Chronic arsenic toxicity through contaminated drinking water in Bangladesh: Magnitude of the problem, health effects and detoxification

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Introduction
Various concentrations of arsenic in drinking water and soil are found in many countries in the world including developed and developing countries. The source of this arsenic in drinking water is the earth's crust where arsenic occurs widely. The arsenic contamination of drinking water may also be due to industrial pollution. In Bangladesh, the arsenic concentration in drinking water is alarmingly higher than the standard set by WHO. Together with the poor socio-economic and nutritional status of the population, the chronic exposure to arsenic in drinking water is causing widespread health hazards in Bangladesh.

Drinking water normally contains inorganic arsenic as arsenate (As(V)) and arsenite (As(III)). Inorganic arsenic is more dangerous than many other toxic substances. It is four times as toxic as mercury. Anyone who drinks arsenic in water at 60 parts per million (ppm) will soon die. But, organic arsenic in food is less toxic than inorganic arsenic. Most of the ingested arsenic is excreted from the body through urine, stool, skin, hair, and nail. Nonetheless, if the ingestion of arsenic through drinking water is very high, as in Bangladesh, our body normally cannot escape its toxic effects. Arsenic is deposited in tissues and causes oxidative stress to cells resulting in multiple organ dysfunctions.

A recent article in The New York Times on 10 November 1998 observes: "...Bangladesh is in the midst of a mass poisoning in history, dangerous levels of arsenic have been found in the ground water, entering millions of people, sip by sip as they drink from over 4 million tube wells." The report says "...if this were the United States, they'd call out National Guards and get everyone bottled water", "...arsenic in drinking water poses the highest cancer risk ever found, ...we could be talking about hundreds of thousands of deaths -this is really a medical emergency."

The problem is new to Bangladesh, and little is known about the health effects and pathogenesis of chronic arsenic poisoning through contaminated drinking water. We still do not know how we can remove arsenic contamination from our ground water nor do we know the effective treatment to detoxify arsenicosis patients.

Genesis of the problem
About 3.5 to 4 million tube-wells (hand pumps) were installed in 1960s, all over the country by the aid agencies (mainly UNICEF) and the Government of Bangladesh to provide her 120 million people with safe drinking water at a minimum cost. Again, after liberation of Bangladesh, shallow tube well water was heavily promoted and developed as a safe and environmentally acceptable alternative to microbiologically unsafe untreated surface water. Although the tube well programme significantly reduced the burden of diarrhoeal diseases and saved millions of lives, it has now turned into a major cause of tragedy.

In the 1980s, scientists began finding evidence of arsenic contamination, but only very recently (mid-1990s) has the crisis emerged into broad public awareness. The origin of the arsenic pollution is geological in this case -the arsenic is released to groundwater under naturally occurring aquifer conditions. Aquifers less than 300 m deep (mostly <100 m) provide Bangladesh with more than 90% of its drinking water. Another contributing factor for arsenic pollution appears to be the unrestricted use of

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underground water for agriculture. Withdrawal of large volume of underground water, often with insufficient recharge, led to a sharp fall in water table, causing aeration of the underground water and chemical contamination.

In the adjoining Indian state of West Bengal, ground water contamination by arsenic has been known for several years, and a likelihood of similar condition in the adjacent western Bangladesh had been predicted by the Indian scientists several years ago. However, it was not until June 1996, when arsenic poisoning was first detected in a few Bangladeshi patients presenting with skin changes in a northwest town bordering India'. Later, laboratory investigations confirmed the diagnosis of chronic arsenicism, showing more than normal arsenic contents in the hair, nail, skin, and urine samples of 96 patients. A higher than normal content of arsenic (Bangladesh standard 0.05 mg/L, i.e., 50 ppb) was also found in 66% of the water samples taken from the shallow tube wells in that area.

Further studies carried out by the Dhaka Community Hospital, in collaboration with the School of Environmental Studies in Calcutta detected high arsenic content in the tube well water wherever it has been looked for. About 60% to 90% of the tube wells providing 97% of the country's drinking water supply were found to contain unacceptable levels of arsenic (0.05 to 3.0 mg/L), whereas the World Health Organization's safety standard for arsenic is 0.01 mg/L. Early observations by other organizations, including the government's public health department, NGOs and international aid agencies (UNICEF, World Bank) also indicated an alarming rate of arsenic contamination of the tube well water and prevalence of arsenic affected patients throughout the country.

The magnitude of the problem
Many sporadic reports of arsenic contamination of tube well water and of poisoning cases that had appeared in the local press and newsletters are summarized in the Table. It is observed' that by early 1998, a total of 8,065 tube-well water samples from 60 out of the 64 districts of the country were tested for the presence of arsenic by using field test kits and atomic absorption spectrophotometer. In 41 districts, the arsenic contents exceeded 0.05 mg/L, the maximum permissible limits recommended by Bangladesh standard, thus exposing 76.9 million people in these districts to the risk of arsenic poisoning'. However, according to various estimates reported to the press, the actual proportion of the population exposed to the risk may be more. Up till now, four people were reported to have died of arsenic poisoning'; however, there may be more deaths that were not reported.

Tube well water samples from Dhaka district and nine elevated districts in the northern Bangladesh, including the hill districts in Chittagong, were found to contain arsenic in the permissible range (0.01-0.05 mg/L). The reasons for this difference have not yet been found out. The distribution of arsenic contaminated tube wells in different districts of Bangladesh is shown in the map (Figure 1). A case study by Dhar et al. of the Samata village in Jessore district illustrates the scenario of arsenic poisoning in Bangladesh. The total area of the village is 3.2 sq km with 4,841 people and 279 tube wells. It has been found that water of only 5 (2%) tube wells was safe for drinking (arsenic content <0.01 mg/L), 18 tube wells were moderately safe (arsenic content <0.05 mg/L), and 90% tube well water was unacceptable for drinking .by the Bangladeshi standard. Three hundred thirty people, including 27 children aged less than 12 years were identified as having arsenical skin lesions (mostly melanosis, leukomelanosis, and keratosis); arsenic content in urine, hair and nail samples of these patients exceeded the normal limit in 97%, 85%, and 96% cases, respectively.

A recent case-controlled study by Rahman et al. showed that the long-term exposure to arsenic through drinking of arsenic contaminated water was associated with high prevalence of diabetes mellitus among the Bangladeshi population. The same group of authors have also assessed the risk of
Table. Estimates of arsenic contaminated tube wells and arsenic-affected population in Bangladesh. From: Arsenic contamination in groundwater: testing pollution mechanisms for sedimentary aquifers in Bangladesh. J.M. McArthur, P. Ravenscroft, S. Safiullah and M.F. Thirlwall. Water Resources Research, in press. Enumerations based on 18,417 (4,125 lab) aggregated by union. The surface estimated based on the union-wise probability assigned to the centroid of each union. Calculation by IDW using a fixed radius of 7.5 km, a 1.5 km grid, and 3.125 union points.


Clinical presentation and risk to human health

The health effects of chronic human exposure to non-overtly toxic doses of arsenic in drinking water and food can be broadly divided into noncancer effects and cancer effects. Chronic exposure to arsenic causes its toxic effects to all organs and cells of the body. It interferes with the action of enzymes, hypertension in a group of Bangladeshi adults exposed to high level of arsenic in drinking water and found a significant correlation between arsenic ingestion and hypertension. Long-term epidemiological studies to determine the biomedical and environmental characteristics of arsenic poisoning with regard to age, gender, time, and place have not yet bee undertaken and the related risk factors have not been identified.

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essential cations and transcriptional events ensuing a multitude of multisystemic noncancer effects. Chronic arsenic exposure may cause hyperpigmentation and keratosis leading to skin cancer, gastrointestinal disturbances ranging from mild abdominal cramping and diarrhea to severe life-threatening gastrointestinal hemorrhage secondary to esophageal varices, hepatocellular necrosis, insidious development of peripheral vascular disease leading to gangrene of the extremities, hypertension and ischemic heart disease, hematological abnormalities, obstructive and restrictive pulmonary diseases, generalized immunosuppression, peripheral neuropathy, and metabolic disorders including diabetes. In recent times, an increase in the prevalence of some diseases in Bangladesh such as diabetes may be explained by the chronic exposure to arsenic.

In a study, arsenic-affected population in southwestern district (Jessore) in Bangladesh and in the neighboring Indian state of West Bengal, it is reported that the usual clinical manifestations are diffused and spotted melanosis, diffused and spotted keratosis, and non-pitting edema; the common symptoms are bronchial problems and burning sensation of the skin. Khan et al. reviewed the clinical data from Bangladeshi arsenic-affected patients and reported that the most common clinical manifestations are melanosis (87.4%), keratosis (67.7%), leukomelanosis (35.5%), and hyperkeratosis (38.7%). Other findings are conjunctivitis (6.3%), bronchitis (10.5%), and hepatomegaly (2.2%).

Recently, in an ongoing study, we have documented typical skin changes (photographs) including other systemic involvement in patients in the study area of Hajiganj, Chandpur. We have observed typical skin changes including plantar and palmar keratosis, gastrointestinal symptoms, anaemia, signs of liver disease, and peripheral neuropathy. Chronic arsenic toxicity is already known to cause liver damage. Guha et al. have recently described 13 Indian patients who have developed hepatomegaly and non-cirrhotic portal fibrosis associated with arsenical dermatosis due to prolonged exposure to arsenic (0.2 -2 mg/L) through drinking water. Although similar findings have not yet been reported from Bangladesh (due to lack of studies), the risk of liver involvement cannot be excluded because of the similarity of biological and environmental characteristics between these two populations.

It has been observed that skin manifestations of arsenic toxicity develop slowly, usually over three to six months depending on the dose and duration of the toxic material, and age and nutritional status of the exposed individual. The arsenic contents of 90% of tube well water in our study site at Hajiganj, Chandpur as well those reported by Biswas et al. from Jessore district were more than the maximum permissible limit by the Bangladesh standard (>0.05 mg/L). The lowest arsenic concentration in water producing dermatosis was found to be 0.02 mg/L.

Arsenic is an important cause of skin cancer, and the high incidence of keratosis, hyperkeratosis, and skin cancer has been associated with drinking water containing more than 0.3 to 0.5 mg/L of arsenic. Most authorities believe that ingestion of approximately 1 mg/L of arsenic per day in drinking water may give rise to skin changes within a few years.

Pathogenesis of arsenic poisoning

The inorganic arsenic is absorbed more readily than the organic forms because of its high lipid solubility. Once arsenic is within the body, it binds to hemoglobin, low molecular weight plasma proteins, and leukocytes and is redistributed to the liver, kidney, lung, spleen, and intestines. Over a
period of weeks, manifestations may be found in skin, hair, nails, bone, muscle, and even nervous tissue. As mentioned above, chronic exposure to arsenic causes carcinogenesis and other non-carcinogenic diseases. There are a number of possible modes of action of arsenic carcinogenesis: chromosomal abnormalities, oxidative stress, altered DNA repair, altered DNA methylation patterns, altered growth factors, enhanced cell proliferation, promotion/progression, gene amplification, and suppression of p53. In vitro studies of human and animal cells show that genotoxic effects occur at submicromolar concentrations of arsenide that are similar to those found in urine of humans consuming drinking water\textsuperscript{17,18}. Arsenic poisoning has inhibitory effects on mitochondrial respiratory function by inhibiting the pyruvate dehydrogenase complex (Figure 2).

![Figure 2. Mechanisms of arsenic toxicity. As(V) competes with inorganic phosphate for ADP. Therefore, ADP-As(V) is formed, inhibiting formation of ATP from ADP. Ultimately, this causes oxidative stress. As(V) is biotransformed to As(III). As(III) inhibits cellular enzymes, especially binding to the sulphhydryl groups ultimately causing oxidative stress. It also inhibits cellular glucose uptake gluconeogenesis and fatty acid oxidation.](image)

Inhibition of mitochondrial respiration results in decreased cellular production of ATP and increased production of hydrogen peroxide. These effects cause formation of reactive oxygen species, resulting in oxidative stress. There is evidence that intracellular production of reactive oxygen species inhibits the heme biosynthetic pathway. It is known that oxidative stress is a cause of DNA damage. It is likely that oxidative stress induced by chronic exposure to arsenic also mediate DNA damage. The intracellular production of reactive oxygen species might play an initiating role in the carcinogenic process by producing DNA damage\textsuperscript{17}.

By using human-hamster hybrid cells, Liu et al. have shown arsenide induces a dose-dependent increase in intracellular oxyradical production\textsuperscript{18}. Concurrent treatment of cells with arsenide and the radical scavenger dimethyl sulphoxide (DMSO) reduced the oxyradical concentration to control levels. This provides that reactive oxygen species, particularly hydroxyl radicals, play an important causal role in the genotoxicity of arsenical compounds in mammalian cells. Barchowsky A et al. measured the reactive species generated in cultured porcine vascular endothelial cells exposed to levels of arsenide that initiate cell signaling\textsuperscript{19}. They found that superoxide and H\textsubscript{2}O\textsubscript{2} are the predominant reactive species produced by endothelial cells after arsenide exposures that stimulate cell signaling and activate transcription factors. Flora SJ provides in vivo evidence of arsenic-induced oxidative stress in liver, brain and RBC\textsuperscript{20}. He reports that twelve weeks of arsenic (12 mg/kg) exposure was found to deplete glutathione (GSH) levels, increase oxidized glutathione (GSSG) and promote malondialdehyde (MDA) production in both liver, brain and RBC samples.
Glutathione (GSH) acts as a reducing agent for As(V) species, and the resulting As(III) species can then accept a methyl group from S-adenosylmethionin (SAM) to produce methylarsenic (V) (MeAs(V)) species in an oxidative-addition reaction\textsuperscript{30,31} (Figure 6). The MMA and DMA are the major end products in mammals. MMA and DMA are excreted in the urine faster than the inorganic arsenic.

**Therapeutic goal**
From the mechanism of biotransformation of inorganic arsenic (Figure 5), it is clear that GSH plays a crucial role in detoxifying and eliminating arsenic from the body. GSH is also necessary to neutralize free radicals produced during arsenic toxicity, in chronic or acute poisoning (Figure 6). But we find from our results (Figure 3 and Figure 4) and form published reports that arsenic poisoning (chronic or acute: causes an increase in TBARS and a depletion of GSH levels. This means that chronic arsenic poisoning not only causes injury to cells, also depletes the body’s defense system, ultimately aggravating the clinico-pathological condition. So, in any medical therapy, we must target to transform toxic forms of arsenic to nontoxic forms, inhibit free radical injury, help repair the injury already done and maintain a robust antioxidative defense system. An ideal antiarsenosis drug should fulfill all these criteria.

The treatment goal of the poisoning due to chronic exposure to arsenic is to eliminate the poison (arsenic) from the environment, to neutralize the poison in the body or eliminate it from the body, to reduce the toxic effects and repair the damage to organs and cells. Rapid elimination of the poison from the environment is certainly a difficult task if we consider the huge strategic planning and cost. Therefore, we need to rapidly detoxify the poison in our body before it can cause any toxic effects.

Now, the question is how we can target to detoxify arsenic once inside the body. Detoxification can be enhanced by immediate biotransformation of inorganic arsenic to less toxic organic arsenic, by rapid elimination of arsenic from the body and preventing tissue...
deposition and by increasing the ability of body’s antioxidative defense system. Detoxification can be done by chelation of arsenic. One such chelating agent is dimercaptosuccinic acid, but even this best chelating agent for arsenic is reported to show no encouraging benefits compared with placebo in a recent study. Furthermore, dimercaptosuccinic acid has many adverse effects as well as it is very costly.

Therefore, any drugs, chemicals, and nutrients that have strong antioxidative properties could be effective in reducing the arsenic toxicity in the body. It is necessary to emphasize that the supplementation of antioxidant must be sufficient to neutralize the toxicity and to build up antioxidative system. So, new agents with strong anti oxidative properties need to be explored. Dose of the known antioxidant need to be evaluated to match the level of toxicity in Bangladeshi patients. Efficiency of combination of various antioxidant needs to be evaluated to effectively neutralize the arsenic toxicity. Recently, we have made some progress in this area of research and hope to communicate in the near future.

**Conclusion**

An environmental health disaster is unfolding in Bangladesh and neighboring countries due to a high concentration of arsenic in drinking water and in soil. Tens of millions of people in many districts are drinking ground water with arsenic concentrations far above acceptable levels. The ground water contains more than 0.05 mg/L (50 ppb) of arsenic. Thousands of people have already been diagnosed with poisoning symptoms, even though much of the at-risk population has not yet been assessed for arsenic-related health problems. Basic research in the area of arsenic toxicity, its mechanisms and pathogenesis should be given priority so the evolving knowledge can be used to identify an ideal medical therapy for chronic arsenic toxicity. Considering the huge strategic planning necessary for the elimination of arsenic from the environment and the fact that we can hardly avoid health hazards related to arsenic in an environment where we are constantly exposed to some degree of arsenic contamination not only in drinking water, but also in foods grown in heavily arsenic contaminated soil, we must find an ideal agent to detoxify ingested arsenic before it can cause any injury to the body.

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**References**