J. Dhaka National Med. Coll. Hos. 2013; 19 (01): 58-60

Review Article

Role of Selected Antioxidants in Arsenic Toxicity: An Update

Abul Kalam Mohammad Yousuf[1], Md. Mazharul Islam[2], Ayasha Aktar[3], Md. Rafiqul Bari[4], A. K. M. Shahidur Rahman[5], Muhammad Mahbubul Alam[6], Jannatul Ferdous[7], Md. Anwar Hussain[8] Shafique Md. Jashim Uddin[9]

[1]Assistant Professor, Dept. of Pharmacology, Northern International Medical College (NIMC), Dhaka. [2]Assistant Professor, Dept. of Forensic Medicine, NIMC, Dhaka. [3]Dept. of Physiology, Sir Salimullah Medical College, Dhaka. [4]Associate Professor, Dept. of Forensic Medicine, NIMC, Dhaka. [5]Assistant Professor, Dept. of Pharmacology, Khwaja Yunus Ali Medical College, Shirajganj. [6]Assistant Professor, Dept. of Pharmacology, East-West Medical College, Dhaka. [7]Assistant Professor, Dept. of Biochemistry, NIMC, Dhaka. [8]Professor and Head, Dept. of Forensic Medicine, NIMC, Dhaka. [9]Professor and Head, Dept. of Forensic Medicine, Dhaka National Medical College (DNMC), Dhaka.

Abstract:

Arsenic is an element in the environment causing oxidative damage in the exposed people leading to cell damage. Free radicals were generated during arsenic metabolism in cells. These free radicals are directly involved in oxidative damage in cells exposed to arsenic. Antioxidant levels are decreased in the body after arsenic exposure. Antioxidants can reduce or eliminate cellular damage caused by arsenic. This review article summarizes the role of some selected antioxidants in arsenic toxicity and also attempts to provide some update information regarding these selected antioxidants as better treatment regimen. We have selected vitamin A, C, E and zinc as antioxidants for this article keeping in view current concerns and literature available.

Key words: Arsenic, Free radicals, Reactive oxygen species (ROS), Oxidative stress, Antioxidants, Vitamin A, Vitamin C, Vitamin E, Zinc

Introduction:

Arsenic is a common naturally occurring element in the earth's crust. Arsenic exposure in Bangladesh is wide spread and involves thousands of wells and an estimated 35-77 million people in Bangladesh have been chronically exposed to increased concentrations of arsenic through drinking water[1].

The improper balance between free radicals and antioxidant defenses results in oxidative stress. In order to counteract the lethal effects of oxidative damage in cells exposed to arsenic, antioxidative defenses are required for the body[2].

Yousuf et al.'s recent study demonstrating a 2:1 molar ratio of zinc: arsenic and increased zinc and vitamin E in skin secretions of arsenicosis cases suggest potential therapeutic supplementation to accommodate these biochemical requirements. Vitamin E, zinc and other nutrients are required for methylation and detoxification of arsenic within the body[3].

Antioxidants play a vital role for methylation and detoxify the arsenic in the body mainly by reducing the free radical-mediated oxidative stress and also fulfill nutritional demand to the arsenicosis cases. Antioxidants have long been known to reduce the free radical-mediated oxidative stress[4]. Antioxidants such as - vitamin A, C, E and zinc are expected to play an important role in arsenic toxicity.

In view of above consideration, this review article summarizes the role of some selected antioxidants such as- vitamin A, C, E and zinc in arsenic toxicity and also attempts to provide some update information regarding these selected antioxidants as better treatment regimen.

Arsenic and Oxidative Stress

Evidence of oxidative stress has been measured in humans with arsenic exposure[5]. Arsenic binds to the –SH groups of enzymes in the pyruvate dehydrogenase system and inhibits pyruvate dehydrogenase, consequently prevents oxidation of dihydrolipoate to lipoate, which is needed in the formation of acetyl-coA from pyruvate[6]. Arsenic blocks the Krebs cycle and interrupts oxidative phosphorylation[7]. It results in decrease cellular ATP production and increase production of hydrogen peroxide, superoxide anion, singlet oxygen, hydroxyl radical and nitric oxide. These free radicals are directly involved in oxidative damage to lipids, proteins and DNA in cells exposed to arsenic. Enhanced oxidative stress

might be associated with the development of arsenic related diseases including cancers[2, 8].

Arsenic and Antioxidants :

Antioxidants are the substances that have the ability to inhibit free radical generation, scavenge free radical, and/or reduce the oxidation and damage caused by these radicals. The use of different antioxidants has been found beneficial in various cellular systems exposed in arsenic [2]. The following data provide some experimental evidence of the beneficial role of vitamin A, C, E and zinc against arsenic toxicity.

Vitamin A:

Vitamin A is a fat-soluble vitamin often used as a collective term for several related biologically active molecules such as- retinol, retinal, retinoic acid and β-carotene[9]. Vitamin A scavenges oxygen radicals formed during arsenic metabolism[10]. β-carotene, a precursor of retinol (Vitamin A), lipid-soluble antioxidant with properties somewhat analogous to that of vitamin E[11]. Treatment with vitamin A analogues (retinoids) might be useful in chronic cutaneous arsenism[12]. Vitamin A is useful to treat chronic arsenic poisoning[13].

Vitamin C:

Vitamin C is a water-soluble antioxidant occurring in the organism as an ascorbic anion. It also acts as a scavenger of free radicals and plays an important role in regeneration of α-tocopherol[11]. It prevent lipid peroxidation and protect the antioxidant system in arsenic-intoxicated rats[4]. It alleviates arsenic-induced alterations in mitochondria[14]. It was observed that vitamin C significantly reduced lipid peroxidation due to arsenic toxicity in rat brain cells[15]. Vitamin C acts a detoxifying agent by forming a poorly ionized but soluble complex[16]. A beneficial role of L-ascorbate co-administration against sodium arsenite-induced toxicity in maintaining normal ovarian activity and brain monoamines was reported[17].

Vitamin E:

Vitamin E is known to be one of the most potent endogenous antioxidants. α-tocopherol is a term that encompasses a group of potent, lipid soluble, chain-breaking antioxidants that prevents the propagation of free radical reactions[11]. Arsenic exposure increases oxidative damage to lipids and proteins and decreases the levels of antioxidants. Co-administration of arsenic-treated rats with vitamin C and alpha-tocopherol showed significant reduction in the level of lipid peroxidation[18].

Vitamin E scavenges oxygen radicals formed during arsenic metabolism[10]. It was observed that vitamin E prevented the arsenic induced killing of human fibroblast[19]. It was found that vitamin E significantly reduced lipid peroxidation due to arsenic toxicity in rat brain cells[15]. The protective mechanism of vitamin E could be attributed to its antioxidant property or its location in the cell membrane and its ability to stabilize membrane by interacting with unsaturated fatty acid chain[20].

Zinc:

Zinc is a known antioxidant and is shown to prevent acute arsenic toxicity in animals. Zinc protects animals against arsenic toxicity due to induction of metallothionein synthesis in animals, which reduces the toxicity of arsenic[21]. Supplementation of zinc also reduces the accumulated arsenic from different tissues of rat, following chronic exposure to arsenic[22]. Inadequate zinc has been linked to a reduction *in vivo* arsenic methylation capacity[23]. Zinc has a potential role for ameliorating the signs and symptoms of chronic arsenic poisoning in human[24]. A study conducted by Modi et al. (2004) suggested that toxic effects of arsenic could be minimized by increasing the adequately intake of essential metals such as- zinc, selenium[25].

Discussion :

In Bangladesh, arsenic toxicity has become the major public health problem[1]. Arsenic toxicity is mediated by oxidative stress increasing the free radicals production leading to lipid peroxidation and cell death[26]. Exposure to arsenic increases the secretion of vitamin E and zinc in skin[3].

Wu et al. (2001) stated that ingestion of arsenic contaminated well water may cause deleterious effects by increasing the levels of reacting oxidants and decreasing the level of antioxidant capacity in plasma of Northeastern Taiwan individuals[27]. Several studies showed that a combination of arsenic-safe water and antioxidants was the most effective for the management of arsenicosis patients[13, 28]. Vitamins, zinc and selenium are useful for arsenic detoxification[29]. Combination of vitamins and minerals are suggested to treat the cases of chronic arsenic poisoning[13, 24].

Antioxidants are thought to play a crucial role in counteracting free radical mediated cell damage. Nutritional antioxidants act through different mechanisms and in different compartments but are mainly free radical scavengers: (i) they directly neutralize free radicals, (ii) they reduce the peroxide concentrations and repair oxide membranes, (iii) they quench iron to decrease ROS production, (iv) via lipid metabolism, short-chain free fatty acids and cholesteryl esters neutralize ROS[16].

Conclusion :

This review article provides update information concerning the role of antioxidants in arsenic toxicity. It can be concluded that proper treatment with antioxidants either individually or in combination with chelating agents, minerals and provision of arsenic-safe drinking water may remain of importance in managing patients with arsenic toxicity.

References:

1. Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh.: A public health emergency. Bull WHO. 2000; 78: 1093-2003.
2. Shi H, Shi X, Liu KJ. Oxidative mechanism of arsenic toxicity and carcinogenesis. Molecular and Cellular Biochemistry 2004; 255: 67-78.
3. Yousuf AKM, Misbahuddin M, Rahman MS. Secretion of arsenic, cholesterol, vitamin E and zinc from the site of arsenical melanosis and leucomelanosis in skin. Clin Toxicol. 2011; 49 (5): 374-378.
4. Ramanathan K, Balakumar BS, Panneerselvam C. Effects of ascorbic acid and α-tocopherol on arsenic induced oxidative stress. Human Exp Toxicol. 2002; 21: 675-80.
5. Pi J, Yamauchi H, Kumagai Y, et al. Evidence for induction of oxidative stress caused by chronic exposure of Chinese residents to arsenic contained in drinking water. Environ Health Perspect 2002; 110: 331-336.
6. Schiller CM, Fowler BA, Woods JS. Effets of arsenic on pyruvate dehydrogenase activation. Environ Health Perspect. 1977; 19: 205-07.
7. WHO. Arsenic. Environmental health criteria 18. 1st ed. Geneva. World Health Organization. 1981.
8. Dai J, Weinberg RS, Waxman S, Jing Y. Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system. Blood 1999; 93: 268-77.
9. Champe PC, Harvey RA. Lippincott's illustrated reviews: Biochemistry, 2nd ed. 1994; pp. 330-331.
10. Peraza MA, Ayalo-Fierro F, Barber DS, Casarez E, Rael LT. Effects of micronutrients on metal toxicity. Environ Health Perspect. 1998; 106 suppl 1: 203-16.
11. Young IS, Woodside IS. Antioxidants in health and disease. J Clin Pathol 2001; 54: 176-186.
12. Kosnet JM. Clinical approaches to the treatment of chronic arsenic intoxication: from chelation to chemoprevention. Arsenic exposure and health effects, Elsevier Science, 1999, pp 349-54
13. Ahmad SA, Faruquee MH, Sayed MHSU, Khan MH, Hadi SA, Khan AW. Chronic arsenicosis: Management by vitamin A, E, C regimen. J Pre Social Med (JOPSOM). 1998; 17: 19-26.
14. Ramanathan K, Shila S, Kumaran S, Pannerselvam C. Ascorbic acid and alpha-tocopherol as potent modulators on arsenic induced toxicity in mitochondria. J Nutr Biochem. 2003; 14: 416-20.
15. Chattopadhyay S, Bhaumik S, Purkayastha M, et al. Apoptosis and necrosis in developing brain cells due to arsenic toxicity and protection with antioxidants. Toxicol Lett 2002; 136: 65-76.
16. Flora SJS. Nutritional components modify metal absorption, toxic response and chelation therapy. J Nutr Environ Med. 2002; 12: 51-65.
17. Chattopadhyay S, Ghosh S, Debnath J, Ghosh D. Protection of sodium arsenite-induced toxicity by co-administration of L-ascorbate (vitamin C) in mature wistar strain rat. Arch Environ Contam Toxicol 2001; 41: 83-89.
18. Ramanathan K, Shila S, Kumaran S, Pannerselvam C. Protective role of ascorbic acid and alpha-tocopherol on arsenic induced microsomal dysfunction. Hum Exp Toxicol. 2003; 22: 129-36.
19. Lee TC, Ho IC. Modulation of cellular antioxidant defense activities by sodium arsenite in human fibroblasts. Arch Toxicol 1994; 69: 498-504.
20. Ganther HE. Modification of methyl mercury toxicity and metabolism by selenium and vitamin E: possible mechanisms. Environ Health Perspect 1978; 25: 71-76.
21. Kreppel H, Lin J, Liu Y, Reichl FX, Kladden CD. Zinc-induced arsenite tolerance in mice. Fundam Appl Toxical. 1994; 23: 32-37.
22. Uddin MK. Effect of zinc and iron supplementation on arsenic accumulation in different tisues of rat. Thesis (BSMMU) 2002.
23. Steinmaus C, Carrigan K, Kalman D, Atalla R, Yaun Y, Smith AH. Dietary intake and arsenic methylation in a U. S. population. Environ Health Perspect. 2005; 113: 1153-59.
24. Misbahuddin M, Islam AZMM, Khandker S, Mahmud IA, Islam N, Anjumanara. Efficacy of spirulina extract plus zinc in patients of chronic arsenic poisoning: A randomized placebo-controlled study. Clinical Toxicol. 2006; 44: 1-7.
25. Modi M, Gupta R, Prasad GBKS, Flora SJS. Protective value of concomitant administration of trace elements against arsenic toxicity in rats. J Tissue Research 2004; 4 (2): 257-262.
26. Chaudhuri AN, Basu S, Chattopadhyay S, Das Gupta S. Effect of high arsenic content in drinking water on rat brain. Indi J Biochem Biophy. 1999; 36: 51-54.
27. Wu MM, Chiou HY, Wang TW, Hsueh YM, Wang IH, Chen CJ, Lee TC. Association of blood arsenic levels with increased reactive oxidants and decreased antioxidant capacity in a human population of northeastern Taiwan. Environ Health Perspect. 2001; 109: 1011-17.
28. Khandker S, Dey RK, Islam AZMM, Ahmad SA, Mahmuh IA. Arsenic-safe drinking water and antioxidants for the management of arsenicosis patients. Bangladesh J Pharmacol. 2006; 1: 42-50.
29. Rabbani GH, Saha SK, Marni F, Akhter M, Alauddin M, Mitra AK et al. Antioxidants in detoxification of arsenic induced oxidative injury in rabbits: Preliminary results. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2003; 38: 273-87