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Heavy Metal Toxicity

Therapeutic OverviEW

Therapies to remove heavy metals from humans include chelation and decontamination procedures, as well as supportive measures, often used in combination. The therapies can be very complex and highly individualized, tailored to the specific needs of each individual and requiring the expertise of trained and experienced professionals, sometimes a team of professionals. Self-diagnosis and treatment is not appropriate.

Chelation Therapy

Chelation is a chemical process that has applications in many areas, including medical treatment, environmental site rehabilitation, water purification, and so forth. In the medical environment, chelation is used to treat cardiovascular disease, heavy metal toxicity, and to remove metals that accumulate in body

tissues because of genetic disorders (hemochromatosis). This protocol will address the use of chelation therapy for the removal of heavy metals as a result of ingested or environmental exposure.

Chelation therapy, simply defined, is the process by which a molecule encircles and binds (attaches) to the metal and removes it from tissue (Dr. Joseph F. Smith Medical Library 2001). Depending on the drug used, chelating agents specific to the heavy metal involved are given orally, intramuscularly, or intravenously. Once the bound metal leaves the tissue, it enters the bloodstream, is filtered from the blood in the kidneys, and then is eliminated in the urine (Dupler 2001). The decision to chelate should be made only by professionals with experience using chelation therapy, preferably in consultation with a poison control center or a medical toxicologist.

Typically, a patient receives a programmed series of intravenous infusions, intramuscular injections, or oral administration of a chelating agent (possibly a combination of the three). The therapy is often lengthy (from a few hours in an emergency room to several days of in-patient treatment in a hospital). Sometimes repeated courses of treatment are required (Wentz 2000). Chelation may be uncomfortable because of the side effects of the medicine itself or from the route of administration (e.g., pain in the area surrounding an injection site) (Ferner 2001). Frequent follow-up testing is required to determine the amount of the metal that is being removed. Sometimes, as in the case of lead, testing may show a rapid decline initially, but then a leveling off occurs over time. In the case of lead, this leveling off is caused by lead that continues to enter the blood from the bones where it has been stored (the "rebound effect"). The leveling off effect is used as a guide for determining how long chelation therapy should be continued (Wentz 2000). As time passes following exposure, chelation therapy is less effective in reducing the severity of poisoning and the risk of serious delayed effects (see the ATSDR Medical Management Guidelines). It cannot reverse neurological damage that has already been sustained.

Acutely poisoned symptomatic persons or persons with a clear history of exposure to a toxic heavy metal may require chelation therapy to start before confirmation can be obtained from a laboratory (see the ATSDR Medical Management Guidelines). However, asymptomatic patients are not usually treated with chelation therapy until after test results reveal levels that require treatment. Interestingly, Goyer (1996) points out that there is growing interest in removing toxic metals from asymptomatic persons who are known to have received low-levels of environmental exposure to heavy metals.

This interest has been generated because of the toxic effects (or damage) that may occur at levels that were previously thought to be safe. According to Goyer, "It is clear that the margin between the levels of exposure for persons living in the industrialized nations of the world and levels of exposure currently recognized as producing the lowest adverse effect is small." Goyer listed low-level exposure to lead as possibly causing impaired cognitive and behavioral development in children, accumulation of cadmium being associated with renal tube dysfunction, and allegations that mercury vapor from dental amalgam may be a possible cause of chronic heath problems (Goyer 1996). Mercury vapor is released from amalgam in new fillings, when old amalgam fillings are replaced (Omura et al. 1996), and even when amalgam is scraped during cleaning.

Chelation is effective in treating arsenic, lead, iron, mercury, and aluminum poisoning. However, chelation is not considered to be particularly effective in treating cadmium poisoning, although it may be used to prevent further absorption in the gastrointestinal tract. To date there is no effective treatment for cadmium poisoning (ATSDR ToxFAQs for Cadmium1999; Wentz 2000; Dr. Joseph F. Smith Medical Library 2001).

Chelating Agents

An agent frequently used in chelation therapy is dimercaprol (also known as BAL or British Anti-Lewisite). Oral chelating agents used as alternatives to BAL are 2,3-demercaptosuccinic acid (DMSA), dimercaptopropanesulfonate (DMPS), and D-penicillamine (ATSDR MMG). Another agent, deferoxamine, is often used to chelate iron. Ethylenediamintetraacetic acid (ETDA) also has an affinity for lead and was one of the first chelators developed.

BAL (Dimercaprol). BAL (British Anti-Lewisite) is a chelating agent administered by injection in the treatment of acute poisoning by certain heavy metals (e.g., arsenic, lead, mercury, gold, bismuth, and antimony). Contraindications to using BAL are preexisting kidney disease, pregnancy, hypertension, and current use of medicinal iron. BAL has significant side effects that are frequent and include pain at the injection site; hypertension and tachycardia; abdominal pain, nausea, and vomiting; headaches; burning sensation of the lips, excessive salivation, rhinorrhea, and tearing; fever; muscle pain, muscle spasms, and a feeling of chest constriction; and profuse sweating. It is considered to be the most toxic of the chelating agents (Wentz 2000). However,

side effects can be medically managed and are seldom severe enough to cause treatment to be ended (Micromedex 1999).

DMSA (Dimercaptosuccinic Acid). DMSA is an oral chelating agent and an analogue of (similar to) BAL. DMSA is used in conjunction with or as an alternative to BAL for lead and mercury toxicity. DMSA is less toxic than BAL, and it is sometimes substituted for BAL when the patient's condition improves. It is also used when intolerance to BAL develops. Although DMSA is similar to BAL, it has fewer and milder side effects (e.g., nausea, vomiting, and diarrhea; rhinitis and cough; and rash) (see the ATSDR Medical Management Guidelines). An interesting study on thiol chelating substances showed that DMSA was more effective than DMPS and SAMe (S-adenosylmethionine) in protecting mice from acute hepatic or renal toxicity caused by arsenic, and that all three substances were nontoxic to the liver or kidneys of mice (Tripathi et al. 1998). Contraindications to using DMSA are preexisting kidney or liver disease and pregnancy. Hydration is essential. DMSA is not used in conjunction with ETDA or D-penicillamine (USNML/NIH 2001b).

DMPS (Dimercaptopropanesulfonate). DMPS is another analogue of BAL. It has been shown to be less effective and to have more side effects than DMSA (Aaseth et al. 1995). DMPS is the drug of choice in Europe and Asia; however, the FDA has not approved DMPS for chelating purposes in the United States. It does, however, appear on the FDA list of drugs that appear to be safe. In the United States, DMPS is distributed to pharmacists in bulk form for compounding and dispensing in oral and injection forms (FDA 1999; Marcus 2001).

D-penicillamine. D-penicillamine is an oral chelating agent used to treat heavy metal toxicity, particularly arsenic and mercury. Side effects are gastrointestinal intolerance, nausea and vomiting, and itchy skin (wheals). Contraindications are allergy to penicillin, possible interaction with other drugs (immunosuppressants, digoxin), severe blood disorders, kidney insufficiency, and pregnancy (USNML/NIH 2001d).

Deferoxamine. Deferoxamine is used to chelate iron, especially in acute iron poisoning in small children. It is also used to chelate aluminum. Deferoxamine is administered by injection or intravenously. Common side effects are blurred vision, wheezing, rapid heartbeat, seizures, itching, skin rash, bluish skin, and redness and pain at the injection site. Gastrointestinal discomfort, fever, cramping, and bruising are less common. Contraindications are allergies to certain foods or dyes, other medicines currently being taken, pregnancy or breast feeding, and kidney disease (USNML/NIH 2001a).

EDTA (Ethylenediamintetraacetic Acid, Edetate Disodium). EDTA is one of the oldest chelating agents, coming into prominence in the 1950s. EDTA has an affinity for lead. It is often used as a second-line of treatment in combination with BAL and given by IV infusion. Common side effects are gastrointestinal upset and headache. More serious side effects can include seizures, numbness or tingling in the hands and feet, irregular heartbeat, skin rashes, fever or chills, and blood in the urine (Ferner 2001). EDTA is contraindicated in pregnancy and if there is kidney disease. It can also interact with insulin and heart medicines (USNML/NIH 2001c).

The following table summarizes chelating agents, the heavy metals they are used to treat, their route of administration, and their brand name.

Chelating Agent	Toxin	Route**	Drug
Dimercaprol (BAL)	Arsenic Lead Mercury (inorganic)*	i.m.	Dimercaptol Injection B.P. BAL in Oil
Dimercaptosiccinic acid (DMSA) (Succimer)	Arsenic Lead Mercury	p.o.	Chemet
Dimercaptopropane- sulfonate (DMPS)	Arsenic	p.o. i.m.	Bulk form (for compounding by pharmacists)

D-pencillamine	Arsenic Mercury Lead	p.o.	Metalcaptase Pencillamine Cuprimine Depen
Ethylenediamintetra- acetic acid (EDTA) (Edetate disodium)	Lead	IV	Chealamide Versenate

**Not methylmercury poisoning.*

***Under supervision of a physician: i.m., intramuscular; p.o., peroral or by mouth; IV, intravenous.*

Source: Data from Beers et al. 1999; Micromedex 1999; Roberts 1999; Wentz 2000; Anon. 2001; Ferner 2001; Marcus 2001; USNML/NIH Drug Information 2001a; 2001b; 2001c; 2001d.

Gastrointestinal DecontaminatiON

- Gastric Lavage
- Whole Bowel Irrigation
- Emesis
- Charcoal
- Cathartics
- Supportive Measures

In addition to chelation therapy, decontamination procedures are often required: gastric lavage, whole bowel irrigation, emesis, charcoal, or cathartics.

Gastric Lavage

Gastric lavage is washing out of the stomach with sterile water or a salt solution to remove swallowed irritants or poisons (Dr. Joseph F. Smith Medical Library 2001). Gastric lavage is accomplished by placing a plastic tube into the stomach via the mouth and esophagus. Normal saline, water, or a combination is introduced into the stomach via the tube. Gastric lavage is not indicated if the substance ingested is an alkaline corrosive. It is done in a health care environment or hospital and is most effective within the first hour of ingestion. Gastric lavage is not effective in removing large tablets or large clumps of tablets or other material (Klein-Schwartz et al. 2000), but it is indicated for arsenic (Ferner 2001). Insertion of the tube may injure the esophagus. Gastric lavage is more effective in adults than in children because a larger tube can be used (Klein-Schwartz et al. 2000; James 2001).

Whole Bowel Irrigation

Bowel irrigation is emptying of the bowel with large volumes of solutions such as Golightly, Colyte, sterile water, or some other fluid to remove swallowed irritants or poisons from the bowel (e.g., arsenic and lead) (Ferner 2001; James 2001). The fluid may be administered orally or by gastric tube until the bowel fluid has the same appearance as the solution administered (Klein-Schwartz et al. 2000; James 2001). Whole bowel irrigation is indicated if some time has elapsed since ingestion of the toxin and if the toxin will not be effectively bound by charcoal. It can take several hours and has the side effects of nausea and vomiting, diarrhea, and cramping. Whole bowel irrigation is not indicated if mental status is impaired or bowel sounds are decreased (Anon. 2001).

Emesis

Emesis is forceful emptying (vomiting) of the stomach and is most effective for recent oral ingestion of noncorrosive substances. Ipecac Syrup USP is considered to be an essential emesis agent in many homes with young children and for years has been the cornerstone of poison management (Anon. 2001). If instructed by a physician, Ipecac may be given in the home prior to the arrival of emergency personnel or treatment in an emergency department, often preventing significant absorption from stomach contents (Klein-Schwartz et al. 2000). However, use of Ipecac is only effective when administered within the first 5-20 minutes after ingestion of a toxin. After a toxin has left the stomach, inducing emesis with Ipecac is useless. Administering it after the first few minutes may actually delay beginning further medical treatment (Anon. 2001). Ipecac may take 20 minutes to produce forceful vomiting (James 2001), and the vomiting may last for some time (2-4 hours). Emesis should not be induced if the patient is having difficulty maintaining consciousness, the toxin is caustic or might cause choking (e.g., a clump of pills), or if the person has gastrointestinal bleeding (Anon. 2001). When appropriate, emesis is induced in cases of acute arsenic or mercury poisoning (Dr. Joseph F. Smith Medical Library 2001).

Contact a physician, emergency department, or poison center before using emesis..

Charcoal

Charcoal is administered in single- or multiple-dose regimens, either intravenously or orally. Single doses are most effective if administered within the first hour after ingestion. Multiple-dose regimens are often used in complicated cases and in children because the smaller doses (half of a single dose) appear be better tolerated than the larger single dose (Anon. 2001). Charcoal should not be administered for caustic or corrosive materials, and bowel sounds must be present. Its usefulness is limited in certain pesticides and compounds that are poorly water soluble (e.g., iron and elemental metals) (Anon. 2001). Gastrointestinal decontamination with activated charcoal is indicated to aid in removal of mercury (Ferner 2001).

Cathartics

Cathartics are used to aid moving toxic material through the gastrointestinal tract, to remove and reduce concentrations, or to decrease absorption of toxic materials (Anon. 2001; James 2001). A cathartic agent increases intestinal action, increases the bulk of feces, makes feces soft, or adds water to the wall of the intestines, the term implying fluid bowel materials (Glanze 1996). Cathartics are often used in conjunction with charcoal in adults, particularly to prevent impaction or formation of charcoal "briquettes." Cathartics are not recommended for children under 1 year and should be used with caution in children under 3 years of age. Cathartics can produce significant diarrhea and electrolyte imbalance. They are not indicated if bowel sounds are absent (Anon. 2001).

Supportive Measures

IV fluids, dialysis, and drugs to treat complications resulting from heavy metal toxicity and treatments, such as shock, anemia, kidney failure, breathing difficulties, cardiac irregularities, infections, and so forth, may be required. Close monitoring of symptoms by medical personnel and immediate response to them are also required (Anon. 2001; Dr. Joseph F. Smith Medical Library 2001; James 2001; ATSDR Medical Management Guidelines).

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