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NEPHROLOGY – CASE REPORT

Lessons learned from a fatal case of mercury intoxication

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Abstract
Context While many cases of metallic mercury poisoning have been reported, cases of metallic mercury poisoning from multiple exposure routes are rare.
Case presentation We report the case of a 36-year-old Latin American male who presented with rash, sore throat, fever, chills, cough, and diarrhea after chronic mercury vapor exposure and likely intravenous injection. Despite chelation treatment with meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercaptopropanesulfonic acid (DMPS), the patient's clinical course was complicated by renal failure and he passed away after 18 days.
Discussion The most striking aspect of this case is that despite use of chelators, a dramatic *increase* in blood mercury level occurred. We discuss the rationale for combined use of chelators with hemodialysis and other treatments such as plasma exchange in the setting of acute mercury poisoning. This case also illustrated the potentially serious side effects of the chelation drug DMSA, and we discuss the potential relevance of dosing frequency to the occurrence rates of such side effects.
Relevance to clinical practice Despite the tragic outcome, on review of case literature, we believe this case provides valuable lessons concerning the use of DMSA and DMPS to treat mercury toxicity, particularly with regard to the combined use of chelation agents and hemodialysis.

Keywords Mercury · Chelation · DMPS · DMSA · BAL · Dialysis · Heart · Hemofiltration

Abbreviations

DMSA	Meso-2,3-dimercaptosuccinic acid
DMPS	2,3-Dimercaptopropanesulfonic acid
ECG	Electrocardiogram
BAL	British anti-lewisite
CT	Computed tomography
PT	Prothrombin time
CK	Creatine kinase
ICU	Intensive care unit
CVVHD	Continuous veno-venous hemodialysis

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Introduction

The chemical forms of mercury can be classified into three groups with distinct biochemical interactions: metallic mercury, inorganic mercury, and organic mercury. Due to its unique physical and chemical properties, metallic mercury (also known as elemental mercury) has found widespread use both within industry and in many everyday objects such as thermometers, dental amalgams, batteries, fluorescent light bulbs, and many others.

Metallic mercury vapor has long been recognized as a potent toxin and cases prominently feature respiratory symptoms [1, 2]. Severe cases can result in death. Cases of injection of metallic mercury have also been reported. Typically, these occur with suicidal intent [3, 4], but occasionally occur with other motives in mind—such as to ward off evil [5]. In the case of IV injection of metallic mercury, pulmonary embolization of mercury globules is common and cases present with dyspnea, chest pain, cough, and fever [3]. ECG changes [3, 6], renal impairment, and dermatological symptoms [3] can also occur. By contrast, subcutaneous injections typically lead to localized inflammation, granulation tissue, and abscess formation [4, 5], with systemic involvement arising from the absorption of mercury by the tissues [4].

Treatment frequently involves the dithiol chelators meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercaptopropanesulfonic acid (DMPS), which have largely replaced the older drug British anti-lewisite (BAL). While these drugs are known to increase mercury excretion and relief from symptoms has been reported [3], these drugs carry an appreciable risk of side effects [7].

Case report

A 36-year-old Latin American male with no prior medical history presented to the Emergency Department with a chief complaint of itchy macular rash on his trunk of 10-day duration. Review of systems was positive for sore throat, fever, chills, generalized joint pain, cough productive of white sputum, and watery diarrhea that developed during the same period. He had no allergies, did not take any medications regularly, smoked one packet of tobacco daily for 20 years, smoked marijuana and snorted cocaine, and rarely drank alcohol. He lived with his wife in El Paso and worked as a metal scrubber. On presentation, his temperature was 102.2°C (*provide temperature in °C as well*), pulse 94 beats per minute, blood pressure 110/65 mmHg, and respiratory rate 20 breaths per minute. Physical examination was remarkable for pharyngeal erythema, macular erythematous rash over the trunk and extremities, and multiple scars related to burns and trauma at his work. Laboratory test results revealed a leukocyte count of 11,400/dl, 51% were Segmented, 12% Eosinophil, 12% lymphocytes and 19% bands. Aspartate aminotransferase (AST) was 36, and Alanine aminotransferase (ALT) was 40. A chest radiograph showed massive radio-opaque material in the lungs, the right atrium and the right ventricle, which was later confirmed by a non-contrast computed tomography scan (CT) of the chest (Fig. 1). The radiologist expressed concerns that the patient might have been exposed to oleous iodine contrast and could be suffering from a chemical pneumonitis. However, the only previous imaging of the patient was a CT of the abdomen without contrast, performed 1 year prior to admission after a minor accident.

A consult for Infectious Diseases was placed, and the patient was "covered" with an empirical broad-spectrum antibiotic regimen, and a wide range of tests were ordered. On further questioning, the patient mentioned that he had been employed to recycle thermometers for 1 year, where he took thermometers

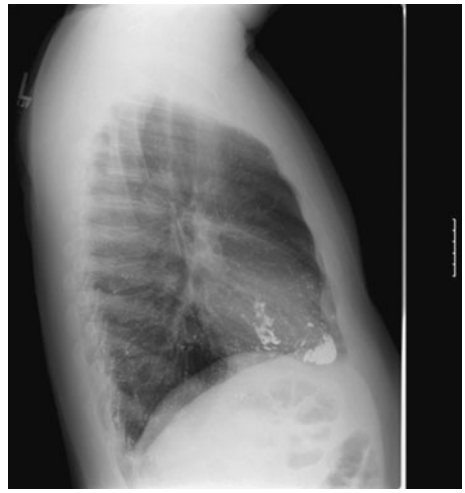

Fig. 1 Lateral chest radiograph showing intra-cardiac metallic mercury deposits

apart on a daily basis with a cutting device, vaporizing mercury in the process. He reported heavier exposure than usual 1 month prior to admission. *He denied any mercury injection.* A skeletal survey showed scant radio-opaque deposits in the kidneys, bowel wall, and bladder wall. However, a concentrated focus of material was not noted in peripheral sites.

Based on imaging, symptoms, and a positive history of exposure, a diagnosis of mercury intoxication was established and the toxicology team was informed. Chelation therapy was started on day 4 with DMSA 500 mg P.O. every 8 h. Mercury, lead, and cadmium levels were requested in blood and urine. Diagnosis was confirmed on day 6 with a mercury concentration of 244 ng/ml in the blood and 552 μg/spec in a 24-h urine collection (*provide normal levels if any*). Urine lead levels and blood cadmium levels were within normal limits.

Cardiology and cardiothoracic surgery were consulted. They determined that surgical intervention or intervention via cardiac catheterization was impossible. Given the finding of mercury in the right heart and that no markers of *subcutaneous* mercury injection were found on the patient's body surface, we believe that intravascular injection is the only way for mercury to have accumulated in his heart, despite the patient's denial. This would be consistent with previous reports [6, 8]. Given that the previous CT abdomen did not reveal any metallic cardiac deposits, we must assume they were present for less than 1 year. The motives behind a mercury injection in this case remain a mystery.

Up to day 6, the patient was feeling well and the DMSA was tolerated well, except for nausea. However, his generalized pain worsened and was not adequately alleviated with morphine injections. Emotional lability was also noted. He started to act aggressively with his family and house staff and began exhibiting fluctuations between a laughing and smiling state, and a sad and tearful state 1 minute later. In the ensuing 2 days, his AST and ALT doubled, the prothrombin time (PT) rose to 15.5 s, and the leukocyte count dropped to 1,900/dl. Increases in liver transaminases and mild to moderate neutropenia have been reported post-DMSA administration [7]. Therefore, there were concerns that the decreased leukocyte count and the increased liver transaminases were secondary to DMSA. Thus, it was held in the evening of day 8. A further decline in the total leukocyte and neutrophil count developed in the next day to reach 500/dl, 60/dl, respectively.

Despite the cooling measures, temperature increased to 104.3°C (*provide also in °C*). The patient developed rigors throughout the night. A complete metabolic panel the morning of day 10 revealed an increase in creatinine from 0.9 to 3 mg/dl, an increased anion gap metabolic acidosis, with normal potassium and magnesium. The total creatine kinase (CK) was 16,660 IU/l. Based on the presentation and the rise of creatinine and CK, the patient was diagnosed with acute kidney injury secondary to rhabdomyolysis, which was likely due to his severe chills. The administration of intravenous fluids of normal saline was initiated. However, within a few hours, the patient developed hypotension at 85/49 mmHg, pulse of 141 beats per minute, respiratory rate 27 breaths per minute, and oxygen saturation 87%, while he was breathing 6 l of oxygen by nasal canula. He appeared cyanotic, agitated, and in acute distress. Therefore, he was intubated and transferred to the ICU where hemodialysis was performed and supportive measures were given. As an alternative to DMSA, on day 12, DMPS was prescribed 250 mg intravenously every 4 h. Continuous Veno-Venous Hemodialysis (CVVHD) was established on day 13. The patient displayed severe skin desquamation on the neck and the trunk on day 14. On day 15, while there was a decrease in the transaminases and an increase in white cell count, *blood mercury concentration rose to 1,268 ng/ml*. The patient remained intubated, febrile, and hypotensive, despite the dopamine drip. At this point, DMPS was held due to concern over side effects. Despite IV fluids, the dopamine drip and DMPS being held, the patient continued to have low blood pressure until day 18 when he developed cardiovascular collapse and was pronounced dead.

On autopsy, a 2-cm diameter area of fresh necrosis was identified in the myocardium near the septum, and many small drops of metallic mercury were found in the blood and myocardium.

Discussion

The chelating agents DMPS and DMSA are considered to play a major role in the management of the mercury toxic patient. However, this unusual case

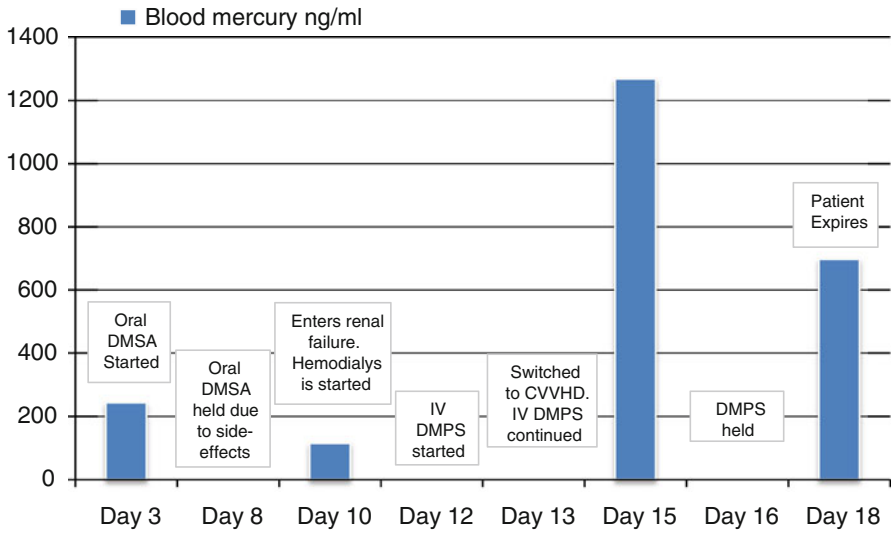

Fig. 2 Combined graph of treatment events and blood mercury levels in ng/ml

highlights several important aspects with regard to the clinical use of DMPS and DMSA.

Primarily, it is a *striking* feature of this case that despite treatment with chelators, *the patient's blood mercury level dramatically rose*. Unfortunately, daily mercury levels were not taken but we can see from Fig. 2 that between day 10 and day 15, mercury levels increased by >1,000 ng/ml. In analyzing why this occurred, it must be considered that DMPS was started after renal failure developed and hemodialysis was started. Since DMPS is primarily excreted via the urine, administration of DMPS in a setting of renal failure could mobilize mercury from any extracellular deposits within the body and redistribute it into the blood and organs due to failure to eliminate the mercury from the body. In this particular case, a large deposit of mercury was present within the heart.

While reports on the use of chelators in conjunction with dialysis are mixed [9–15], we believe that this can be explained. Recent studies on the binding of both DMSA and DMPS have shown that their binding ratios with mercury are typically not 1:1 and that $Hg_2(DMSA)_2$, $Hg(DMPS)_2$, and larger structures are typically formed [16]. Similar findings for BAL have previously been reported [17]. (It should be noted that these experiments were done at mercury concentrations above the physiological range). It is possible that such larger structures are too large to be filtered out by a standard hemodialysis membrane. (Note: the FDA label for Chemet (DMSA) advises that chelates with lead are non-dialyzable [7]). This would explain why, both in the current case and in past cases [10, 11, 14, 15], hemodialysis in combination with chelation failed to reduce the blood mercury level and in this case apparently increased it. Indeed, only one study we reviewed showed hemodialysis in combination with chelation to be effective at removing mercury from the blood; however, in this case, a "large pore dialyzing membrane" was used *specifically* to allow for the large size of Hg-BAL complexes [9].

Conversely, plasma exchange [11, 13, 15] and hemofiltration [11] have been reported as decreasing the blood mercury level effectively—plasma exchange being more efficient than hemofiltration [11]. Peritoneal dialysis has also been shown to be ineffective at clearing mercury [12, 13]. This is most likely explained by exchange/filtration of larger molecules such as blood proteins by both hemofiltration and plasma exchange and the fact that at least 99% of blood mercury is protein bound [12, 13, 18]. In the current case, blood mercury level decreased after DMPS was stopped. This was likely due to tissue absorption of blood mercury.

Finally, as seen in this case, the side effects of dithiol chelators can be significant in the acutely ill patient. According to FDA labeling of Chemet(DMSA) [7], it should be administered every 8 h. It should be noted that this schedule does not correspond with the half-life of DMSA (3.2 h [19]). This is significant since prescribing drug doses at half-life intervals can minimize fluctuations in blood levels of the drug, better maintaining the drug within its therapeutic range—thus decreasing the likelihood

of entering the toxic range of the drug [20]. Therefore, we propose that using lower chelator doses in accordance with drug half-life could minimize the risk of such serious side effects. We are not aware of any studies investigating the safety or efficacy of DMSA or DMPS administered on different dosing schedules.

Conclusion

We describe an unusual and fatal case of chronic elemental mercury inhalation coupled with suspected element mercury intravenous injection. Oral DMSA chelation was seen to produce side effects of elevated transaminases, neutropenia, and increased generalized pain after 6 days. Prescribing lower doses with a frequency equivalent to chelator half-life may be an effective strategy to reduce such side effects. Combined CVVHD with IV DMPS administration was seen to dramatically increase blood mercury levels (likely due to the redistribution of mercury from deposits in the heart). Analysis of this observation in the context of the published literature indicates that chelator-mercury complexes are non-dialyzable using a standard dialysis membrane and that plasma exchange and use of larger pore dialysis membranes are preferable methods to more efficiently remove mercury from the blood.

Conflict of interest We declare no competing financial interests.

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