Cadmium

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Jan Meulenbelt

Contents

Together with zinc and mercury, cadmium belongs to group IIb of the periodic table. It can be found in rocks, soil, water, coal, zinc ore, lead ore, and copper ore. In the environment, cadmium is present predominantly as the oxide or as the chloride, sulfide, or sulfate salt. It has no recognizable taste or odor. Cadmium sulfide, carbonate, and oxide salts are practically insoluble in water, whereas the sulfate, nitrate, and halides are soluble in water.

Cadmium is utilized widely in industry for the production of glass and metal alloys as well as many consumer products, such as batteries or pigments in plastics. Exposure to relatively high cadmium concentrations occurs predominantly in the workplace. Workers also can be exposed during welding and soldering. Cadmium oxide is the compound most frequently inhaled. Cadmium is also present in tobacco smoke.

Biochemistry and Kinetics

The major route of cadmium exposure for the nonoccupational setting and nonsmoking persons is via food (e.g., leafy vegetables or potatoes). Normal daily exposure is approximately 30 μg/day, of which about 1–3 μg/day is absorbed. In smokers, 2–6 μg/day can be absorbed. The smoke of one cigarette contains about 1–2 μg of cadmium.

In water, insoluble cadmium salts can be solubilized with changes in pH. Consequently,

This chapter was submitted shortly before the death of Dr. Meulenbelt, a sophisticated medical toxicologist, highly respected intensivist, and a great friend. He will be sorely missed.

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insoluble cadmium compounds, such as cadmium oxide and carbonate, can dissolve at gastric pH. Iron deficiency increases cadmium absorption, whereas oral zinc supplements decrease its absorption [1]. Approximately 25% of cadmium administered with food is still retained after 3–5 days. Retention decreases to approximately 6% after about 20 days [2, 3]. Whole-body retention ranges from 1.2% to 7.6% (mean 2.7%) [4]. Following Satarug et al. a safe daily intake of cadmium should be kept below 25–30 μg/day per person [5, 6]. The Permissible Exposure Limit, or PEL, which defines the limit to which an employee may be exposed to cadmium in the workplace is set at 5 $\mu g/m^3$ air [7]. The Separate Engineering Control Air Limit, or SECAL, apply to select and defined industries and processes, is 15 or 50 $\mu g/m^3$ for cadmium, depending on the processes involved [7].

Depending on the kind of cadmium compound and particle size, 50% of inhaled cadmium can be absorbed. Some authors stated that exposure to relatively more soluble compounds in biologic fluids seemed to be relatively more harmful [8, 9], but this was not confirmed by others [10]. The initial lung burden declines slowly after exposure [9, 11, 12]. Most inhaled or ingested cadmium is excreted in the feces. The excretion of cadmium via the kidneys is low.

Cadmium (+2) ions bind to anionic groups (especially sulfhydryl groups) in proteins (notably albumin and metallothionein) [13]. They are absorbed by the intestinal mucosa, after which a cadmium-metallothionein complex is transported to the target organs. Cadmium does not undergo any direct metabolic conversion, such as oxidation, reduction, or alkylation. The cadmium concentration in most tissues increases with age, especially in the kidneys and liver. The spleen, pancreas, and testes also contain relatively high concentrations after chronic cadmium exposure. After reviewing the literature, Kjellström and Nordberg [14] concluded that cadmium half-life in the kidney is 6–38 years (mean approximately 12 years) and in the liver is 4–19 years (mean approximately 7.5 years). Placental transfer of cadmium is slow and incomplete [15]. A kidney cadmium concentration of 50 μg/g wet weight is a maximum tolerable level in order to avoid abnormal kidney function [16]. This renal concentration corresponds to a urinary cadmium excretion of 2 μg/d [5].

Clinical Presentation

Symptoms After Acute Exposure

Acute intoxication by inhalation of air with high cadmium levels rarely occurs except in cadmium welding, when exposure to high concentrations may cause severe pulmonary damage. During exposure, the symptoms are generally mild (comparable to symptoms seen in metal fume fever, such as cough, dyspnea, chest pain, and fever), but within a few days severe acute respiratory distress syndrome can develop, leading to respiratory failure, which can be fatal [17]. The lowest observed adverse effect level necessary in acute exposure to cause serious effects in humans seems to be 10 mg/m^3. If a patient recovers from acute cadmium poisoning, the improvement seems to be rapid and complete. Limited data on follow-up after acute exposure are available.

Acute intoxication by ingestion may cause retrosternal pain (caused by esophageal irritation), nausea, vomiting, abdominal cramps, and diarrhea. Shock may be observed, which can be caused by fluid loss or cardiovascular depression or both. Ingestion of more than 150 g should be considered life threatening [18, 19].

Chronic Exposure

Cortona and colleagues [20] measured respiratory function parameters (forced expiratory volume, forced vital capacity, residual volume, and carbon monoxide diffusion) in 69 smoking and nonsmoking male subjects exposed for years to concentrations of 0.008–1.53 mg/m^3 of cadmium fumes in a factory producing cadmium alloys. In exposed workers, residual volume was more than 8% higher than in unexposed workers. In severely exposed workers, residual volume was increased by more than 10%.

Lung cancer risk also may be increased after long-term inhalational cadmium exposure. Stayner and coworkers [21] calculated that chronic exposure to 0.10 mg/m^3 cadmium oxide dust or fume 7 days/week and 8 h/day may cause 50–111 excess lung cancer deaths per 1000 workers.

Eating or inhaling lower levels of cadmium for a long period may cause a high cadmium body burden, which may result in renal damage. The kidney is the main target organ of cadmium toxicity, particularly the proximal tubules. Although intracellular metallothionein is induced by cadmium, offering partial protection, nephrotoxicity may occur at times when this protection is insufficient. Cadmium not bound to metallothionein presumably is responsible for the cadmium-related tissue injury. The mechanism of kidney damage is not fully understood. The role of zinc transporters, calcium transporters, divalent metal-ion transporter-1, and metallothioneins in the accumulation of cadmium in the kidney cell is nicely reviewed by Yang and Shu [22]. The early stages of cadmium-induced proximal tubule injury may involve specific changes in cell-cell adhesion, cellular signaling pathways, and autophagic resposes, which occur before the onset of necrosis and apoptosis [23]. The lowest observed adverse effect level for chronic inhalational exposure causing renal effects in humans has been reported to be 0.05–0.1 mg/m^3, and the no-effect level is 0.02–0.05 mg/m^3 [24–27]. Proteinuria has been reported at inhalational exposure levels of 0.067 or 0.0379 mg/m^3 [28, 29].

There is no convincing evidence that cadmium causes hypertension. There is weak support that increased cadmium body burden may alter central nervous system function as evaluated by neuropsychologic tests [30]. A modest difference was found between cadmium-exposed and nonexposed workers in attention, psychomotor speed, and memory tests.

Cadmium exposure has been shown to alter zinc, iron, and copper metabolism, causing deficiencies of these trace elements [31]. Cadmium also influences selenium metabolism, inducing reduction in the activity of the selenoenzyme glutathione peroxidase [32].

Cadmium affects calcium metabolism. Painful bone disorders, including osteomalacia, osteoporosis, and spontaneous bone fractures, have been reported in persons chronically exposed to cadmium in food (e.g., itai-itai disease) [33, 34]. Dietary deficiencies of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects after cadmium exposure [35]. Cadmium-exposed people exhibit a progressive disturbance in renal metabolism of vitamin D to its biologically active form [16, 36, 37]. Cadmium exposure is associated with risk of renal stones [38, 39]. Mason and associates [40] reported decreased renal reabsorption of calcium among cadmium alloy workers. This decreased calcium reabsorption is presumably responsible for the higher risk of renal stones in cadmium-exposed persons.

Diagnosis

Cadmium can be measured in blood, urine, hair, and nails. The blood concentration of cadmium is the best indicator of recent exposure [41, 42]. Urinary excretion of cadmium correlates with body burden and renal damage [41, 42]. Cadmium-exposed persons with proteinuria generally have increased cadmium excretion. The urine cadmium excretion may decrease, however, if renal damage is severe [15]. Hair and nails are less reliable because they can be contaminated easily. Within 1 day after exposure, the cadmium in blood is contained mainly in the red blood cells, and the plasma concentration may be low [43]. Whole-blood cadmium concentrations normally range from 0.4 to 1 μg/L (approximately 4–9 nmol/L) for nonsmokers and 1.4–4 μg/L (approximately 13–36 nmol/L) for smokers [13]. Whole-blood cadmium concentrations of 10 μg/L (approximately 89 nmol/L) are considered acceptable for occupational exposures [44]. The urine cadmium concentration is normally less than 1 μg/g of creatinine (approximately 1 nmol/mmol of creatinine) [13]. The average urine cadmium concentration is 0.35 μg/g of creatinine (approximately 0.35 nmol/mmol of creatinine) in nonsmokers; levels greater than 2 μg/g of creatinine (approximately 2 nmol/mmol of creatinine) are rare.

Proximal renal tubular damage can be diagnosed by increased concentrations of low-molecular-weight proteins in the urine. The leakage of these proteins is not specific for cadmium toxicity but is a marker of proximal tubular damage. These proteins, such as β_2-microglobulin, light-chain immunoglobulins, retinol-binding protein, lysosomal enzyme *N*-acetyl-β-D-glucosaminidase (NAG), and ribonuclease, are filtered by the glomerulus and normally reabsorbed in the proximal tubules of the kidney. When kidney injury is present, the reabsorption of these low-molecular-weight proteins is hampered. NAG and β_2-microglobulin are the most commonly used biomarkers of cadmium-induced proximal tubule injury. Of these, NAG is more sensitive. A novel marker that has shown promise in preclinical studies is kidney injury molecule-1 (KIM-1). KIM-1 is a transmembrane protein that is not detectable in normal kidney but is expressed at high levels in the proximal tubule after ischemic or toxic injury. Urinary KIM-1 serves as an earlier diagnostic indicator of kidney injury when compared with any of the conventional biomarkers [45]. In severe kidney damage, high-molecular-weight proteins, such as albumin, also can be detected in urine. Decreased reabsorption of amino acids or glucose may be more sensitive for tubular dysfunction than the leakage of low-molecular-weight proteins.

Treatment

Acute Exposure

Therapy should begin by removal of the subject from the exposure. There is inadequate documentation on the usefulness of gastrointestinal decontamination in the case of ingestion of cadmium. Activated charcoal has no proven benefit after cadmium exposure. Hemodialysis and hemoperfusion are not useful in the treatment of cadmium intoxication. In cases of severe renal damage, hemodialysis is useful to replace kidney function.

In acute cadmium poisoning, chelation efficacy depends on the chelating agent used, the molar ratio between the chelator and cadmium (Cd^{2+}), the route of exposure, and the time elapsed between exposure and the initiation of therapy. Sodium calcium edetate (EDTA), penicillamine, and British antilewisite have been used, but these seem to be of limited value and may increase kidney burden and damage [46]. Andersen [47, 48] reported that 2,3-dimercaptosuccinic acid (DMSA) was effective in acute cadmium poisoning in mice. DMSA and 2,3-dimercapto-1-propane sulfonate (DMPS) were effective in reducing mortality and reducing cadmium burden in liver and kidneys in cadmium-intoxicated mice [49, 50]. DMPS is also active intracellularly; DMSA is not. Chelation therapy for acute cadmium exposure may be useful, but this needs to be confirmed in human clinical practice. Doses of DMSA or DMPS normally used during the chelation of other heavy metals should be used (see ▶ Chaps. 165, "Succimer," and ▶ 168, "Unithiol", respectively, for a further discussion of these agents).

Indications for ICU Admission in Cadmium Poisoning

- Acute inhalational exposure with respiratory failure due to pneumonitis, pulmonary edema, or both
- Severe metabolic disturbances due to renal failure from chronic exposures

Chronic Exposure

The treatment of chronic cadmium poisonings is complicated by the difficulty in evaluating the body burden and the lack of data regarding chelating agents in this setting [51]. At present, chelation generally is not advised for chronic cadmium exposure. DMPS and DMSA may decrease cadmium body burden effectively. It has not been established, however, whether this therapy would decrease cadmium-induced end-organ toxicity and advice should be sought from a medical toxicologist on a case-by-case basis.

In chronic cadmium exposure, removal from exposure is of fundamental importance. Adequate

occupational hygiene, environmental monitoring, and worker surveillance are important to limit occupational vapor exposure.

Criteria for ICU Discharge in Cadmium Poisoning

- Patient weaned from the mechanical ventilator
- Metabolic disorder mainly corrected

Key Points in Cadmium Poisoning

1. Cadmium accumulates in the body.
2. The kidney is the main target organ.
3. Measure whole-blood cadmium concentration to validate acute exposure.
4. Measure urine cadmium concentration to validate chronic exposure and increased body burden.
5. Treatment is primarily supportive.
6. The efficacy of chelation therapy is not proven.
7. In chronic cadmium exposure, be aware of osteomalacia and osteoporosis (itai-itai disease).
8. Chronic cadmium exposure is associated with risk of renal stones.

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