CHAPTER 222

Lead and Heavy Metals and the Kidney

Paolo Lentini, Luca Zanoli, Massimo de Cal, Antonio Granata, and Roberto Dell'Aquila

OBJECTIVES

This chapter will:
1. Discuss the mechanisms of the renal toxicity related to heavy metals exposure.
2. Describe the clinical features of poisoning by heavy metals.
3. Analyze the therapeutic approaches to heavy metal intoxication.

Heavy metals are chemical elements with a specific gravity that is five times the specific gravity of water (1°–4°C). Specific gravity is a measure of density of a given amount of a solid substance when compared with an equal amount of water. The toxic metals arsenic, cadmium, iron, lead, and mercury are defined heavy metals according to this definition. Heavy metals typically are used in agriculture and industrial activities, but natural phenomena such as earthquakes and volcanic eruptions also have been reported to significantly contribute to environment pollution. Heavy metals are used in industrial applications such as production of pesticides, batteries, alloys, and textile dyes. Excessive exposure may lead to specific disorders. The use of cisplatinum for cancer therapy and that of barium during radiologic examinations also can produce unexpected forms of toxicity resulting from heavy metals.

There are more than 30 metals that can cause renal damage through occupational, therapeutic, or accidental exposure. The more common substances involved in renal damage are arsenic, barium, cadmium, cobalt, copper, lead, lithium, mercury, and platinum. Small amounts of these elements are important factors and cofactors in many biochemical reactions.

Heavy metals availability and toxicity are determined by physical factors (phase association, temperature, adsorption), chemical factors (lipid solubility, kinetics), and biochemical factors such as human trophism.

Heavy metals may enter into the human body through food, water, or air; acute poisoning can occur as the result of accidental contamination, suicide attempt, or an inappropriate use of some therapeutic measures.

MECHANISM OF HEAVY METALS TOXICITY

The kidney is a target organ in heavy metal toxicity because of its ability to reabsorb and concentrate divalent metals.

The extent of renal damage depends on the nature, the dose, and the time of exposure. In general, acute damage differs from chronic damage in its mechanism of toxicity. As a consequence, the clinical features and therapeutic approach are also different.[1]

Heavy metals in plasma exist in nondiffusible (protein-bound) and diffusible (complexed and ionized) forms. The luminal fluid in the early proximal tubule can contain the bound form and the free form. The ionized form is toxic and produces direct cellular toxicity; the mechanism consists of membrane rupture and uncoupling of mitochondrial respiration, with the release of numerous death signals such as reactive oxygen species and cytokines.[2]

Metals are cleared quickly from the blood and are sequestered in many tissues. In acute intoxication, the main site of reabsorption is the apical membrane of the first zone of the proximal tubule, but the loop of Henle and the terminal segments can participate in reabsorption of heavy metals. During chronic intoxication, on the other hand, the bound, inert form is conjugated with metallothionein and glutathione, which then are released into the blood by the liver and the kidney. These compounds subsequently are reabsorbed through an endocytotic process in segment S1 of the proximal tubule.[1,2]

THERAPEUTIC APPROACH

Treatment regimens include chelation therapy, decontamination procedures (e.g., charcoal, cathartics, emesis, gastric lavage), supportive care (e.g., intravenous fluids, cardiac stabilization, mechanical ventilation, exchange transfusion), and extracorporeal therapy. The choice of treatment depends on clinical parameters such as age; preexisting pathologies of the liver and kidney (affecting endogenous clearance); cardiovascular disease; toxicologic parameters such as total body, liver, and renal clearances; elimination half-life; molecular weight; toxic dose; protein binding; and the apparent distribution volume.[3]

Considerations for some of the most common metals are reported in the following sections (Table 222.1).

LEAD

Lead (Pb) is one of the oldest occupational toxins, and evidence of lead poisoning can be found dating back to Roman times. Lead is the most ubiquitous of the nephrotoxic metals, and humans are exposed to this agent in air, food, and water.

Source of Exposure

Lead exists in three different forms: metallic lead, inorganic lead (water-soluble lead salts), and organic lead such as tetramethyl lead, which is more toxic than the inorganic form.

Acute Exposure

Acute intoxication is extremely rare and occurs after accidental or intentional ingestion of water-soluble inorganic lead salts or inhalation of tetramethyl lead.

Chronic Exposure

Lead paint, drinking water, lead-glazed ceramics, and herbal remedies from Asia are potential sources of lead exposure. Workers in certain occupations are exposed to high levels of lead, including manufacture of ammunition, batteries, sheet lead, bronze plumbing, radiation shields, and intravenous pumps. Lead also contaminates emissions from motor cars with antiknock additives (tetramethyl lead).[4]

Mechanism of Kidney Damage

Acute Exposure

Acute lead poisoning disrupts the proximal tubular architecture, with histologic changes featuring eosinophilic intranuclear inclusions in tubular cells consisting of lead-protein complexes as well as mitochondrial swelling.[5]

TABLE 222.1

Therapy in Acute Heavy Metal Toxicity

METAL	HD	PD	CVVH	CVVHDF	TPE	HP	CHELATORS
Aluminum	No	No	?	?	No	Yes	DFO
Arsenic	HD + DMSA or HD + BAL	PD + DMSA or PD + BAL	?	?	?	?	BAL, DMSA, D-penicillamine
Barium	Yes	Yes	?	Yes	?	?	—
Bismuth	Yes	Yes	?	?	?	?	BAL, DMSA, DMPS
Cadmium	No	No	No	No	No	No	Calcium-EDTA
Chrome	No	No	No	No	No	No	—
Copper	HD + D-penicillamine	?	?	CVVHDF + D-penicillamine	No	Yes	D-penicillamine, BAL
Lead	No	No	No	No	?	No	Calcium-sodium-EDTA, BAL, DMSA
Lithium	Yes	Yes	Yes	Yes	No	No	No
Mercury	No	No	No	CVVHDF + DMPS	?	No	BAL, DMSA, DMPS (inorganic only)
Platin	Yes	Yes	?	?	Yes	No	No
Thallium	HD + Prussian blue	?	?	?	No	No	Prussian blue

BAL, Dimercaprol; *CVVH,* continuous venovenous hemofiltration; *CVVHDF,* continuous venovenous hemodiafiltration; *DFO,* desferrioxamine; *DMPS,* dimercapo-1-propane sulfonate; *DMSA,* dimercaptosuccinic acid; *EDTA,* ethylenediamine tetra-acetic acid; *HD,* hemodialysis; *HP,* hemoperfusion; *PD,* peritoneal dialysis; *TPE,* therapeutic plasma exchange.

Chronic Exposure

The damage extends to the proximal tubule and to the distal tubule with increased urate secretion, vasoconstriction, and glomerulosclerosis with hypertension and interstitial fibrosis.[6]

Clinical and Laboratory Features

Acute Exposure

Lead poisoning produces a metallic taste in the mouth, nausea, vomiting, diffuse abdominal pain, paresthesias, muscle weakness, and severe anemia with acute hemolytic crisis. Renal impairment may manifest as acute tubular necrosis with hematuria, casts, and aminoaciduria and may be so severe as to progress to frank acute renal failure. This damage occurs in 1 or 2 days. Severe toxicity, with a blood lead level of 50 μg/dL or more, also affects the central and peripheral nervous systems, with frank paralysis, tremors, decreased nerve conduction velocity, and papilledema.[6]

Chronic Exposure

Patients present with myalgias, fatigue, dyspnea, nonspecific abdominal pain, and anorexia. Renal damage includes glycosuria, aminoaciduria, and phosphaturia (Fanconi-like syndrome).

Laboratory Tests

Normochromic or hypochromic anemia with basophilic stippling; elevated reticulocyte count; elevation of blood urea nitrogen (BUN), creatinine, and serum uric acid; with amino acids, glucose, and ALA in the urine (proximal tubule damage) are common laboratory features.

The lead level in the whole blood is an indicator of recent exposure; the selected diagnosis to evaluate the lead level is the ethylenediamine tetra-acetic acid (EDTA) lead mobilization test.[5]

Treatment of Acute Lead Intoxication

Supportive Measures

Gastric lavage and decontamination with activated charcoal are indicated if lead salts have been ingested. Fluid-electrolyte balance must be maintained. Diuretic therapy is indicated, not to eliminate lead but to remove the chelators.[7]

Chelating Agents

In an inorganic lead intoxication, there is an indication to use EDTA, dimercaprol (BAL), dimercaptosuccinic acid (DMSA), and D-penicillamine.

Extracorporeal Therapies

Extracorporeal detoxification measures are ineffective because 95% of lead is stored in the erythrocytes; however, chelators, which are nephrotoxic, can be removed effectively by hemodialysis.[7] The half-life of lead in blood is 9 hours during combined hemodialysis and EDTA and 96 hours when EDTA is given alone.[8] Peritoneal dialysis, hemoperfusion, continuous renal replacement therapies (CRRTs), and therapeutic plasma exchange are generally ineffective.

MERCURY

Mercury (Hg) is a silvery white liquid that is volatile at room temperature because of its high vapor pressure. Mercury exists in three forms: elemental, inorganic, and organic.

Source of Exposure

The general population is exposed primarily to this metal from dental amalgam and the diet; amalgam fillings are the most important source of inorganic mercury, and fish are the most important source of the organic one. Occupational exposure occurs in dentistry, in thermometer factories, and in the alloys and chloralkali industries.[9]

Mechanism of Kidney Damage

Mercury accumulates in the kidney and induces epithelial injury and necrosis in the pars recta of the proximal tubule.[10] After acute exposure to mercury, acute tubular necrosis appears, usually accompanied by oligoanuria.

Clinical and Laboratory Features

Acute Exposure

Elemental mercury in vapors produces symptoms after a few hours such as chills, vomiting, diarrhea, acute dyspnea with the occasional fatal form of interstitial pneumonitis, and neurologic symptoms with hypotension and profuse salivation.

Chronic Exposure

Organic mercury gives skin manifestations and neurologic disturbances such as ataxia, paresthesias, and deafness. Mercury now is recognized as causing different types of kidney damage, such as nephrotic syndrome with membranous nephropathy pattern and tubular dysfunction with elevated urinary excretion of albumin, transferrin, retinol binding protein, and β-galactosidase.[10]

Laboratory Tests

A mercury concentration greater than 45 mg/dL in blood suggests acute poisoning.

Treatment of Acute Mercury Exposure

Supportive Measures

Immediate elimination of the metal by gastrointestinal decontamination and rapid administration of chelators, followed by intensive monitoring of hemodynamics and breathing, is necessary.

Chelating Agents

Treatment with chelators should be considered in patients with acute symptoms arising from the central nervous system. The antidotes currently available are BAL, dimercapo-1-propane sulfonate (DMPS), and DMSA.

Extracorporeal Therapies

Plasma protein binding of mercury is 95%, and the toxin is distributed in a large apparent volume of distribution; for these reasons, hemodialysis, peritoneal dialysis, and hemoperfusion with charcoal are poorly efficient.[7] On the other hand, hemodialysis is useful to eliminate chelators that are highly water soluble. Continuous venovenous hemofiltration (CVVH) is more effective in removing the complex mercury-DMPS than is hemodialysis.[11] Among the extracorporeal elimination methods, plasma exchange appears to be the most efficient treatment to remove inorganic mercury and could be useful in association with chelation therapy.[12]

CADMIUM

Cadmium (Cd) can cause severe toxicity in humans. There are many cases of chronic intoxication resulting from exposure to cadmium but only a few cases of acute poisoning from oral ingestion or accidental inhalation of cadmium-containing fumes.

Sources of Exposure

Exposure to cadmium mainly results from eating contaminated food, smoking cigarettes, and working in cadmium-contaminated work places. Major industrial applications for cadmium are in the production of alloys and batteries.

Mechanism of Kidney Damage

Acute Exposure

The ionized free form is primarily responsible for acute intoxication. It induces cellular toxicity by reduction of phosphate and glucose transport and by inhibition of mitochondrial respiration with membrane rupture of the proximal tubular cells of the nephron.[5]

Chronic Exposure

After ingestion or inhalation, cadmium is transported to the liver and to the kidney by metallothionein, which binds cadmium. A chronic tubular-interstitial nephropathy is produced by the accumulation of this metal in the S1 segment of the proximal tubule and in the medulla. Signs of cell apoptosis and cytokine pathway activation are common in this syndrome.

Clinical and Laboratory Features

Acute Exposure

The toxic symptoms include dyspnea, nausea, vertigo and vomiting, hypotension, shock, and acute renal and liver failure.

Chronic Exposure

Emphysema, cough, chronic kidney damage, and gastrointestinal ulcerations occur during chronic exposure. Renal damage by cadmium may result in tubular proteinuria with renal glycosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, and polyuria with loss of concentration capacity.

Laboratory Tests

Exposure to cadmium is commonly determined by measuring 24-hour urinary cadmium excretion; an elevated urinary excretion of β_2-microglobulin has proved to be useful in detecting subtler signs of cadmium nephrotoxicity.[13]

Treatment of Acute Cadmium Exposure

Supportive Measures

Within 3 hours from the ingestion, it is recommended that gastrointestinal decontamination be performed, with support for cardiac and pulmonary function. Forced diuresis is not indicated, because cadmium is highly nephrotoxic.

Chelating Agents

Very soon after absorption, cadmium is stored in the erythrocytes and bound with metallothionein. There are no antidotes for cadmium intoxication. In contrast to the other heavy metals, chelators actually may increase cadmium nephrotoxicity.

Extracorporeal Therapies

The extracorporeal measures of detoxification are ineffective, because cadmium is fixed to cells; peritoneal dialysis, hemodialysis, and CRRT are used to remove chelators in acute renal failure caused by cadmium.[7]

CISPLATIN

Cisplatin is an antineoplastic agent that is used against various types of solid and hematologic tumors; however, cisplatin is a drug with potential side effects, including nephrotoxicity, neurotoxicity, myelotoxicity, and ototoxicity.

Sources of Exposure

The typical source of exposure is chemotherapy.

Mechanism of Kidney Damage

The toxicity is dose related. Cisplatin is a strong renal tubular toxin that can damage the S3 segment cells of the proximal tubule; the distal nephron also may be involved. The earliest change in tubule function is decreased protein synthesis resulting from the formation, via cytochrome P-450 enzymes, of highly reactive hydroxyl radicals that produce injury by DNA binding.[14]

Clinical and Laboratory Features

Accidental overdose of cisplatin may manifest as severe nausea, vomiting, loss of hearing, and oligoanuria with hematuria and casts in the urine. The urine osmolality is similar to that of plasma; this concentrating defect reflects platinum-induced damage to the loop of Henle.

Laboratory Tests

Liver damage, as indicated by elevated aspartate transferase (AST), alanine transferase (ALT), gamma-glutamyl transferase (GGT), and bilirubin values, and elevated renal dysfunction markers are common findings during acute cisplatin intoxication. Cisplatin frequently is associated with anemia resulting from erythropoietin deficiency induced by kidney injury.

Treatment of Acute Cisplatin Intoxication

Supportive Measures

The most common measures used to prevent cisplatin-induced nephrotoxicity are hydration with electrolyte replacement, forced diuresis, and antiemetic therapy; severe myelosuppression often requires the administration of granulocyte colony-stimulating factors.[15]

Chelating Agents

There is no specific chelation therapy for cisplatin intoxication. Amifostine, an organic thiophosphate, may diminish cisplatin-induced toxicity by donating a protective thiol group.

Extracorporeal Therapies

Hemodialysis is able to reduce free cisplatin in plasma, but the metal binds to plasma proteins after administration very quickly and cannot be further eliminated by this procedure. There is also a large rebound of cisplatin into plasma from an exchangeable pool after hemodialysis.

Plasmapheresis appears capable of removing the protein-bound fraction and the cisplatin free form. Practical experiments have been conducted using a plasma filter and the substitution of 3 L of plasma for three to four sessions.[15]

ARSENIC

Arsenic (As) exists in inorganic forms (arsine gas, arsenite, and arsenate) and in organic forms (the trivalent and pentavalent forms). Acute high-dose exposure to arsenic can cause severe systemic toxicity and death.

Source of Exposure

Trivalent arsenic or arsenite compounds are considered the most toxic forms; common sources of exposure are pesticides, herbicides, homeopathic remedies, and contaminated water and food supplies.

Mechanism of Kidney Damage

Arsenic compounds are well absorbed after ingestion or inhalation. On entering the circulation, arsenic strictly binds hemoglobin. After 24 hours, it is accumulated in soft tissue; after 2 weeks, arsenic is incorporated in hair and nails.

Trivalent (+3) arsenic, the most toxic form, avidly binds to sulfhydryl groups and interferes with numerous enzyme systems, such as those of cellular respiration, with uncoupling oxidative phosphorylation.[7]

Clinical and Laboratory Features

Acute Exposure

Acute exposure can occur after ingestion or acute inhalation of high levels of arsenic dusts or fumes and in suicide or poisoning attempts. Acute toxicity symptoms include nausea, vomiting, abdominal pain, and diarrhea. These symptoms are soon followed by a diffuse pruritic macular rash, dehydration, hemodynamic instability, and acute respiratory distress syndrome. Renal injury can lead to oligoanuria, proteinuria, hematuria, and acute tubular necrosis; renal damage is intensified by hemoglobinuria resulting from hemolysis and hypotension.[16]

Chronic Exposure

In chronic poisoning, peripheral neuropathy and encephalopathy with cognitive impairment are the predominant manifestations.

Laboratory Tests

ACUTE EXPOSURE. Measurements of arsenic levels in the urine are more significant than those in the blood, because arsenic is cleared rapidly from the blood. Excretion of more than 200 µg in a 24-hour urine collection is suggestive of arsenic overload.

CHRONIC EXPOSURE. Chronic arsenic exposure can be confirmed by a 24-hour urine collection and arsenic concentration determination.

Treatment of Acute Arsenic Intoxication

Supportive Measures

The first step is the elimination of further exposure. Gastrointestinal decontamination with charcoal and forced emesis is recommended, with careful assessment of the intravascular volume and administration of fluids and electrolytes. Moreover, because arsenic is well eliminated by urine, it is useful to force diuresis.

Chelating Agents

In a severely ill patient with acute arsenic poisoning, chelation may be required; BAL and DMSA are the most frequently used agents.

Extracorporeal Therapies

Hemodialysis has very limited capacity in arsenic removal, but it can be used to remove chelators that are nephrotoxic.

Furthermore, hemodialysis and other extracorporeal blood purification techniques should be used if acute renal failure develops. CVVH-CVVHDF with a large-pore membrane is preferred to help maintain greater hemodynamic stability. In association, exchange transfusion has been used in severe arsenic intoxication, providing some benefit.[7]

Peritoneal dialysis and hemoperfusion are inefficient and are not indicated.

LITHIUM

Lithium (Li) carbonate commonly is prescribed for the treatment of bipolar manic-depressive disorder. Either during chronic maintenance therapy or in acute treatment/overdose, lithium may lead to severe toxicity.

Sources of Exposure

Lithium ingestion can occur accidentally or in suicide attempts. Antidepressive therapy also may lead to excessive exposure.

Mechanism of Kidney Damage

Lithium carbonate is absorbed almost completely by the tissues within 8 hours after distribution into the intravascular space; therefore there is a rapid disappearance from the plasma and a slow excretory phase. In fact, 95% of a dose is excreted in urine 30% to 60% during the first 12 hours and 70% to 40% during the next 10 to 14 days. Lithium is a small ion that does not bind to proteins; however, lithium diffusion between intracellular and extracellular compartments is slow.[7]

Clinical and Laboratory Features

The patient with acute lithium intoxication has stupor, tremor, confusion, hemodynamic instability, vomiting, diarrhea, hyperreflexia, and acute renal failure, sometimes with polyuria and casts in the sediment. Chronic lithium ingestion is a common cause of nephrogenic diabetes insipidus, renal tubular acidosis, nephrotic syndrome (minimal change or focal-segmental glomerulosclerosis), and chronic interstitial nephropathy.[17]

Laboratory Tests

The serum lithium therapeutic range is 0.4 to 1.2 mmol/L. Values exceeding this range are significant for intoxication; however, values in the normal range do not exclude excessive exposure.

Treatment of Acute Lithium Intoxication

Supportive Measures

Gastric lavage and administration of emetics should be carried out within 8 hours after acute overdose. Patients with normal renal function initially should be treated with a rapid infusion of saline with sodium bicarbonate to increase the urinary lithium output. If the patient has a severe intoxication with coma, convulsions, and acute renal failure, the only treatment should be the application of renal replacement therapy. Cardiac monitoring and mechanical ventilation are recommended during acute intoxication.

Chelating Agents

There are no chelating agents specific for acute lithium intoxication.

Extracorporeal Therapies

To accelerate lithium clearance when levels are higher than 3.5 mmol/L, as in the case of acute intoxication, various modalities of extracorporeal blood purification may provide adequate results.

HEMODIALYSIS. Being a small, non–protein-bound molecule, lithium is removed rapidly by hemodialysis with simultaneous correction of acid-base and electrolyte disorders. High-efficiency bicarbonate dialysis is recommended. Mixed diffusive-convective therapies such as hemodiafiltration and dialysis with high-flux membranes (e.g., polysulfone, polyamide, polymethylmethacrylate [PMMA]), seem to be even more efficient, and they represent the first-choice therapy for severe acute lithium intoxication.[18] The efficiency of extracorporeal removal is limited by a high postdialysis rebound of lithium levels resulting from compartmentalization of the molecule.

PERITONEAL DIALYSIS. Lithium can be removed by peritoneal dialysis, although its clearance is much lower than in hemodialysis. Peritoneal dialysis can be considered an alternative when hemodialysis is not available.[18]

HEMOPERFUSION. Because the adsorption of lithium with activated charcoal or resins is very limited, the technique of hemoperfusion is poorly efficient.

CONTINUOUS RENAL REPLACEMENT THERAPIES. CRRT can result in a remarkable blood purification, removing also intracellular lithium by preventing postdialysis rebound. However, CRRT in cases of acute intoxication does not reduce the lithium level as rapidly as hemodialysis does. The best treatment for acute lithium intoxication appears to be the combination of hemodialysis for rapid lithium removal, followed by continuous hemodiafiltration to prevent postdialysis rebound.[18]

OTHER HEAVY METALS

Few papers in the literature report about acute renal failure caused by other heavy metals such as uranium, bismuth salts, hexavalent chromium, aluminum, vanadium, and copper. Treatment for poisoning by these agents is not well codified, and evidence for various therapies is scanty.

BIOMARKERS AND KIDNEY INJURY

Given the limitations of serum creatinine as a marker of renal function, different urinary and serum molecules have been investigated as possible acute or chronic kidney diseases.

One of the most promising novel biomarkers is neutrophil gelatinase-associated lipocalin (NGAL). Urine NGAL also has been shown to predict kidney injury and dialysis requirement in welding workers.[19]

Peddemenas et al. showed that urinary kidney injury molecule (KIM-1) levels are correlated positively with urinary cadmium concentration and early cadmium kidney damage.[20]

CONCLUSION

Thanks to improvements in industrial safety, cases of acute heavy metal poisoning are less frequent, but they remain a cause of acute renal failure that always should be considered in suicide attempts, cases of accidental contamination, and environmental or industrial disasters. Nephrotoxicity (e.g., renal tubular injury) should be considered an emerging concern in occupational health.

Key Points

1. Acute toxicity differs completely from chronic toxicity in its clinical, diagnostic, and therapeutic aspects.
2. The extracorporeal treatments, even if not always as decisive as chelation, are nevertheless the key strategy in accelerating detoxification and improving the outcome of patients with acute poisoning; these treatments also play an important role in renal detoxification related to nephrotoxicity of chelating agents.
3. The use of continuous renal replacement therapy, particularly continuous venovenous hemofiltration and hemodiafiltration, as yet not well codified, appears to offer particular advantages under the conditions of hemodynamic instability that characterize the poisoning state, without reducing the purifying effect.

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