Medical Toxicology Case Presentations: to Chelate or Not to Chelate, Is that the Question?

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Abstract Four case studies described in this article were presented to a panel of physicians participating in the ACMT “Use and Misuse of Metal Chelation Therapy” Symposium in February 2012. The individuals who participated in the panel are listed in the appendix. These cases highlight some of the practical questions facing medical providers when issues of metal toxicity and its treatment arise. Medical toxicologists are valuable resources for information, public debate, consultation, and treatment of patients with concerns about heavy metal exposure.

Keywords Chelation Therapy · Heavy Metals · Metal Toxicity · Case Presentations · Panel Discussion

Introduction

The author chose these cases involving his practice, based on their demonstration of issues related to toxicity from lead, mercury, arsenic, and uranium. Building on the information from the

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American College of Medical Toxicology (ACMT) chelation symposium and the papers published in this issue of *the Journal of Medical Toxicology*, the author’s management of these individuals can be assessed. The framework should be applicable to questions regarding exposure to other elements as well. Although some clinical information is not available or presented for all of the cases, the focus of each presentation is to address the following five issues:

- (1) The nature of the patient’s or individual’s concern
- (2) Information being relied on by the patient or individual
- (3) The role of testing for heavy metals
- (4) The role for chelation therapy
- (5) Information or systemic issues to reduce confusion or error and improve future care.

Case 1: Lead Exposure in an Extended Family

A 4-year-old boy came to medical attention because of a blood lead level (BLL) of 105 mcg/dL. This lab test was obtained as a delayed whole blood lead screen prior to school entry; he had missed earlier screening (at 1 or 2 years of age) because of frequent moving and family travel to Pakistan. Although he had no specific symptoms, a review of systems identified some intermittent abdominal pain for an indeterminate period of time. An additional five family members living in the same residence were subsequently identified as having elevated BLLs ranging from 68–84 mcg/dL. Reported symptoms were limited to crampy abdominal pain, constipation, a general sense of malaise, or just “not concentrating as well” as usual. Some individuals had no symptoms. Abdominal x-rays were obtained in some individuals; there were no discrete radiopacities. Of note, one woman (with a BLL of 51 mcg/dL) had a first trimester miscarriage several months earlier. Additionally, a 2-month-old infant family member had a BLL below the detection limit for that particular laboratory. Figure 1 depicts the BLL measurements of the family members over time. The red boxes indicate onset of 19-day courses of chelation with oral succimer.

An investigation by local and state public health departments, facilitated by a physician of similar cultural and language background, identified several potential low-level lead sources in the home, such as mini-blinds and candle wicks. A “test cook” of tomatoes performed in a frequently used cooking pot identified trace amounts of lead. None of these potential sources seemed of any significance, given the degree of BLL elevation. In addition, the lack of exposure in the infant suggested either a more remote timeframe of exposure and/or lack of a shared exposure source. These considerations—and the rebounding BLL in several individuals (identified in Fig. 1 as “Mother,” “Child,” and “Father”) implicating re-exposure—eventually led to the identification of an orange-yellow food coloring (Fig. 2). This was assayed in a public health laboratory as being 47 % lead by weight. The depicted bag had apparently been provided to the family from a relative who reportedly operated a restaurant somewhere in New York City, but that could never be confirmed. Communication between the family, area health departments, and others became difficult because of concerns about inter-family relationships and repercussions. Eventually, it appeared that relatives within at least four states had used this material or shared meals where exposure was likely. The very late rebound in the BLL of the person labeled “Father” in Fig. 1 occurred after a visit back to Pakistan, suggesting re-exposure in that country.

Addressing the questions posed to the panel at the ACMT Chelation Symposium:

- The nature of the patients’ concern:
The family was sufficiently concerned about Pb exposure and toxicity to agree to treatment and follow-up. However, their overriding concern was preservation of cultural and familial ties.
- Information being relied on by the patient:
As has been described elsewhere in this issue [1], cultural practice—in particular reference to this case, the

Fig. 2 Plastic bag containing an orange-yellow dye being used as food coloring in home meal preparation; contains 47 % Pb by weight

Ayurvedic medicine tradition—considers metals to be a component of the balance of *doshas* leading to strength as they do not degrade or decompose. [2, 3] The addition of a medical professional with cultural familiarity was an important step by the area health department, but that did not overcome the issues above.

- The role of testing for heavy metals:
Once the index case was serendipitously identified, blood lead testing was very useful in identifying exposed individuals. Serial BLL testing was also useful in assessment of the adequacy of exposure source identification and removal. As discussed elsewhere in this issue, the impact of chelation treatment on BLL decline can also be tracked, although correlation is lacking to clinical or subclinical improvement [4, 5].
- The role for chelation therapy:
Each of the individuals identified as having BLLs above 45 mcg/dL was treated with oral succimer in a standard fashion. It was pointed out by panelists at the ACMT Symposium that the FDA-listed indication for Pb treatment is for children with BLL >45 mcg/dL, and that does not

Fig. 1 Graph depicting BLLs in a family with a single-source Lead (Pb) exposure. Note impact of chelation on BLL (chelation course indicated by red squares) and rebounding BLLs with repeated exposure

necessarily include adults or common workplace exposures where removal from ongoing exposure and retesting is standard treatment. Some have argued that similar treatment strategies should be applied to adults as are currently recommended for children [6]. In particular, one of the symposium presenters, Dr. Donald Smith, noted that much of the recrudescence blood lead (even in children) comes from bone mobilization [7]. This makes the decision to chelate a given BLL even more problematic in view of redistributing lead from bone versus reducing brain exposure to lead [4, 5].

- Information or systemic issues to reduce confusion or error and improve future care:

Following identification of this case, an Epi-X report was filed. The FDA responded with additional interactions with FDA liaison employees overseas as part of the FDA's emergency management group in an attempt to prevent import of hazardous cultural products based on both potential and actual human health harm. Similar cases have led to a number of public health messages and warnings to consumers [8–10].

Case 2: Interpretation of Post-Provocation Challenge Specimens

An adult woman presented to the Toxicology Clinic with a chief complaint of difficulty sleeping. She had been to another practitioner who noted that she had several dental amalgams and, concerned that her insomnia reflected mercury poisoning, obtained a “red blood cell elements” test and post-provocation (parenteral DMPS dose) 6-h urine collection for a variety of elements. Her blood lead and mercury measurements were described and depicted as elevated, but they were actually at the 90 and 95 % values for the reference population. The urine mercury was described as “very elevated” at 21 mcg/g creatinine, with a reference range of 0–3 mcg/g creatinine listed in the lab report (contrasted to most commercial laboratory reference ranges of 0–25 mcg/g creatinine).

Addressing the questions posed to the panel at the ACMT Chelation Symposium:

- The nature of the patient's concern:

This patient was experiencing difficulty with sleep. Upon questioning, she revealed a number of stressful situations in her personal and vocational life that were adequate explanations for interval sleep difficulty.

- Information being relied on by the patient:

This person was relying on a post-provocation blood test result obtained by a practitioner who made a diagnosis of mercury toxicity attributed to dental amalgams. As detailed in the first case above, and elsewhere in this issue [11], metal toxicity occurs in the setting of extraordinary exposure. Dr. Jeffrey Brent, one of the panelists, stated that although this woman initially had concerns about her

health condition, that concern “has been inappropriately changed to being concerned about mercury toxicity. The job of the practitioner is to redirect her away from that and to go back to addressing her initial concerns, assuming her belief systems have not become fixed...”

- The role of testing for heavy metals:

The panelists agreed that it would likely be necessary to obtain a properly performed test, since a reportedly abnormal test result has already been obtained. Dr. Brent provides a discussion of an approach to retesting elsewhere in this issue [12]. One example of a proper test would be a non-provoked 24-h collection using an acid-washed container provided by a reliable laboratory. Critical issues in the patient preparation, performance, and interpretation of a mercury blood or urine test include the following:

- (1) Documentation of dietary contribution to short-term elevations or dietary modification during collection;
- (2) Use of trace metal-free collecting equipment and containers;
- (3) 24-h collection (for verification) without post-chelation provocation;
- (4) avoiding the inappropriate use of creatinine correction values derived in men for a woman due to large inter-individual variability in this measurement;
- (5) comparing values to established reference ranges; and
- (6) distinguishing reference range values from those associated with toxicity.

- The role for chelation therapy:

The panel agreed that there was no role for chelation therapy, in as much as this patient's symptoms were not consistent with mercury toxicity of any type, the testing performed was invalid, and an alternative explanation for symptoms was readily available. Of note, minor elevations in mercury concentrations are readily demonstrable in settings of increased chewing behavior in the presence of dental amalgams [13]. Such processes (jaw clenching, bruxism, chewing) could certainly accompany stress and poor sleep hygiene.

- Information or systemic issues to reduce confusion or error and improve future care:

For the individual patient, providing redirection to many of the stresses and patterns of response that lead to non-specific symptoms (stress response) may be beneficial. The need to address provoked challenge testing for heavy metals as currently promoted is an important part of this process. Informing the patient that the test was performed in a manner to maximize excretion of chelated elements, while then comparing that result to a reference range of non-challenged individuals may be sufficient. If not, comparisons to healthy populations undergoing chelation challenge as discussed elsewhere in this issue may

be useful [14]. Professional societies and state medical boards should use this information when assessing medical practice standards as well.

Case 3: Response to Concerns Raised by Media Reports or Studies

A mother called the poison center concerned that she may have poisoned her child with arsenic because a television personality (“TV doctor”) said there was too much arsenic in apple juice. She wanted to know if she should have her child tested for arsenic. This call was one of many similar calls, including those asking about boycotting juice, requesting schools dump the juice from lunch containers, etc.

Addressing the questions posed to the panel at the ACMT Chelation Symposium:

- The nature of the individuals’ concern:
These callers were concerned that something they had done was going to cause harm to their children because media reports used the words “poison,” “cancer,” and “contaminant” in conjunction with a beverage given to their children.
- Information being relied on by the patients:
Media portrayals of science or investigations are often characterized as lacking both depth and accuracy. This is unfortunate in that the media can be important in disseminating information regarding events and health-related warnings [15].
- The role of testing for heavy metals:
The panelists agreed that no testing was indicated in any situation related to such minimal exposure.
- The role for chelation therapy:
The panel was in agreement that there was no indication for consideration of chelation in this setting.
- Information or systemic issues to reduce confusion or error and improve future care:
While “sound bites” can never adequately convey the methods and limitations of a study or the problems with interpreting or applying the results, it would seem that a guideline sorting facts from fancy would include statements addressing:
 - (1) Characteristics of sample or population studied
 - (2) Comparison group
 - (3) Nature of findings
 - (4) Public health or personal impact

In the case of the arsenic and juice analysis (and subsequent reports on lead in juice and arsenic in brown rice sweetener) [16–18], the media reporting did not emphasize that only a minority (<10 %) of the samples contained arsenic or lead; nor that the elevations above a selected standard were minimal; nor that the comparisons were being made to risk-avoidant public health measures for drinking water (juice being

consumed in much lower quantities); nor that those public health levels were for theoretic prevention of chronic health impacts due to a lifetime of consumption [19]. It is incumbent upon medical toxicologists to educate the public as to the difference between “public health concerns” and actual “individual health risks.” By way of comparison, the US Environmental Protection Agency changed the drinking water standards for arsenic from 50 to 10 mcg/L in 2001 (enforceable for public water systems as of 2006) [20]; however, individuals with actual serious health effects from chronic exposure often consume water with arsenic at concentrations well above 500 mcg/L [21]. Some sense of social justice would suggest that more funding and attention should go to these worldwide issues. Alternatively, focus on US standards or the role of foreign imports and regulation of food or beverage “contaminants”—all reasonable policy issues—can be addressed without sensationalistic portrayals of imagined harm.

Case 4: Response to Broad-Spectrum Element Testing

An adult woman called for evaluation of testing results that “found 30 times the limit for aluminum and uranium and all these things in my system...I want to find out where I have been exposed and how to get rid of these things so I can be a well person again.” This particular person received her water from a private well. She had testing done that identified uranium at 100 mcg/L (threefold elevation above the Environmental Protection Agency (EPA) drinking water standard of 30 mcg/L) [22]. Subsequently, she had post-provocation urine testing with the results referred to above, as well as reported elevations of three other elements. There were no identified extraordinary sources of exposure to aluminum or other metals.

Addressing the questions posed to the panel at the ACMT Chelation Symposium:

- The nature of the patients’ concern:
This woman identified her concerns as general health status and fear about possible future kidney damage, chronic renal failure, a life of hemodialysis, and cancer.
- Information being relied on by the patient:
While some information came from her practitioner and material provided by the esoteric testing laboratory used, she also performed internet searches for the compounds of interest, including the EPA’s National Primary Drinking Water Regulations [22]. She assumed that exceeding a maximum contaminant level meant that one would be harmed by that substance. She was not aware of the protective role of default regulatory assumptions (“uncertainty” or safety factors) between concentrations and doses that have been demonstrated to cause harm and regulatory limits. Since these are many-fold different,

Table 1 Prioritization for response regarding inappropriate chelation practices

Action Response	Identified as within top 3 priority areas for action	Priority (on-site audience; <i>n</i> =38; % of responses)			Priority (webinar audience; <i>n</i> =9 sites; % of responses)		
		1st	2nd	3rd	1st	2nd	3rd
Public education	80 %	24	32	18	33	22	22
Medical practitioner education	75 %	29	24	18	22	33	11
Increased oversight by state medical boards	59 %	21	18	21	11	22	0
Increased product regulation (food, med, toys...)	39 %	16	11	16	11	0	0
Mandated laboratory proficiency testing for metals	32 %	0	13	13	11	0	33
Increased oversight by professional societies	16 %	5	0	8	0	11	11
Outreach to media	14 %	3	0	3	11	11	22
Other	3 %	3	0	0	0	0	0
No action is needed	0 %	0	0	0	0	0	0

Priority areas (1=highest) from ACMT Chelation Symposium audience survey (on-site and webinar) [listed as percent of total responses]

crossing a regulatory threshold does not mean that harm will occur, but only that safety factors are being encroached. In other words, public health standards are not the same as individual health risk limits.

- The role of testing for heavy metals:

The panelists were in agreement that testing in the absence of symptoms or findings referable to the agent of concern was not indicated. The use of post-provocation testing yields uninterpretable results. In addition, as discussed elsewhere in this issue [23], chelation increases delivery of uranium to the kidney, which is the target organ of concern for uranium toxicity.

- The role for chelation therapy:

The panel agreed that there was no indication for chelation in this or similar cases.

- Information or systemic issues to reduce confusion or error and improve future care:

For this person, attention to her water supply and actions to decrease exposure to elevated elements from the bedrock groundwater sources to increase the safety of her water supply would be appropriate. Public education regarding the role of safety factors (uncertainty factors) in protecting public health should be undertaken as a component of a national conversation on the impact of environmental exposures. An important part of this conversation is attention to particular populations considered susceptible or at-risk for exposures, and a frank discussion of the issues of risk and risk tolerance.

Audience Response

Participants in the ACMT “Use and Misuse of Metal Chelation” Symposium were polled to determine their opinion

regarding priority areas for intervention or action to address some of the issues raised by the presentations. Of the 65 attendees and speakers on-site at any time, 38 responded at the end of the day to questions soliciting priority areas for action by ACMT and its partners from a list of eight potential actions. The same questions were posed to the webinar audience. There were a maximum of 68 webinar participating sites with between 1 and 20 people at each site. Of the 19 sites still logged in at the end of the day, responses were received from 9 sites. Responses from both groups were consistent. As depicted in Table 1 above. The majority of responders indicated that education of the public and medical practitioners should be supplemented by increased regulatory and enforcement actions.

Table 2 Components of the assessment of metal toxicity and need for chelation

- Valid clinical suspicion for diagnosis
- If appropriate, proper patient preparation for testing
- Correct specimen preparation and handling
- Use of valid comparison groups
 - There is no role for provoked challenge in screening/diagnosis
 - Distinguish and report
 - Laboratory reference population
 - Population-based “norms”
 - Toxicity ranges
- Distinguish and communicate the difference between “individual health effect” and “public health concern”
 - Differentiate biochemical changes vs organ dysfunction vs clinical symptoms
 - Identify “at-risk” or susceptible population vs entire population

Conclusion

Management of patients concerned about environmental exposure to metals or those with demonstrated toxicity can be difficult. Media portrayals and commercial interests often distort scientific findings. Medical toxicologists have an opportunity to provide a valuable public service in the interpretation of scientific data, as well as the assessment and treatment of individuals. Beginning from the premise that the most important consideration in initiating a course of therapy (in this instance, chelation) is having the correct diagnosis, we should strive to ensure that these diagnoses are not based on false interpretation or manipulation of laboratory data. Furthermore, we should emphasize the importance of removal of a harmful substance (decorporation) as opposed to redistribution with the potential for harm associated with that action [24]. Efficacy of chelation treatment should be determined by the combination of demonstrated removal and improvement of causally related symptoms. The impact of the placebo effect with treatment should be recognized. Table 2 provides a bulleted list of considerations that are important when discussing concerns regarding metal toxicity and chelation treatment.

Conflict Delineations For the work under consideration for publication, Dr. McKay received a consulting fee/honorarium and reimbursement for travel through the ACMT/ATSDR Cooperative Agreement. Relevant financial activities outside the submitted work included money paid by the state DPH and various private attorney's firms to Dr. McKay and to Dr. McKay's institution for consulting on cases involving chelation issues. Dr. McKay is on the Scientific Advisory Council for the Environmental Health Research Foundation, which addresses issues related to bio-monitoring for environmental chemicals.

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Appendix: Panel participants—ACMT “Use and Misuse of Metal Chelation Therapy”

Charles McKay, MD, FACMT (moderator)
 Jeffrey Brent, MD, PhD, FACMT
 Michael Kosnett, MD, MPH, FACMT
 Charles Lee, MD
 Lewis Nelson, MD, FACMT
 Michelle Ruha, MD, FACMT
 Silas Smith, MD
 Richard Wang, DO, FACMT
 Paul Wax, MD, FACMT

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