J. Med. Toxicol. (2013) 9:303–307
DOI 10.1007/s13181-013-0347-2

PROCEEDINGS

Current Use of Chelation in American Health Care

Paul M. Wax

Published online: 12 October 2013
© American College of Medical Toxicology 2013

Abstract The National Center for Health Statistics estimates that more than 100,000 Americans receive chelation each year, although far fewer than 1 % of these cases are managed by medical toxicologists. Unfortunately, fatalities have been reported after inappropriate chelation use. There are currently 11 FDA-approved chelators available by prescription although chelation products may also be obtained through compounding pharmacies and directly over the internet. Promotion of chelation training is prominent on some alternative and complementary medicine websites.

Keywords Chelation therapy · Heavy metal poisoning · Inappropriate chelation practices · FDA-approved chelators · Chelation training

Background

The word *chelate* comes from the Greek word referring to a claw. Scientifically, a chelate refers to a ligand binding to a central metal atom at two or more points. Chelation therapy involves the administration of a chelating agent. Chelation therapy is a controversial and divisive topic because many practitioners encouraging such therapy eschew traditional science. The National Center for Complementary and Alternative Medicine (NCCAM) was founded within the National Institutes of Health (NIH) in 1992 to investigate and evaluate promising unconventional medical practices. The NCCAM newsletter from September 2010 states that "chelation has been scientifically proven to rid the body of excess toxic metals" [1]. It should be emphasized that evidence that chelation can remove metals does not mean that it is indicated for treatment whenever a "high" measurement is identified. Clinical evidence of symptoms consistent with excess exposure should be sought, and efforts should be made to reduce any ongoing exposure to clinically significant sources. Importantly, chelation therapy may affect many different elements not only resulting in enhanced elimination of toxic metals such as lead and arsenic, but also potentially increasing elimination of essential trace metals such as chromium, cobalt, copper, and iron that are needed for normal physiologic function. Chelators have the potential of causing harm because of what they may do to these essential metals. Evidence that chelation improves outcome is scarce, and such data, or lack thereof, is addressed elsewhere in this issue [2, 3].

In 2005, Agency for Toxic Substances and Disease Registry (ATSDR) scientists, John Risher and Sherlita Amler, published a paper in neurotoxicology about the inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning [4]. The report stated that each year ATSDR receives dozens of calls from individuals who have been chelated with either dimercaptopropanesulfonic acid (DMPS) or dimercaptosuccinic acid (DMSA) prior to the collection of any urine samples, and who have been subsequently diagnosed with mercury poisoning. The paper states that it is unfortunately all too common for practitioners to make a diagnosis of mercury intoxication and begin treatment without performing an adequate clinical workup. The American College of Medical Toxicology (ACMT) organized a symposium, supported by a Cooperative Agreement with ATSDR, to provide guidance for properly assessing these patients [5].

This paper will provide a review of currently available chelating agents and their indications, describe the various ways chelators are obtained, and discuss the frequency of use of these chelators and the types of health-care providers who are involved with chelation therapy. To provide a proper context for these objectives, three cases of inappropriate chelation practices that have come to the attention of medical toxicologists and public health organizations will be presented.

Previously presented at the conference "Use & Misuse of Metal Chelation Therapy" held on February 29, 2012, at the Centers for Disease Control, Atlanta, GA. This conference was jointly sponsored by the American College of Medical Toxicology and the Medical Toxicology Foundation with support from the Agency for Toxic Substances and Disease Registry.

P. M. Wax (✉)
Southwestern School of Medicine, University of Texas,
Dallas, TX, USA
e-mail: paul.wax@me.com

Inappropriate Chelation Practices: Case Examples

The first case is a health consultation that was performed by ATSDR several years ago involving the Higgins Farm National Priorities List site [6]. The case involved a family who was currently using a private well adjoining the Higgins Farm. ATSDR was asked to assist in the interpretation of environmental and medical test results that were previously obtained and evaluate the potential impact of contaminants from the Higgins Farm on the family. Apparently, two children had developed neurological impairments. One of them, who was 5 1/2 years old, previously had been diagnosed with attention deficit hyperactivity disorder and was undergoing chelation therapy for metal exposures. In these cases, heavy metal testing was performed after a chelator was administered. The spot mercury in the 5 1/2-year-old after DMSA was 10 μg/g creatinine; the spot mercury level in one of the adults after DMPS was 21 μg/g creatinine. Although these levels were used to justify treatment, interpreting such postchelation levels is very problematic. Typical reference ranges are based on measurements performed prior to any chelation treatment. Moreover, in this case no source of mercury could be located, suggesting that there may not have been any mercury exposure in the first place.

The second case involved a 43-year-old female who visited a medical toxicologist for a second opinion after her naturopath had diagnosed her with heavy metal poisoning. She had a history of chronic fatigue, difficulty concentrating, inability to get out of bed or talk, and was too fatigued to write a letter. She went to several "regular doctors," including a psychiatrist and a dermatologist, but they were unable to relieve her symptoms. Out of frustration, she sought treatment from a naturopath who she had seen for about a year. This naturopath ordered a urine heavy metal screen to be collected both before and after the administration of DMPS. The urine mercury levels were 1 and 18 μg/g creatinine, respectively. She was started on a course of chelation based on this "positive" response to the chelation challenge. However, the patient never had any symptoms of mercury toxicity, nor did she have any known exposure to mercury.

The third case was published in the Morbidity and Mortality Weekly Report (MMWR) in 2006 [7]. This case involved a 53-year-old female who was treated with 700 mg of ethylenediaminetetraacetic acid (EDTA) administered intravenously over 10 to 15 min in a naturopathic practitioner's clinic. The EDTA was intended to remove heavy metals from her body, but 10 to 15 min after she received this treatment, she suddenly became unconscious and had a cardiac arrest. During the resuscitation, she was given calcium gluconate and calcium chloride intravenously. Despite that treatment, her ionized calcium remained critically low at 3.8 mg/dL (normal, 4.5–5.3 mg/dL), and she died. This tragic case, along with two other deaths from EDTA described in the same MMWR report, brought needed attention to the inappropriate use of chelation therapy and its dangers.

Currently Available Chelating Agents

Currently, there are 11 FDA-approved chelators on the market (see Table 1) [8]. British Anti-Lewisite, also known as BAL or dimercaprol, is a dithiol chelator that was first developed by Peters in 1945 [9]. It is only available by prescription. It is formulated with peanut oil and can only be administered parenterally by deep intramuscular injection. It is approved for treatment of arsenic, gold, and mercury poisoning. It is also approved for the treatment of acute lead poisoning when given concomitantly with edetate calcium disodium. BAL use is associated with many adverse effects, including elevated blood pressure, painful injections, and potential for sterile abscess formation, as well as being contraindicated in those with peanut allergy, but it is an effective chelator and can be used in the treatment of arsenic and mercury poisoning and in certain cases of lead poisoning.

EDTA, another of the early chelators, was first synthesized in the 1930s and has both non-medicinal as well as medicinal uses. Among its many nonpharmaceutical uses, EDTA is used extensively in the paper industry. It is found in some laundry detergents and is used in water treatment facilities and the food and beverage industry.

There are two different types of EDTA that have been formulated for pharmaceutical use—EDTA complexed with calcium and EDTA without calcium. The formulation with calcium is known as edetate calcium disodium, also known as disodium versenate. The formulation without calcium is edetate disodium, no calcium in its name. One can easily be confused between these types of EDTA, but the difference is critically important, as the formulation with calcium will not bind calcium, while the one without calcium will bind calcium.

Table 1 FDA-approved chelators

Dimercaprol (BAL)
Edetate calcium disodium (calcium EDTA)
Succimer (DMSA)
Penicillamine
Trientine hydrochloride
Deferoxamine mesylate
Deferiprone
Deferasirox
Pentetate calcium trisodium (Ca-DTPA)
Pentetate zinc trisodium (Ca-DTPA)
Prussian blue (Radiogardase)

Edetate calcium disodium was first approved in 1953. It is available by prescription and is approved for the treatment of lead poisoning. It is only administered parenterally, and in recent years there have been periodic shortages of the drug. Currently, there are no oral formulations of calcium disodium EDTA that are FDA approved. Adverse reactions associated with the use of edetate calcium disodium include acute renal failure, mild increase in hepatic transaminases, hypotension, cardiac arrhythmias, and allergic reactions.

Edetate disodium was also approved in the 1950s and was used predominantly in the treatment of hypercalcemia. As mentioned above, a 2006 MMWR report noted that three patients died after receiving disodium EDTA from the effects of severe hypocalcemia. In part because of these tragic deaths, disodium EDTA was withdrawn from the market in 2008. It is no longer FDA approved and is no longer available through traditional routes.

The most commonly prescribed chelator today is succimer, also known as Chemet or by its chemical acronym, DMSA. This is a prescription drug available in an oral formulation only; it is approved for use in the treatment of lead poisoning in pediatric patients with blood lead levels >45 μg/dL. While generally safe, DMSA has been associated with mild elevations in hepatic transaminases and allergic reactions. As discussed elsewhere in this issue, DMSA is also used in the treatment of mercury and arsenic poisonings although these are not FDA-approved indications [10].

Penicillamine is another chelator. Unlike the others discussed above, penicillamine is a unithiol possessing only one thiol group. It is an oral chelator and is available by prescription only. It is approved for the treatment of Wilson's disease, which is a chronic copper storage disease, cystinuria, and refractory rheumatoid arthritis. It has also been used to treat lead poisoning, but that use has been off-label. Serious hematological and renal adverse reactions have been associated with penicillamine including leukopenia, thrombocytopenia, aplastic anemia, proteinuria, hematuria, and nephrotic syndrome.

There are several FDA-approved iron chelators. Deferoxamine, originally approved in the 1960s, is an intravenous chelator that is approved for the treatment of acute iron poisoning and chronic iron overload due to transfusion-dependent anemia (such as thalassemia) in the setting of numerous blood transfusions. Adverse reactions associated with deferoxamine use include hypotension, hypersensitivity reactions, ARDS, renal failure, and susceptibility to *Yersinia* infections. Deferasirox and deferiprone are two oral iron chelators, recently introduced to the USA that are also approved for chronic iron overload.

Prussian blue, which can be used in the treatment of thallium and cesium poisoning, was FDA approved in 2003. In 2004 the FDA approved calcium DTPA and zinc DTPA to enhance the elimination of various radioactive nuclides including plutonium, americium, or curium.

There is also one chelator that is sometimes used in the USA that is not FDA approved, DMPS. This chelator is structurally related to DMSA or Chemet and is available both intravenously and orally. It is currently not FDA approved, but it can be obtained through some compounding pharmacies. It has been used in the treatment of mercury and arsenic poisonings and some other less common heavy metal poisonings.

Alternate Sources of Chelating Agents

Depending on the specific product, chelators are available by prescription, through compounding pharmacies, and at times sold directly over the internet. Any licensed medical provider can prescribe a chelator, including naturopaths and other types of alternative medicine physicians.

Compounding pharmacies customize preparations of medicine that are not otherwise commercially available. A physician or veterinarian or other prescribing practitioner writes a prescription for a customized preparation, and a licensed pharmacist at a compounding pharmacy prepares the prescription, utilizing active pharmaceutical ingredients. This process has been subject to ongoing legal and regulatory debates because compounding pharmacists essentially design their own customized pharmaceutical product. The question of whether this is a new compound that should be subject to FDA scrutiny remains controversial. Questions arise about the safety of some of these compounded pharmaceuticals because they are not currently subject to the stringent safeguards of FDA-approved products (see Fig. 1). Recently, a large outbreak of fungal meningitis resulting in more than 60 deaths was attributed to a preservative-free methylprednisolone acetate (MPA) preparation that was produced by a compounding center in New England [11]. This outbreak resulted in renewed calls for greater FDA regulation of compounding pharmacies [12].

The Federal Register from January 1999 provided a list of drugs that were nominated for inclusion on the bulk drug list that may be used in compounded products. One of these drugs was DMPS. The Federal Register states that "DMPS appears to be relatively nontoxic, and serious adverse affects associated with its use has not been commonly reported" [13]. This conclusion may understate the potential problems with DMPS, as DMPS has been associated with Stevens–Johnson syndrome [14].

One can also obtain a chelator without a prescription. Searching for "DMSA" on amazon.com yields results for not only DMSA but also calcium disodium EDTA [15]. Some of these DMSA products are described as "guaranteed pharmaceutical grade." One of the DMSA preparations available through Amazon is Captomer-250, which is 250 mg of DMSA. This formulation is considerably stronger than prescription

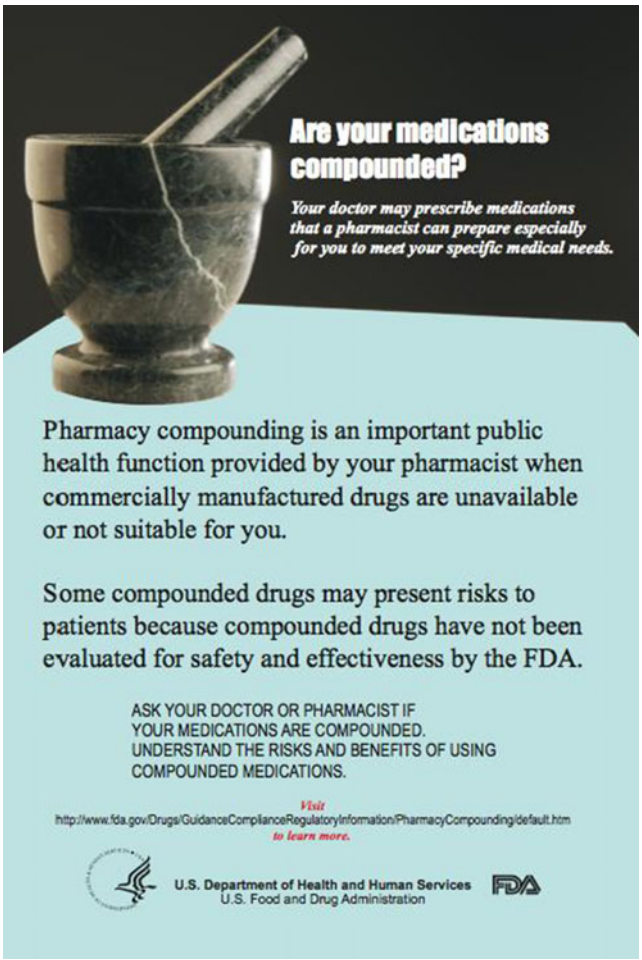

Fig. 1 FDA advertisement about compounding pharmaceuticals

DMSA, which is 100 mg per capsule, potentially leading to dosing errors.

Extent of Use of Chelating Agents

According to a 2008 National Health Statistic Report published by the National Center for Health Statistics, approximately 66,000 adults received some sort of chelation in 2002, and in 2007 the number was 111,000 adults [16]. In 2007, it was estimated that 72,000 children received chelation, for a total of 183,000 adults and children.

Comparing these data to national poison center data reveals markedly different numbers. The National Poison Data System (NPDS) collects data on antidote usage reported to poison centers. Strikingly, in 2007, only 466 cases involving the use of chelators were reported to poison centers, compared to 183,000 chelation cases estimated in the National Health Statistic Report cited above [17]. In a registry of 17,500 patients cared for by medical toxicologists across the USA between 2010 and 2012 in both the inpatient and outpatient settings, only 66 patients received chelation therapy [18]. These discrepancies suggest that not only treatment philosophy, but the nature of reporting, differs greatly across medical practitioners regarding the diagnosis of metal poisoning. Moreover, in many instances, chelators may have been administered to chelate mercury in children with autism spectrum disorders, chelate calcium in adults with atherosclerotic plaques and coronary or peripheral artery disease, or even chelate lead in some children with modest elevations in lead levels to treat ADHD. Unfortunately, data on chelator use by indication is not available. While data on which type of health-care practitioners most commonly prescribe chelation treatments is also not easily obtainable, poison center and medical toxicology registry data suggest only a small fraction of these treatments are prescribed by medical toxicologists.

According to the NIH, complementary and alternative medicine refers to "the array of health care approaches with a history of use or origins outside of mainstream medicine" [19]. They include a broad range of practices and beliefs such as acupuncture, chiropractor care, and also chelation. It is estimated that nearly 40 % of Americans use alternative medicine therapies on a regular basis [19]. This accounts for hundreds of millions of visits and over $20 billion spent on alternative therapies on a yearly basis, according to a 2005 Institute of Medicine report [20].

Several professional societies whose focus seems to be on complementary, alternative, and integrative medicine appear to have a keen interest in chelation training based on information provided on their websites [21, 22]. The American College for the Advancement of Medicine (ACAM) website states that "whether you're new to detoxification education or are a seasoned practitioner, ACAM's rigorous training will enhance your practice treatment options and improve health outcomes" [21]. The American Board of Clinical Metal Toxicology (ABCMT) offers board certification in clinical metal toxicology. Certification by the ABCMT requires the applicant to pass a written and oral examination and to be "responsible for the administration of two thousand intravenous infusions for the treatment of heavy metal toxicity" [22].

Conclusion

In summary, at this time there are almost a dozen FDA-approved chelators. While these are typically dispensed by prescription, chelators may also be available through compounding pharmacies and directly over the internet. National Health Statistics data suggest that more than 100,000 Americans may receive chelation each year, although far fewer than 1 % of these cases are managed by medical toxicologists. Finally, chelation therapy appears to be prominently promoted by some of the alternative and complementary medicine societies, raising concern about the validity of

both diagnosis and treatment of heavy metal poisoning in the USA.

Conflict of Interest The ACMT/ATSDR Cooperative Agreement provided grant funds to Dr. Wax and/or to ACMT for support of the chelation conference, for speaker honorarium, for travel reimbursement, and for editorial assistance.

References

1. National Institutes for Health, National Center for Complementary and Alternative Medicine (NCCAM) (2010) Complementary and Alternative Medicine Newsletter. http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CDQQFjAB&url=http%3A%2F%2Fwww.wakehealth.edu%2FRecreation-Therapy%2FNational-Institute-of-Health-National-Center-for-Complimentary-and-Alternative-Medicine.htm&ei=K8jpUZq4O6qyiQKy0IGoDQ&usg=AFQjCNGW1CCMoOG0hkQWA-2T9OeGy92XfA&sig2=-ueGq0yfktHToUF3G4bBEA&bvm=bv.49478099,d.cGE. Accessed August 2013
2. Smith D, Strupp BJ (2013) The scientific basis for chelation: animal studies and lead chelation. JMT 9(4). doi:10.1007/s13181-013-0339-2
3. McKay C (2013) Role of chelation in the treatment of lead poisoning: discussion of the treatment of lead-poisoned children trial (TLC). JMT 9(4). doi:10.1007/s13181-013-0341-8
4. Risher JF, Amler SN (2005) Mercury exposure: evaluation and intervention the inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning. Neurotoxicology 26: 691–699
5. American College of Medical Toxicology (2013) American College of Medical Toxicology conference presentations. http://www.acmt.net/2012_Use_Misuse_of_Metal_Chelation_Therapy.html. Accessed August 2013
6. New Jersey Department of Health and Senior Services, Agency for Toxic Substances and Disease Registry (2013) Health consultation: Franklin Township residential mercury investigation: Higgins Farm. http://www.atsdr.cdc.gov/hac/pha/HigginsFarmHC091704-NJ/HigginsFarmHC091704-NJ.pdf. Accessed August 2013
7. Centers for Disease Control and Prevention (2006) Deaths associated with hypocalcemia from chelation therapy—Texas, Pennsylvania, and Oregon, 2003–2005. MMWR Morb Mortal Wkly Rep 55(8): 204–207
8. US FDA (2013) Drugs at FDA: FDA approved drug products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed August 2013
9. Peters R, Stocken L, Thompson R (1945) British anti-lewisite (BAL). Nature 156:616–619
10. Kosnett MJ (2013) The role of chelation in the treatment of arsenic and mercury poisoning. JMT 9(4). doi:10.1007/s13181-013-0344-5
11. CDC (2013) Multistate fungal meningitis outbreak investigation. http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html. Accessed August 2013
12. Outterson K (2012) Regulating compounding pharmacies after NECC. N Engl J Med 367:1969–1972
13. Federal Register (1999) List of bulk drug substances that may be used in pharmacy compounding. Federal Register/vol. 64, no. 4/Thursday, January 7, 1999/Proposed Rules. http://www.gpo.gov/fdsys/pkg/FR-1999-01-07/html/99-277.htm. Accessed August 2013
14. Van Der Linde AA, Pillen S, Gerrits GP, Bavinck JN (2008) Stevens-Johnson syndrome in a child with chronic mercury exposure and 2,3-dimercatopropane-1-sulfonate (DMPS) therapy. Clin Toxicol 46: 479–481
15. Amazon.com. Search results for DMSA. http://www.amazon.com/s/ref=nb_sb_noss_1?url=search-alias%3Daps&field-keywords=dmsa. Accessed July 2013
16. Barnes PM, Bloom B, Nahin RL (2008) Complementary and alternative medicine use among adults and children: United States, 2007. National Health Statistics Report, December 10, 2008. http://nccam.nih.gov/sites/nccam.nih.gov/files/news/nhsr12.pdf. Accessed August 2013
17. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Heard SE et al (2007) Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th annual report. Clin Toxicol 46:927–1057
18. Wiegand TJ, Wax PM, Hart K, Smith E, Brent J, Toxicology Investigators Consortium Case Registry Investigators (2012) The toxicology investigators consortium case registry—the 2012 experience. J Med Toxicol 8:360–77
19. NCCAM (2013) Complementary, alternative, or integrative health: what's in a name? http://nccam.nih.gov/health/whatiscam. Accessed August 2013
20. Institute of Medicine (US) (2005) Committee on the Use of Complementary and Alternative Medicine by the American Public. Complementary and alternative medicine in the United States. National Academies Press, Washington DC
21. ACAM (2013) ACAM homepage. http://www.acamnet.org/site/c.ltJWJ4MPIwE/b.6805203/k.BD39/Detoxification__IV_Chelation.htm. Accessed August 2013
22. American Board of Clinical Metal Toxicology (2013) Homepage. http://abcmt.org. Accessed August 2013

ATSDR Disclaimer

This publication was supported by the cooperative agreement award number 1U61TS000117-04 from the Agency for Toxic Substances and Disease Registry (ATSDR). Its contents are the responsibility of the authors and do not necessarily represent the official views of the Agency for Toxic Substances and Disease Registry (ATSDR).