24 Metals

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24.1 INTRODUCTION

Metals are the most numerous of all elements. Even though some are necessary in biological systems, they are usually required only in trace amounts. Even essential metals in excess can be toxic if not fatal. They are involved in enzymatic reactions or, as in the case of iron, are involved with oxygen transport. Some metals such as Na^+, K^+ and Ca^{2+} act as ions in neurotransmission and muscle contraction. Most metals function as metal complexes and are involved in electron transfer reactions. It is the misplacement of these electrons or competition between metals that results in toxicity. Metals are known to generate free radicals, which may result in membrane and organelle degradation. They are also known to combine with normally occurring molecules, such as proteins, and inhibit or alter their activity. The metals discussed in this chapter represent the toxicologically important ones (Table 24.1) of those present in the Periodic Table.

24.2 CHELATION THERAPY

24.2.1 Description

Exposure to metals and metallic elements can be a source of serious toxicological effects. These effects will largely depend on the type of exposure (inhalation, dermal absorption, or ingestion), the species (salt, element, vapor), dose, and time of exposure. Whenever possible, removal of the individual from the source of exposure is the first course of action. For some cases of metal exposure, gastric lavage and induction of vomiting are recommended. This can only be safely and effectively accomplished if the toxicant is not corrosive and the exposure is recent.

Once absorption occurs, chelation therapies are often suggested to lessen body burdens of metals that have been absorbed and distributed to body tissues.* The chelator may have one or more attachment points for the metal, and its affinity for a particular metal will vary with its structure and the properties of the metal. There are inherent risks involved with the use of chelators. The chelator-metal complex must be excreted from the body without causing additional toxicity. In addition, chelators can bind to essential metals or cause the movement of metals from storage sites, thus increasing potential for toxicity. Chelators can move metals from innoc-

*The word chelate comes from a Greek word meaning "claw" (for example, the chelicerae or claw shaped mouthpart of *Crustacea*). A chelator acts as a claw to attach itself to the metal and hastens its removal from the organism.

TABLE 24.1
Chemical Characteristics and Methods of Detection of Some Metals

Metal	Chemical Symbol	At. #	At. Wt.	Appearance	Method of Detection	Clinical Sample
Antimony	Sb	51	121.76	Silvery-white, brittle crystalline metalloid	AAS, ESI-MS, GC-ICP-MS	Urine, blood
Arsenic	As	33	74.9216	Grey metalloid	AAS, ICP-AES, ICP-MS	Hair, nails, blood, urine
Asbestos	—	—	—	Mixture of minerals	PCM, TEM, Polarized light and x-ray diffraction	—
Cadmium	Cd	48	112.40	Silvery-white metal	GF-AAS, ICP-MS	Urine, blood
Copper	Cu	29	63.546	Brownish-red metal	ICP-MS, AAS	Blood
Iron	Fe	26	55.847	Silvery-white metal	AAS	Blood
Lead	Pb	82	207.2	Bluish-gray metal	GF-AAS, radiographic techniques, (lead lines)	Blood
Mercury	Hg	80	200.59	Silvery liquid metal	AAS, ICP-AES, ICP-MS	Hair, nails, blood, bone, urine
Selenium	Se	34	78.96	Brick red powder, red crystals, gray crystals, metalloid	AAS, GC, x-ray diffraction, NAA	Blood, urine, placenta, hair, nails
Zinc	Zn	30	65.38	Brittle bluish-white metal	AAS, ICP-AES, ICP-MS	Urine, blood, bone, hair

Note: **AAS**, atomic absorption spectroscopy; **ESI-MS**, electron spray ionization mass spectroscopy; **GC-ICP-MS**, gas chromatography – inductively coupled mass spectroscopy; **ICP-AES**, inductively coupled plasma atomic emission spectroscopy; **ICP-MS**, inductively coupled plasma mass spectroscopy; **GF-AAS**, graphite furnace AAS; **NAA**, neutron activation analysis; **PCM**, phase contrast microscopy; **TEM**, transmission electron microscopy.

uous locations in the body to more sensitive areas (e.g., lead trapped in bone released into the circulation by the chelator).

Some commonly used chelators are mentioned below. It is important to realize that chelators, depending on the metal and clinical situation, may increase toxicity.

24.2.2 Dimercaprol

Dimercaprol (2,3-dimercapto-1-propanol, British anti-Lewisite, BAL) is an effective chelating agent for heavy metals such as As, inorganic Hg, Bi, Cd, Cr, Co, Ni, Sb, and Au (see Table 24.1 for abbreviations).* These metals form strong bonds with sulfur atoms in this compound. Once the metal is chelated, it is unable to enter the cell and may be excreted from the body.

24.2.3 Ethylenediaminetetraacetic Acid (EDTA)

EDTA forms four or six bonds with metal ions and forms chelates with both transition-metal ions and main-group ions. The Ca salt of EDTA is the chelator of choice for Pb toxicity. EDTA is used as an anticoagulant for stored blood in blood banks; it prevents coagulation by sequestering the Ca ions required for clotting. As an antidote for Pb poisoning, Ca disodium EDTA exchanges its chelated Ca for Pb, and the resulting Pb chelate is rapidly excreted in the urine. The Ca salt of EDTA, administered i.v., is also used in the treatment of acute Cd and Fe poisoning. Because of its potential for nephrotoxicity, Ca EDTA should be administered only when necessary. EDTA can be used in combination with other chelators in an effort to reduce the toxic effects of either agent used individually.

24.2.4 Penicillamine

Penicillamine (cuprimine) is a chelating agent for Hg, Pb, Fe, and Cu. It forms soluble complexes, thus decreasing toxic levels of the metal.** Penicillamine is well absorbed from the GI tract and excreted in urine. Food decreases the absorption of penicillamine over 50%. Since penicillamine is a hydrolytic product of penicillin, it should not be used in patients who are allergic to this antibiotic.

24.2.5 Deferoxamine

Deferoxamine is an Al and Fe(II) chelator that has been used in the treatment of acute Fe poisoning and chronic Fe or aluminum overload. It is isolated from the bacteria *Streptomyces pilosus* and is one of the few chelators available for the treatment of secondary Fe overload. It is not effective orally and requires prolonged subcutaneous injection to achieve efficient Fe excretion. Deferoxamine appears to remove both free Fe and bound Fe from hemosiderin and ferritin but not from hemoglobin, transferrin, or cytochromes.

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* Dimercaprol was originally employed to treat the toxic effects of an As-containing mustard gas (Lewisite, dichloro-(2-chlorovinyl) arsine) used in World War I.

** Penicillamine has been used in the treatment of Wilson's disease, a genetic disease that results in accumulation of Cu.

24.2.6 Succimer

Succimer (dimercaptosuccinic acid, DMSA) and sodium dimercaptopropane-sulfonate (DMPS) are used in the treatment of acute Pb poisoning to remove excess Pb from the body, especially in children. It is also under investigation as a treatment for Hg poisoning due to dental fillings. Succimer combines with Pb in the serum and is excreted by the kidneys. By removing the excess Pb, the chelator lessens damage to various organs and tissues of the body. In healthy individuals, approximately 20% of an oral dose of DMSA is absorbed from the GI tract. About 95% of circulating DMSA is bound to albumin. Most likely, one of the sulfhydryls (SH) in DMSA binds to a cysteine residue on albumin, leaving the other SH available to chelate metals.

24.3 ANTIMONY (Sb)

24.3.1 Chemical Characteristics

Antimony (Sb) displays both metallic and nonmetallic characteristics and is sometimes referred to as a metalloid. It is moderately flammable and presents somewhat of a fire hazard in the forms of dust and vapor when exposed to heat or flame. When heated or on contact with acid, it emits toxic fumes of stibine. Most antimonial salts have been known to cause toxicity.

24.3.2 Uses

Sb is used as solder, in sheet and pipe metal, storage battery casings, pewter, in paints, ceramics, and in enamels for plastics, metals and glass. Sb oxides have been added to clothing as a flame retardant. It has been used clinically for its antiinfective properties and in the treatment of parasitic infections such as leishmaniasis and schistosomiasis.

24.3.3 Mechanism of Toxicity

Like other metals, Sb produces its toxicity by the formation of ligands with cellular organic compounds and constituents. Once the metal-organic compound complex is formed, the molecules lose their ability to function properly, which leads to disruption or death of affected cells. The binding of metals to oxygen, sulfur, and nitrogen can inactivate essential enzymes or protein function.

24.3.4 Toxicokinetics

Sb is poorly absorbed following gastrointestinal ingestion or inhalation, and absorption is a function of the compound's solubility. GI absorption has been estimated to be < 10% in humans. Systemic distribution varies among species and is directly related to its valence state. Sb is not metabolized but binds to macromolecules and reacts covalently with SH and phosphate groups. Excretion occurs via the urine and feces. The absorption of Sb from the respiratory tract is dependent on particle size.

Pentavalent forms of Sb have been detected more frequently in the liver and spleen and trivalent forms with greater frequency in the thyroid gland. It accumulates in the skeletal system and in fur of mammals.

24.3.5 Signs and Symptoms of Acute Poisoning

In humans, acute poisoning has occurred as a result of accidental or suicidal ingestion of Sb compounds with death ensuing within several hours. Symptoms of severe Sb poisoning include vomiting, watery diarrhea, collapse, irregular respiration, and hypothermia. Toxicological effects of Sb in humans following inhalation or ingestion include: pneumoconiosis, altered ECG readings, increased blood pressure, dermatosis, ocular irritation, abdominal distress, headache, nausea, vomiting, jaundice, and anemia. Acute exposure to other forms may result in hair and weight loss, skin problems, and damage to heart, liver, and kidneys. Inhalation of Sb dust by factory workers produced GI irritation, probably as a result of Sb dust transported via the nasal mucosa. Information regarding the acute inhalation toxicity of Sb in humans is lacking.

24.3.6 Treatment of Acute Poisoning

Treatment for acute Sb poisoning is best accomplished by using DMPS, although chelation may not always be indicated. BAL may be the most effective treatment for trivalent Sb in the circulation, although this treatment has little effect following stibine gas exposure. Dialysis has been recommended for treatment of pentavalent Sb exposure. Dimercaprol has also been used in cases of Sb poisoning.

24.4 ARSENIC (As)

24.4.1 Chemical Characteristics

Arsenic (As) is a naturally occurring element that is not a true metal but a metalloid. Organic forms are usually considered to be less toxic than the inorganic forms. Some organic As compounds are gases or low-boiling liquids at normal temperatures. Burning of As, or contact with acid, results in production of arsine, a deadly gas. More than 21 As compounds are of concern based on their environmental presence.

24.4.2 Occurrence and Uses

Inorganic As is found in groundwater, surface water, and many foods such as rice and grains. Exposure is primarily through drinking water, but food is considered a significant source as well. As has been used clinically as an anticancer agent. Arsenic trioxide (As_2O_3) is a major ingredient of traditional Chinese medicine (TCM) and is used against acute promyelocytic leukemia. Fowler's solution (potassium arsenite) had been used as a treatment for patients with asthma. Inorganic As compounds are mainly used as wood preservatives, insecticides, herbicides, and in the production of metal alloys.

24.4.3 Mechanism of Toxicity

The toxicity of As is dependent upon the chemical form and the oxidation state at the time of exposure. The physical state (gas, solution, powder particle size), the rate of absorption into cells, elimination rate, and the nature of chemical substituents determine the toxic outcome. The mechanism of As toxicity may be related to the inactivation of key enzyme systems. Inorganic pentavalent As does not react with the active sites of enzymes directly, but first reduces to trivalent As before exerting toxic effects. Bonding of trivalent As to –SH and –OH groups interferes with enzyme activity. Inactivation of pyruvate dehydrogenase with trivalent As will prevent generation of adenosine-5-triphosphate (ATP). Arsenic inhibits succinic dehydrogenase activity and can uncouple oxidative phosphorylation, a process that results in disruption of all cellular functions. As targets and accumulates within mitochondria.

24.4.4 Toxicokinetics

Arsenate and arsenite are well absorbed by both oral and inhalation routes. As is methylated in the body by alternating reduction of pentavalent As to trivalent As, the latter of which is the more toxic form. Most mammals metabolize As to methylarsonic acid (MMA) and dimethylarsinic acid (DMA). MMA and DMA are readily excreted in the urine, and this acts as a detoxification mechanism. Increases in tissue concentrations result if As methylation is diminished. Glutathione and other thiols act as reducing agents in these reactions. In mammals, the liver is an important site of As methylation, especially following first passage through the liver. Arsenic is also methylated in other tissues such as testes, kidney, liver, and lung.

24.4.5 Signs and Symptoms of Acute Toxicity

Patients with acute exposure experience GI distress characterized by nausea, vomiting, abdominal pain, and profuse watery or bloody diarrhea. Death is common in patients that have ingested large doses. Serious respiratory effects such as pulmonary edema, hemorrhagic bronchitis, and respiratory distress are seen with acute oral poisoning. Hypotension, tachycardia, and complaint of a metallic taste in the mouth and garlic odor on the breath, as well as delirium, are often noted in patients with acute toxicity. Anemia and leukopenia are common effects of acute As poisoning in humans. Acute arsine gas exposure is characterized by headache, nausea, vomiting, diarrhea, and abdominal pain. Dyspnea and severe jaundice are frequent signs.

24.4.6 Signs and Symptoms of Chronic Toxicity

Chronic As toxicity is characterized by changes in skin pigmentation, plantar and palmar hyperkeratoses, GI symptoms, anemia, skin cancers, and liver disease. In patients treated with Fowler's solution, which contains potassium arsenite, nonchirrhotic portal hypertension has been seen. Bone marrow depression resulting in anemia and leukopenia, Raynaud's phenomena, and acrocyanosis may also occur. Peripheral neuropathies have also been reported. Nerve injury was associated with Swedish Cu smelter workers chronically exposed to As_2O_3.

24.4.7 Treatment of Acute Poisoning

Delay or prevention of As absorption in cases of high-dose oral exposure may be accomplished by consumption of large volumes of water, gastric lavage, or cathartics initiated within a few hours of exposure. Chelation therapy is indicated for acute As poisoning, including BAL and D-penicillamine. Patients who are minimally symptomatic and have chronic As poisoning may be removed from the source of their exposure without chelation therapy.

24.4.8 Carcinogenesis

There is convincing evidence from many epidemiological studies suggesting that inhalation exposure to inorganic As compounds increases the likelihood of developing lung cancer. Most cases involved inhalation of arsenic trioxide by workers at copper smelting plants, resulting in a significant increase in respiratory cancer mortality. The likelihood that ingestion of inorganic As results in increased risk of skin cancers and basal cell carcinomas have also been noted.

24.5 ASBESTOS

24.5.1 Chemical Characteristics

Asbestos is composed of a group of six different fibrous minerals (amosite, chrysotile, crocidolite, and the fibrous varieties of tremolite, actinolite, and anthophyllite) that occur naturally in the environment. There are two different silicate mineral groups in which asbestos belongs. Chrysotile belongs to the serpentine family of minerals, while the rest belong to the amphibole family. Chrysotile accounts for over 90% of the world's asbestos production. Of the five members of the amphibole group, crocidolite (blue asbestos) and amosite (brown asbestos) are widely used for commercial purposes.

24.5.2 Occurrence and Industrial Uses

The ancient Greeks spun and wove asbestos into cloth much like cotton. Until the late 1800s, when major deposits were discovered in Canada, asbestos was not widely available. Asbestos deposits are found throughout the world and are still mined in Australia, Canada, South Africa, and the former Soviet Union.

Asbestos was used to make thermal insulation for boilers, pipes, and for fireproofing and reinforcement material. The military used asbestos extensively in ships and other applications during World Wars I and II. Commercial uses in buildings increased greatly thereafter until the 1970s, when growing concerns about health risks led to voluntary reductions. Asbestos has been used in thousands of products, mainly because it is plentiful, readily available, inexpensive, strong, fire retardant, heat resistant, chemical corrosion resistant, and a poor conductor of electricity. Products and building materials made with asbestos are often referred to asbestos-containing materials (ACM) and asbestos-containing building materials (ACBM), respectively. Fibers mixed into asbestos cement,

asphalt, and vinyl are usually firmly bound. Generally, when these materials are in good condition there is no cause for concern. Drilling, cutting, grinding, or sanding may release fibers.

24.5.3 Mechanism of Toxicity

The exact mechanism of toxicity of asbestos fibers to lung cells and pleura has not been fully elucidated. The generation of oxidants by fiber uptake or cellular interaction appears to be involved in the cellular response to asbestos. Information about associated health risks have come from studies of individuals exposed to levels of asbestos fibers that are > 5 μm in length. Inhalation of asbestos fibers may lead to the development of a slow buildup of scarlike tissue in the lungs and the pleura, preventing proper expansion and contraction.

Lung cancer and mesothelioma are two cancers frequently associated with asbestos exposure. The mechanism is not precisely known, but studies have suggested that chromosomal alterations and generation of reactive oxygen species are critical.

24.5.4 Toxicokinetics

Following ingestion of asbestos, some of the fibers penetrate the GI epithelium and distribute to other tissues, such as the lymphatic or systemic circulation, resulting in widespread distribution. Macrophages are probably involved in the uptake and distribution process. Most of the asbestos fibers that are deposited in the lung during inhalation are transported by mucociliary action. Only a small fraction of inhaled fibers penetrate the epithelial layer of the lungs (the retention of asbestos fibers in the lungs of asbestos workers was estimated to have a clearance half-life of greater than 10 years).

24.5.5 Signs and Symptoms of Acute Toxicity

Temporary breathing difficulties have been reported in individuals exposed to high concentrations of asbestos dust, which may be accompanied by local inflammatory response in the terminal bronchioles. Progressive fibrosis followed within a few weeks of the first exposure to dust.

24.5.6 Signs and Symptoms of Chronic Toxicity

Long-term inhalation of asbestos fibers in humans results in chronic, progressive pneumoconiosis (*asbestosis*). The disease is common among occupational groups directly exposed to asbestos fibers, such as insulation workers, but also extends to those working near the application or removal of asbestos. A prolonged inflammatory response caused by the presence of fibers in the lungs is characterized by fibrosis of the lung parenchyma. This can be seen radiographically 10 years after the first exposure. The main clinical symptom is shortness of breath, often accompanied by abnormal chest sounds (rales) and cough. In severe cases, disruption of respiratory function may result ultimately in death.

24.6 CADMIUM (Cd)

24.6.1 Occurrence and Uses

Cadmium (Cd) sulfate is used as an astringent. Cd sulfide (CdS, Cd yellow) and Cd selenide (CdSe) are important pigments. The latter metal is electrolytically deposited on Fe or steel and forms a chemically resistant coating. Cd lowers the melting point of metals with which it is alloyed, thus making it useful in the manufacture of fusible metals for automatic sprinkler systems, fire alarms, and electric fuses. Cd salts are also used in photography and in the manufacture of fireworks, rubber, fluorescent paints, glass, porcelain, and as shielding material in atomic energy plants. Cd sulfide is a component in photovoltaic cells and nickel-Cd batteries.

Most Cd enters the environment through coal burning, waste incineration, metal mining and smelting, disposal of metal-containing products, waste-site leakage, and from the use of phosphate fertilizers. Exposure to the general population occurs through cigarette smoke, food consumption, drinking water, and incidental ingestion of soil. For nonsmokers, food is the largest nonoccupational source of exposure. The U.S. EPA reports that average Cd levels in foods range from 2 to 40 ppb, with grain and cereal products, potatoes, leafy vegetables, and root vegetables containing the highest levels. On the average, each person ingests about 30 μg of Cd daily, while smokers absorb an additional 1 to 3 μg per day. Except in areas near Cd-emitting industries or incinerators, minimal exposure occurs through drinking water or ambient air.

24.6.2 Mechanism of Toxicity

Liver is the primary target in acute Cd exposure. Investigations have revealed hepatocellular necrosis with infiltration by inflammatory cells. Although the underlying mechanism of Cd toxicity has not been elucidated, possible factors include oxidative stress or lipid peroxidation of cell membranes.

In 1993, Cd was classified as a human carcinogen. Occupational exposure is associated with lung and prostate cancers, although the carcinogenic mechanism is not known. Cd does not form stable DNA adducts but stimulates cell proliferation and inhibits DNA repair.

24.6.3 Toxicokinetics

Absorption of Cd varies considerably by the route of exposure. Only about 5% of an ingested dose of Cd is absorbed from the GI tract, while absorption from the lung is as high as 90%. Cd clears rapidly from the blood and concentrates in various tissues. Most of the absorbed Cd is found in the liver and kidney and may be related to the ability of these organs to produce large amounts of metallothionein (MT), a small metal-binding protein with a great affinity for Cd. Although binding with MT lessens the toxic effects of Cd, it also hinders its elimination.

24.6.4 Signs and Symptoms of Acute Toxicity

Heating of Cd and its compounds to high temperature produces Cd oxide fumes, which upon inhalation cause flu-like symptoms (*metal fume fever*). The condition