Public Health Department Response to Mercury Poisoning: The Importance of Biomarkers and Risks and Benefits Analysis for Chelation Therapy

Charles A. McKay, Jr.

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Abstract Chelation therapy is often used to treat mercury poisoning. Public health personnel are often asked about mercury toxicity and its treatment. This paper provides a public health department response to use of a mercury-containing cosmetic in Minnesota, a perspective on two unpublished cases of chelation treatment for postulated mercury toxicity, and comments on the use of a nonsystemic treatment for removal of mercury following the Iraqi seed coat poisoning incident. Physicians should evaluate sources of exposure, biomarkers, and risks and benefits before recommending chelation therapy for their patients. Potential risks to chelation therapy and its little understood subtle or latent effects are areas of public health concern.

Keywords Chelation therapy · Mercury poisoning · Sources of exposure · Biomarkers · Risks and benefits

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C. A. McKay Jr. (✉)
Division of Medical Toxicology, Department of Emergency
Medicine, Hartford Hospital/University of Connecticut School of
Medicine, American College of Medical Toxicology, 10645 N.
Tatum Blvd. Suite 200-111, Phoenix, AZ 85028, USA
e-mail: Charles.McKay@hhchealth.org

Background

Public health department professionals frequently receive inquiries about heavy metal exposure and chelation treatment. A very common call relates to mercury, particularly as most health departments have provided health advisories regarding organic mercury and fish consumption by at risk populations, namely pregnant women [1].

As with any metal, it is critical to understand the sources of exposure for mercury poisoning, as well as the risks and benefits of treatment before considering chelation therapy to treat toxicity. An important first step is to confirm that there has, in fact, been an exposure, and that the exposure is a likely cause of disease or toxicity. Toxicity is caused by extraordinary exposure. This can occur from an atypical environmental exposure to a substance or an occupational exposure. Limited and trivial exposures, such as inhalation exposures to a broken fluorescent light bulb or from living downwind of a coal-fired power plant, will not result in toxicity. However, individuals with repeated exposure in the workplace, for example in a fluorescent light bulb recycling plant, could have exposure-related symptoms.

It is important to evaluate the biomarkers of exposure. The biomarkers of metal exposure are extremely complex, and physicians are not always aware of important caveats in their use. For example, there are three types of mercury: elemental, inorganic, and organic. Testing matrix is very dependent on the chemical species (type) and nature of exposure.

The most effective treatment for metal toxicity is stopping any excessive exposure. The benefits and risks of chelation treatment should be addressed. Chelation may have some impact on health symptoms if the exposure was recent but removing metal from the body does not guarantee an

improvement in symptoms or a positive long-term prognosis. There are risks to chelation therapy; there is additional public health concern regarding its seldom researched subtle and latent effects.

Examples of Historic Exposures and Toxicity

Exposure to elemental mercury vapor was widespread, historically, due to its use in medicines, electrical switches, and medical instruments. In the 1970s, mercury levels in two hospitals in Canada were studied. Investigators estimated that 1,800 mercury thermometers broke yearly in one hospital, creating elevated mercury vapor concentrations in many areas of the hospital [2]. Cultural practices within a home can influence household background air exposures to mercury and are sometimes the cause of exceptional exposures. Cultural practices include the medicinal use of mercury as a bulk laxative agent or religious uses to ward off evil spirits [3] or cosmetic uses in personal care products—primarily skin-lightening creams. This latter use can be a source of inhalation exposure to the elemental mercury vapor as well as dermal exposure to inorganic mercury.

Historically, the most widespread and harmful exposure to inorganic mercury was caused by the use of calomel (mercurous chloride) in teething powder. These exposures caused thousands of cases of acrodynia in children from the 1920s into the 1950s. In the early 1950s, a few years after the link between mercury exposure and acrodynia in children had been discovered, it was estimated that 3.6 % of the pediatric patients admitted to one hospital in England suffered from acrodynia. Of these, an estimated 10 % died. Acrodynia largely disappeared in the 1950s when the use of calomel was discontinued [4]. There are far fewer cases of acrodynia today. In 1989, a child in Michigan had acrodynia from exposure to mercury vapor released from phenylmercuric acetate, an organic fungicide used in paint [5]. This incident led to banning the use of mercuric fungicides in paint. In 2007, there was a case of acrodynia in Minnesota that was caused by exposure to elemental mercury. This case is discussed below.

Recently, some states have seen cases of inorganic mercury exposure attributed to the use of skin-lightening creams, which may contain over 3 % mercury by weight [6]. Mercury in these creams is generally assumed to be inorganic, but other forms may be used as well. Symptoms of exposure have been seen in adults, and elevated biomarkers of exposure (typically urine) have been seen in people using the creams and even in non-using family members [7].

Merthiolate (also known as thimerosal) and mercurochrome were commonly used organic mercurial topical antiseptics that have been replaced in the last 20 years or so by more effective creams. The often-overstated concerns about toxicity of thimerosal are discussed elsewhere in this

publication. Historically, there have been a few extremely high, well-documented population exposures to methylmercury accumulated in fish (e.g., Minamata Bay, Japan [8] and others) and to methylmercury used as an antifungal seed coat (e.g., Iraq [9] and others).

Minnesota Department of Health Response to Mercury-Containing Skin Creams Being Marketed in Ethnic Communities

In 2011, concern was raised in Minnesota and elsewhere around the USA about exposures to mercury in skin-lightening creams. There have been a few reports of health impacts consistent with mercury exposure accompanying elevated urinary mercury measurements in exposed individuals (for example [7]). In Minnesota, a local public health official initiated concerns about exposures in an immigrant community to mercury in these products.

The Minnesota Department of Health (MDH) Public Health Laboratory analyzed 27 samples of skin-lightening cream taken from the shelves of stores in ethnic communities, including Southeast Asian, Middle Eastern, and African immigrant communities in the Twin Cities. Eleven of these samples contained high levels of mercury, ranging from 300 ppm up to 3.3 % mercury. MDH, with assistance from the Regional Poison Center reached out to the potentially impacted communities. Meetings were held with community leaders and physicians serving those communities to inform them about the issue and to try to develop strategies to decrease the use of the mercury-containing skin creams. MDH developed a webpage for public information on the incident (<http://www.health.state.mn.us/topics/skin/>) and also created a one-page guide on skin-lightening creams for physicians (<http://www.health.state.mn.us/topics/skin/provfs.html>). The guide advises physicians to ask about skin-lightening creams while taking a patient's history and to contact the poison center or medical toxicologist if a patient is symptomatic [6].

Case Examples of Chelation Decisions

Case 1: Acrodynia

The MDH is occasionally contacted by physicians or the general public with questions about the possible relationship between exposures to chemicals and disease. In 2007, MDH was contacted by a pediatric nephrologist about a 7-year-old child with symptoms, including hypertension, tachycardia, profuse sweating, and pain in the extremities, who had been initially diagnosed with pheochromocytoma. However, the diagnosis could not be confirmed in imaging studies. Mercury biomarkers were considered by the attending physician as

somewhat equivocal (when inappropriately compared to occupational reference levels). However, the physician contacted MDH for additional information about mercury biomarkers of exposure and mercury toxicity. Because biomarkers in the child were clearly above normal population levels, symptoms matched acrodynia, and experience has shown that biomarkers in children with acrodynia may be lower than levels associated with occupational exposure [10–12], a home investigation was conducted. Using a handheld mercury vapor analyzer, a significant but invisible source of mercury vapor was found in a carpet. The carpet was removed and mercury vapor concentrations in the home decreased to normal levels within hours.

Medication was used to treat the patient's hypertension, successfully lowering it. Other symptoms began to resolve following cessation of the exposure. The child's exposures took place over the period of almost a year, so the exposure was not acute. Nevertheless, the patient was treated by a medical toxicologist with DMSA. The patient had two regimens over a 2-month period, but it still took 5 months for his blood pressure to remain low when he was weaned from medication. In the absence of definitive guidelines, in a patient with severe symptoms with somewhat elevated biomarkers of exposure, it seemed reasonable to treat the symptomatic patient. However, it is unclear if the use of the chelating agent hastened resolution or improved the course of the disease in this child.

Case 2: Patient Described as “Toxic” for Four Metals

A 55-year-old man with memory loss and depression had been told by his physician that he was “toxic” for mercury, selenium, lead, and thallium. The patient had been chelated in multiple sessions covering a period over 6 months. MDH was contacted because the patient was concerned about whether he was going to be able to afford continuing chelation therapy. Chelation therapy was administered by the physician based on “toxin testing” of the patient with a multi-analyte panel by a laboratory frequently used by alternative practitioners. The patient's test results showed that the four metals were above the reference ranges utilized by the laboratory. The explanation for the selenium exceedance was fairly clear as the patient was taking a selenium supplement. There were no known extraordinary exposures to mercury, lead, or thallium.

As will be discussed elsewhere in this publication, there are numerous problems with these multi-analyte “toxin testing” panels. In this case, the patient's sample was obtained “postprovocation,” indicating that he had received a chelating agent prior to collection of the urine specimen. This will elevate levels for most metals in urine and will make comparison with normal population reference ranges useless. In addition, reference ranges for this test were chosen based on

population data (e.g., National Health and Nutrition Examination Surveys (NHANES)), not on information that suggests an association between metal concentrations in urine and disease. The statistical chance that someone will have urine concentrations outside of a population-based reference range increases as the number of tested analytes increases. Even without the false elevation related to postprovocation testing, it is likely that much of the population will be outside a 95 % population reference range (not a “toxic range”) for at least one analyte when many chemicals are assayed. Laboratories catering to “toxic testing” often test for 20 or more metals at a time.

Chelation is not a low-risk treatment. It is very important that the risks and the benefits of such a treatment are realistically considered. The 55-year-old individual was referred to a medical toxicologist for a clinical consultation on metal toxicity. However, he was also advised that the most effective treatment for metal toxicity is removal of exposure.

Mercury Chelation in the Setting of Widespread Methylmercury Toxicity

Chelation therapy is a nonspecific systemic treatment that removes sequestered metals from stores in the body, reactivating some toxic metals and causing indiscriminate excretion of essential metals along with toxic metals. Thiolated resins bind to mercuric compounds and because when administered orally, they are not absorbed into the body, they can scavenge mercury in the GI tract and remove it in feces. Clarkson et al. examined the use of an oral thiolated resin in the methylmercury poisonings in Iraq in 1971–1972 [13]. The thiol resins and systemic chelating compounds sodium 2,3-dimercaptopropane-1-sulfonate (DMPS), D-penicillamine and *N*-acetyl-DL-penicillamine were administered to poisoned individuals one to several weeks following the end of contaminated bread methylmercury exposure. Compared to a nontreatment and placebo treatment groups, the blood half-life for methylmercury was decreased in all treatment groups. Half-lives were decreased from the normal 60–65 to 10 days following treatment with DMPS, 20 days for the thiol resin treatment, and 26 and 24 days following treatment with the two penicillamine derivatives. These data suggest that even with delayed treatment of methylmercury exposure, thiol resin treatment may decrease the total mercury exposure as measured in an area under the concentration–time curve (AUC).

Unlike systemic chelating agents, thiol resins taken orally are not absorbed into the body, but are confined to the GI tract. Methylmercury excretion is primarily in bile; however, much of the methylmercury that is in enterohepatic circulation is reabsorbed in the intestine. Thiol resin appears to increase fecal excretion by binding to methylmercury in the intestine

decreasing its reabsorption [14]. Modeling by MDH suggests that immediate thiol resin treatment might decrease methylmercury AUC exposure by 60–70 %, and if treatment is delayed 4 months, the AUC may be decreased by about 15–20 % compared to no treatment. If, as demonstrated in animal models, 40–90 % of the methylmercury in the blood may come from reabsorption [14], then relatively noninvasive treatment with thiol resins may decrease methylmercury in blood of individuals with high methylmercury levels. These types of treatment may engender less risk than chelation and should be further evaluated for safety and for their effectiveness in treatment of people with high blood methylmercury levels.

Discussion

State health agencies are often consulted about the proper interpretation of biomarkers of exposure. For each specific chemical exposure, the proper matrix needs to be tested. Methylmercury is heavily concentrated in the red blood cells and is excreted in feces, thus urine is an inappropriate matrix to test for methylmercury. On the other hand, the half-life of inorganic mercury in blood is quite short, so looking for inorganic mercury exposure in blood may be problematic. Elemental mercury travels freely in the body, but it is metabolized into inorganic mercury salts in a relatively short time. As a result, exposure to elemental mercury may result in different tissue exposure, but it is excreted in urine as well as feces as inorganic mercury salts. The use of nonstandard biomarkers (such a red cell mass measurements, as opposed to whole blood measurements) is problematic because of the lack of appropriate standards for comparison. However, the most troublesome biomarker testing error is the use of postprovocation data by some health practitioners.

Comparing biomarkers with reference ranges from population statistics is not the same as comparing the levels with health (or toxicity) benchmarks. Biomarkers for most metals outside of the 95 % range for the USA population cannot be assumed to be associated with adverse health effects. Multi-analyte “toxics” testing is conducted for the express purpose of demonstrating that “toxins” need to be removed from the body. It is not conducted to evaluate whether specific symptoms may be associated with an exposure. Reference ranges noted by the commercial laboratories performing multi-analyte “toxics” testing are selected by the laboratories themselves. Furthermore, while different levels of concern are often appropriate for different segments of the population, these details are often lost when toxicologists are not consulted. In the case of methylmercury testing in blood, reference ranges are set based on concern for women of child-bearing age and pregnant women not middle-aged men. [15] Levels of concern for men are considerably higher than levels of concern for women of child-bearing age.

Chelation treatment of asymptomatic or mildly symptomatic patients is unlikely to benefit patients and may actually cause harm, as discussed elsewhere in this publication. Patients seek clear cause–effect relationships for their “poisoning,” but it is not always possible to determine the cause of symptoms. Physicians should seek a thorough diagnosis in spite of the pressure to find a simple environmental culprit. Internet advertising by marketers of “toxic testings” have made testing and treatment popular in some alternative medicine practices and has encouraged some people with health problems to seek these treatments. However, it is not possible to remove all “toxins” from the body, and treatments remove essential elements as well. Furthermore, the efficacy of chelation treatment has not been generally demonstrated for all but severe recent acute exposures to a few metals. In addition to concerns about short-term adverse impacts that may result from chelation, public health practitioners are also concerned about the potential subtle and latent effects that have not been characterized.

In responding to citizen’s requests for information, public health officials are often confronted by extremely emotional appeals to solve personal health problems. Commercial laboratory marketings “toxin testing” offer hope that there is another treatment option. They also appear to prey on the guilt of caregivers, suggesting that not every treatment option has been tried until chelation products are used. However, no assessment of the true risks and benefits of chelation treatments are being provided.

Conclusion

Chelation therapy is typically not the most appropriate treatment for postulated or even proven metal toxicity. Guidance for physicians is needed regarding the appropriateness of chelation, and most importantly, how a proper assessment of chelation risks and benefits analysis can be conducted. More attention to the possibility of subtle and latent effects from both metal exposure and from chelation is needed.

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