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Mercury toxicity and its management: need of the hour

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Abstract
Mercury known as quick silver, it can be easily alloyed with many other metals, such as gold, silver and tin. It exists in several forms namely, organic mercury (ethyl mercury and methyl mercury), elemental mercury, and inorganic mercury (mercuric mercury) compounds. The most devastating tragedies related to mercury toxicity in recent history include Minamata Bay and Niagata, Japan in the 1950s, and Iraq in the 1970s. Recycling from atmospheric emission, deposition in water reservoirs and exposure and bioaccumulation in animals and humans is a known example of mercury cycle in the environment. Metal-induced carcinogenicity has been a research subject of great public health interest. Generally, carcinogenesis is considered to have three stages including initiation, promotion, and progression and metastasis. The impact of Hg exposure on endothelial cell physiology is well established; however, the limit of dietary-derived Hg needed to trigger cardiotoxic effects is still debatable. Diagnosis of mercury overload is difficult. Nanotechnology may help to decrease water pollution problems by removing microorganisms, pesticides, insecticides and heavy metals (lead, mercury, cadmium, zinc).

Keywords: Mercury toxicity, Heavy metal, Minamata disease

Introduction
Mercury is a heavy metal belonging to the transition element series of the periodic table and having an atomic number 80. It is a liquid metal at room temperature and pressure. Known as quick silver, it can be easily alloyed with many other metals, such as gold, silver and tin [1]. It exists in several forms namely, organic mercury (ethyl mercury and methyl mercury), elemental mercury, and inorganic mercury (mercuric mercury) compounds. Each having its own profile of toxicity [2]. US Government Agency for Toxic Substances and Disease Registry ranked mercury third of the most toxic elements or substances on the planet following arsenic and lead that continues to be dumped into our waterways and soil, spilled into our atmosphere, and consumed in our food and water [3]. Mercury has a long and interesting history of the resultant toxicity produced. In high enough doses, all forms of mercury can produce toxicity [4]. The most devastating tragedies related to mercury toxicity in recent history include Minamata Bay and Niagata, Japan in the 1950s, and Iraq in the 1970s [5]. Human activities have nearly tripled the amount of mercury in the atmosphere and the atmospheric burden is increasing 1.5 percent per year. Much of the mercury comes from coal-fired plants and from chlor-alkali plants that use mercury in the process of making chlorine used in plastics, pesticides, polyvinyl chloride (PVC) pipes, and more [6].

States of Mercury
Environmental mercury which exist in its elemental form, as inorganic mercury or as organic mercury. In its elemental form, mercury exists as liquid metal. Elemental (or metallic) mercury is a shiny, silver-white metal and is popularly used in older thermometers, fluorescent light bulbs and some electrical switches [7]. When dropped, elemental mercury may break into smaller droplets can seep through small cracks and gets attached to materials. Having low vapour pressure (2 µm Hg), can be converted to toxic vapour at room temperature due to its low latent heat of evaporation (295 kJ/kg) and its relative absence from ambient air. If heated, it is a colourless, odourless gas [8]. Once oxidized, mercury vapours are lipid soluble and act as the potential risk for bioaccumulation in the renal cortex, liver, and especially the brain. It is estimated that the half-life of mercury in the brain can be as long as 20 years [9]. Elemental mercury is an element that has not reacted with another substance. When mercury reacts with another substance, it forms a compound.
When mercury combines with carbon, methyl mercury and other organic mercury compounds are formed. Microscopic organisms play a substantial role in this stage. They help in converting mercury into methyl mercury [10]. MeHg which is readily transported by water into the aquatic

ecosystems. Because of its low water solubility it is considered to be relatively lipid soluble. MeHg is easily taken up by lower organisms, tends to work its way up the food chain and bioaccumulate in fish [11]. The U.S. Environmental Protection Agency (EPA) has determined that eating mercury-contaminated fish is the primary route of exposure to mercury for most people. Fish are the main source of food for many birds and other animals, and mercury can seriously damage the health of these species. Loons, eagles, otters, mink, kingfishers and ospreys eat large quantities of fish. Because these predators rely on speed and coordination to obtain food, mercury may be particularly hazardous to these animals. Inorganic mercury compounds take the form of mercury salts and are generally white powder or crystals, with the exception of mercuric sulphide (cinnabar) which is red. Most uses of inorganic compounds have been discontinued [12]. Recycling from atmospheric emission, deposition in water reservoirs and exposure and bioaccumulation in animals and humans is a known example of mercury cycle in the environment [13].

Environmental Exposure

There is a serious concern of environmental pollution following handling of mercury compounds, for example; dumping inorganic mercury along the Amazon River in Brazil, pit-working in gold mines in Tanzania, Indonesia, and the Philippines, Ecuador, Faroe islands, French Guiana, New Zealand, Peru, Seychelles island and Slovenia [14, 15] Humans exposure to mercury usually take place via eating mercury contaminated food, dental care procedures (using amalgams in endodontics) using mercury based, thermometers, and sphygmomanometer), occupational exposure (e.g. mining) and others (using fluorescent light bulbs and batteries) [16]. Mercury settles into bodies of water like lakes and streams, or onto land, where it can be washed into water. Other compounds of mercury, like phenylmercury acetate and ethylmercury, have been commonly used as fungicides, preservatives, antiseptics (e.g., Mercurochrome, a trade name of the antiseptic merbromin) or disinfectants. They have also been used in a variety of products. Most uses have been discontinued. Some medicines use small amounts of these compounds as preservatives such as thimerosal [17]. Methylmercury is the most frequently encountered compound of the organic form found in the environment, and is formed as a result of the methylation of inorganic (mercuric) forms of mercury by microorganisms found in soil and water [18]. Mercury is utilized in the electrical industry (switches, thermostats, batteries), dentistry(dental amalgams), and numerous industrial processes including the production of caustic soda, in nuclear reactors, as antifungal agents for wood processing, as a solvent for reactive and precious metal, and as a preservative of pharmaceutical products [19].

Epidemiology

Metallic mercury intoxication was known in ancient times by Aristotle, but that large scale occupational poisoning with mercury had occurred when the great statue of Buddha of Nara was constructed in 8th century in Japan [20]. In 20th century, two big disasters of mercury poisoning had been reported. Minamata disease which resulted in poisoning of 2200 peoples due to consumption of mercury contaminated fishes and shell fish in Kyushu, Japan. During 1950s and 1960s, other case was reported in Niigata (the main island of Honshu, Japan) with approximately 700 victims [21]. During 1955-1956, three epidemics of mercury poisoning cases have been reported in Iraq. The largest outbreak was in 1971-1972 in the rural population following the consumption of mercury contaminated homemade. Based on official reports, 6530 patients were hospitalized and 459 persons died [22, 23]. Governmental and nongovernmental organizations should prepare basic data about mercury poisoning and design informative and educational programs on mercury poisoning in order to substantially reduce the incidence of poisoning with mercury

Molecular Mechanism of Mercury Toxicity

Humans are exposed to all forms of mercury through accidents, environmental pollution, food contamination, dental care, preventive medical practices, industrial and agricultural operations, and occupational operations [24]. According to recent studies it has been shown that mercury vapors from handling of amalgam, can be hazardous for dental staffs [25] In biological systems, heavy metals including mercury have been reported to affect cellular organelles and components such as cell membrane, mitochondrial, lysosome, endoplasmic reticulum, nuclei, and some enzymes involved in metabolism, detoxification, and damage repair [26]. Methyl mercury induces oxidative stress and the free radicals may cause neurotoxicity. On the other hand, it has been reported that accumulation of serotonin, aspartate, and glutamate has a role in mechanism of methyl mercury induced neurotoxicity [27]. Through, oxidative stress mercury has shown mechanisms of sulfhydryl reactivity. Once in the cell, both Hg2+ and MeHg form covalent bonds with cysteine residues of proteins and deplete cellular antioxidants. Antioxidant enzymes serve as a line of cellular defense against mercury compounds [28] both organic and inorganic mercury have been shown to alter calcium homeostasis but through different mechanisms. Organic mercury compounds (MeHg) are believed to increase intracellular calcium by accelerating the influx of calcium from the extracellular medium and mobilizing intracellular stores, while inorganic mercury (Hg2+) compounds increase intracellular calcium stores only through the influx of calcium from the extracellular medium [29]. Methyl mercury is converted to inorganic form in CNS that binds to sulfhydryl containing molecules. Inorganic mercury and methyl mercury bind to thiol containing protein e.g. glutamine, cystein, albumin and etc. These complexes affect the distribution of mercury in the body [30]. Metal-induced carcinogenicity has been a research subject of great public health interest. Generally, carcinogenesis is considered to have three stages including initiation, promotion, and progression and metastasis [31]. Although mutations of DNA, which can activate oncogenesis or inhibit tumor suppression, were traditionally thought to be crucial factors for the initiation of carcinogenesis, recent studies have demonstrated that other molecular events such as transcription activation, signal transduction, oncogene amplification, and recombination, also constitute significant contributing factors [32].

Toxicity and Its Management

Mercury, a systemic toxicant known to induce adverse health effects in humans, including cardiovascular diseases, developmental abnormalities, neurologic and neurobehavioral disorders, diabetes, hearing loss, hematologic and immunologic disorders, and various types of cancer. The main pathways of exposure include ingestion, inhalation, and dermal contact. The severity of adverse health effects is related to the type of heavy metal and its chemical form, and is also time-and dose-dependent [33]. Symptoms of low-grade chronic exposure are

more subtle and nonspecific: weakness, fatigue, anorexia, weight loss, and gastrointestinal distress, sometimes referred to as micromercurialism. At higher exposures, the mercurial fine tremor punctuated by coarse shaking occurs; erethism, gingivitis, and excessive salivation have also been described, as has immune dysfunction [34]. Reduced color vision and visual acuity have also been observed changes in coordination, tremor, mental concentration capacity, facial expression, and emotional state are also described, as are polyarthritis, various forms of dermatitis, and a syndrome mimicking pheochromocytoma [35]. The impact of Hg exposure on endothelial cell physiology is well established; however, the limit of dietary-derived Hg needed to trigger cardiotoxic effects is still debatable. When inorganic mercury compounds are absorbed into bloodstream, the highest concentration (about 85-90%) found in the kidneys. Inorganic mercury salts are taken up and accumulated in the proximal tubules of the kidneys [36]. Clinical findings are polyuria and proteinuria (especially low molecular proteinuria) which are the main indicators of tubular damage in kidneys. In severe conditions, patients suffer from nephrotic syndrome with hematuria and anuria [37]. Chronic inorganic mercury exposure can cause immune complex nephritis, especially membranous nephropathy. In humans, long term exposure to mercury has been accompanied with immunological glomerular diseases which is responsible for mercury-induced nephropathy [38] In addition to salivation, gingivitis, gingival bleeding, oral stomatitis, corrosive damage to the mouth and throat have also been observed. The symptoms of acute inorganic mercury inhalation include dyspnea, chest pain, tightness, and dry cough, which are followed by acute chemical pneumonitis and bronchiolitis [39]. Another clinical manifestation is shock that causes to massive fluid loss, and acute tubular necrosis. The predominant manifestations of sub-acute or chronic mercury intoxication include GI symptoms, neurologic abnormalities and renal dysfunction [40]. Mercury compounds show toxic effects on the skin in many ways. Most common symptoms of contact dermatitis after exposure to mercury compounds include mild swelling, vesiculation, scaling, irritation, urticaria and erythema. Allergic contact dermatitis accompanied by pain, is the most important form of mercurial reaction in skin that can occur by both topical and systemic exposure [4]. Diagnosis of mercury overload is difficult. The commonly used modalities (blood, urine, and/or hair levels) do not correlate with total body burden and offer little diagnostically useful information. Chlorella and cilantro as food materials can detoxify some neurotoxins such as heavy metals (e.g. mercury) and toxic chemicals (e.g. phthalates, plasticizers and insecticides) [42] Nanotechnology may help to decrease water pollution problems by removing microorganisms, pesticides, insecticides and heavy metals (lead, mercury, cadmium, zinc). Nano-catalysts and nano-filters can eliminate toxic contaminants from waste waters [43].

Conclusion

There are currently no consensus criteria for the diagnosis of mercury overload, nor for overload of other toxic metals. Clinicians who specialize in this area generally consider a provoked urine metal output more than 2 standard deviations above the NHANES reference range a positive result. Further research is required to clarify the relation between provoked urine results and clinical disease and to document clinical outcomes. In many areas of mercury metal pollution, chronic low dose exposure to multiple elements is a major public health concern. Elucidating the mechanistic basis, interactions is essential for health risk assessment and management of chemical mixtures. Hence, research is needed to further elucidate the molecular mechanisms and public health impact associated with human exposure toxic mercury.

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