluid loss can result in dehydration, volume depletion and cardiorespiratory collapse or shock states in extreme cases. The important biomarkers of As are sought in the urine, nail, and hair. Treatment with a chelating agent [e.g., succimer (2,3- dimercaptosuccinic acid) and dimercaprol] is vital in patients with a suspicion of severe intoxication.

Keywords: Heavy metals; Arsenic; Poisoning; Toxicity; Diagnosis; Treatment; Chelators

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Introduction

Metals are among the oldest poisons recognized by human being. A major difference of metals from other substances is that they have not been created nor destroyed by humans. Untoward exposure to these metals ensues *via* air, water and food or in certain risky professions. While contamination of the environment with these elements has been alleviated in the Western world in the last decades, developing countries are still exposed to considerable levels of metal pollution. Metals occur naturally in the environment but human activities cause substantial amount of releases of the elements. Exposure to heavy metals may result in many kinds of health effects in humans.

Heavy metals are metallic elements with specific density of >5 g/cm^3 which are available in little quantity in various milieu in the nature [1,2]. Arsenic [As], Lead [Pb], Mercury [Hg], Aluminium [Al] and Cadmium [Cd] can be included in this list. Metals such as these do not carry on any specific role in the organ systems and cause toxicity at low levels.

Mercury, arsenic, cadmium and lead are among the heavy metals metallic elements that are ranked among the top list of known hazardous chemicals. They are present in our body at a low concentration but can adversely affect the environment and living organisms [3]. Heavy metals generate reactive oxygen species, which destroyed the integrity of DNA, triggered lipid peroxidation, and reduction of protein sulfhydryls [4].

Arsenic

Arsenic is among the elements most commonly associated with disease states in primary care medicine [5]. The chemistry of As is a complex issue which encompasses various relevant compounds. It can be found in its trivalent or pentavalent forms in the environment. Arsenic trioxide, sodium arsenite, and arsenic trichloride are among the forms most easily found in the nature [6].

The carcinogenicity of the element is recognized as "Group 1" by the International Agency for Research on Cancer. There is a strong link between exposure to inorganic Arsenic (iAs) in drinking water and the prevalence of cancer. iAs also increases the risk of cardiovascular disease, hypertension

and diabetes [7].

Sources

Sources of As contamination include soil, air, food and drinking water due to contamination from As containing industrial effluent, agricultural pesticide or natural mineral deposition. Millions in the world are obliged to use groundwater and inevitably exposed to As toxicity due to its natural occurrence in many regions of Asia and America. Drinking water contamination with As poses serious global environmental disaster [8].

Food particularly, staple crop such as rice provide the largest source of exposure to the element. In view of the global consumption of rice and greater risk of contamination through this crop, a maximum permissible limit of As in white and brown rice has been set to 200 µg/kg and 400 µg/kg respectively by World Health Organization (WHO) guidelines [9]. Shahid et al. [10] pooled the results of 43 studies and disclosed that three-fourths of the findings for mean As ingredients in these researches had been higher than the limits set by WHO (10 µg/L) for potable water. Based on these data, they foresaw that around 50 million people in Pakistan are living in regions where more than a half of groundwater carrying As values above the WHO limits.

Human exposure to this heavy metal may occur orally, inhalation and through dermal contact [11]. It is one of the outstanding heavy metals with semimetallic property that occur at low concentrations in inorganic forms of Trivalent Arsenite (AsIII) and the Pentavalent Arsenate (AsV). A vast majority of ingested arsenic is absorbed by the gastrointestinal system [4]. The level of arsenic intake from water, soil and air are much lower than from foods. Aerial As concentrations depend on locations, and range between 1 ng/m^3 and 3 ng/m^3 in rural areas, and between 20 ng/m^3 to 100 ng/m^3 in urban centers [2,11]. Its concentration ranges between 20 ng/kg and 140 ng/kg in foods [12], between 1 mg/kg and 40 mg/kg in soil and less than 10 µg/L in water [2].

Arsenic poisoning has also been reported in those with suicidal or accidental intake of As-containing pesticides, insecticides or other chemicals [13].

Mechanism of Arsenic Toxicity

Arsenic is a protoplastic toxicant that primarily affects the sulphydryl group of cells and compromised the integrity of cell enzymes and cellular respiration [4]. The molecular mechanistics underlying carcinogenesis of iAs is not yet outlined clearly, although several mechanisms including genotoxicity, disturbed proliferation, oxidative stress, epigenomic alterations, signal transduction disturbances, and cytotoxic findings were pointed out [7].

During chronic arsenic exposure, iAs are enzymatically methylated by humans and most microorganisms (*fungi*, *bacteria* and *algae*) to produce less harmful Monomethylarsinic Acid (MMA) and Dimethylarsinic Acid (DMA) which can be excreted *via* kidneys.

The biotransformation occurs primarily in the liver, a reaction catalysed by S-Adenosylmethionine (SAM) and Glutathione (GSH)/ NADPH dependent hepatic methyltransferases [14]. The methyl group is donated by S-Adenosylmethionine (SAM) while the Glutathione (GSH) serves as the redundant [15]. Arsenic species binding to GSH enhanced the success of the biotransformation and increases its elimination from the body.

Monomethylarsonic Acid (MMA III) is an intermediate product generated during this biotransformation. It is more toxic than the parent compound due to the bigger affinity for sulfhydryl groups [16]. It is not excretable in the urine. Accumulation of this intermediate compound has been attributed to arsenic-induced carcinogenesis [17]. Evidence from *in vivo* and *in vitro* cytotoxicity study ranked the relative toxicities of arsenic metabolites in order; MMA III>DMA III>As III>As V>MMA V>DMA V [4,16,17].

Dosing Issues in Acute Exposure

The LD50 of the element in acute exposure ranges between 100 mg and 300 mg. The acute lethal dose of iAs to humans has been estimated to be about 0.6 mg/kg/day [18].

Acute Poisoning: Clinical Characteristics

The element has been associated with neurotoxicity, teratogenicity, embryotoxicity and fetal growth retardation in animal species [19]. In humans, metabolic, cardiorespiratory, hematological, gastrointestinal, and neurological abnormalities are encountered following exposure to As. Skin manifestations are evaluated to be among initial and reliable diagnostic criteria for acute and chronic exposure to As compounds [20,21]. In addition, massive fluid loss can result in dehydration, volume depletion and cardiorespiratory collapse or shock states [22].

Effect of exposure on impairments documented in various organ systems has been reported in different populations (Table 1).

Death is generally anticipated within one to four days, depending on the concentration of the element taken [22]. A case study of patients who consumed 8 g and 30 g of As reported that death occur in 8 days and 15 h respectively, despite treatment with antidote (British Anti-Lewisite) and gastric lavage intervention [23,24].

Diagnosis

The important biomarkers of As are sought in the urine, nail, and hair. As is detectible in the blood for only a short period after intake [25]. Arsenic occurs in higher concentrations in human nails and hair than in other parts of the body. The iAs has about 4 days half-life in humans, and urine is the major route of it excretion. The urinary As concentration has been used as an indicator of recent arsenic intoxication [26,27]. A total daily intake of 46 µg/L and 324 µg/L arsenic from drinking water produced 41 µg/L and 178 µg/L concentrations of arsenic in urine respectively [28].

Treatment of As exposures varies with regard to the manifested signs and symptoms. No specific method has been proved to treat arsenic toxicity so far. The removal of the victim from the source is of utmost importance.

Chelators bind to the metals in the bloodstream; and metal-chelator compound is then eliminated in the urine. Treatment with a chelating agent [e.g., succimer (2,3- dimercaptosuccinic acid) and dimercaprol] is vital in patients with a suspicion of severe intoxication [29]. Approved chelating drugs in the US include succimer, dimercaprol (BAL), edetate calcium disodium, deferoxamine, and penicillamine. They are given only for diagnosed metal toxicity because 1) they may have serious side effects, even when their use is needed; and 2) they are non-specific and can bind even essential "trace" metals in the body, for example copper and zinc. They can sometimes bind calcium, too. Chelation of these substances can cause symptoms related to their deficiency.

Table 1: Anticipated clinical characteristics following acute poisoning with Arsenic compounds.

Organ/system	Symptom/finding	Additional notes
Dermatological	Diffuse skin rash palmar, solar keratosis [33] nodules and uniform thickening hyperpigmentation [33] Arsenic deposition in keratin-rich areas (e.g., Mee's lines) [20,21].	Acute changes in the acute exposure, then increased susceptibility to basal cell carcinoma in the long term.
Gastrointestinal	Severe diarrhea [22] hepatomegaly [34] non-cirrhotic portal fibrosis [34] incomplete septal cirrhosis vomiting, nausea and abdominal crampy pain [35]	Not every patient is anticipated to develop these complications, but a markedly increased incidence has been documented.
Circulatory	Ischemic and hypertensive heart disease in the long term [36,37] peripheral vascular impairment, gangrene of the foot toxic cardiomyopathy [38]	Chronic arsenic exposure has been implicated in cardiac arrhythmias, direct myocardial impairment and cardiomyopathy [39].
Respiratory	Chronic exposure was associated with obstructive and restrictive lung disease [40]	Arsenic induced lung disease and bronchitis is more frequently noted in those with skin lesions and black foot disease [41].
Neurological	Peripheral neuropathy [42] Guillain-Barré syndrome severe weakness encephalopathy seizure [38]	Guillain-Barré syndrome-like peripheral neuropathy with similar electromyographic attribute is among the most commonly encountered findings. Increased incidence of cerebrovascular accidents was recorded in populations exposed to arsenic- contaminated water [43].
Hematological	Anemia, intravascular coagulation, hemoglobinuria, bone marrow depression, severe pancytopenia and basophilic stippling	Anemia is mostly normocytic and normochromic which means it is not linked to iron deficiency.
Metabolic	Acidosis, hypoglycemia and hypocalcemia [23]	
Fluid balance	Dehydration, volume depletion	
Other/miscellaneous	Excessive salivation, acute psychosis confusion, behavioural changes hepatorenal damage [42]	Temporal cognitive abnormalities have also been noted in workers exposed to arsenic for 14 to 18 months. As contamination was linked with various types of carcinomas of the kidney, bladder, ureter in both sexes [44].

Renal insufficiency in the course of toxicity can prompt hemodialysis [30]. In addition, antioxidants-particularly endogenous dietary antioxidants from natural products are among the preventive and curative factors to be considered in heavy metal intoxication [31]. In this context, vitamin E and selenium supplements have been used as remedies to alleviate the hazards of As exposure. In their recent review, Rahman et al. [32] pointed out that intracellular oxidative stress due to As toxicity can be minimized, if not eliminated, by metallothionein. Thus MT induction by essential metals such as zinc and selenium supplementation could be beneficial to mitigate hazards of As toxicity. Still, more human studies are needed to support these compounds as useful modes of treatment.

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