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Review Paper

Cadmium and its health effects

Alaettin Unsal[1] and Mustafa TOZUN[2*]
[1]Eskisehir Osmangazi University, Medical Faculty, Public Health Department, Eskisehir, Turkey
[2]Izmir Katip Celebi University, Medical Faculty, Public Health Department, Cigli, Izmir, Turkey
mtzn76@gmail.com

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Abstract

Cadmium (Cd) is an odorless, tasteless and very toxic heavy metal and has been among the Group I carcinogens. Cadmium is used in steel plating, cadmium-nickel battery structure, batteries, coating of metals for corrosion protection, plastics and alloys as durability enhancers. Cadmium is mainly supplied to the body in the form of dust and smoke through air, water, soil and food chains (such as rice, vegetables, seafood), and some inorganic compounds are taken through the skin. Cadmium content in tobacco leaf and smoke is very high. A few days after intense exposure to Cd smoke, pulmonary edema can sometimes develop and even death. Chronic Cd intoxications affect the lungs, the circulatory system and the genital system, especially the kidneys. The most important result of chronic exposure is Itai-itai disease. Cadmium causes prostate, kidney and lung cancers. In terms of protection from the effects of Cd, it is very important to avoid water and foods with high Cd content and tobacco and their products. It would be beneficial to carry out awareness studies on Cd's health hazards and ways of protection to the risk group. It is extremely important to comply with legal requirements for protection from occupational exposures.

Keywords: Cadmium, Exposure, Health.

Introduction

Until the discovery of Friedrich Stromeyer and Karl Samuel Leberecht Hermann (1817), Cadmium (Cd) was not known. It is a heavy metal. It doesn't smell and taste. It is included in group II in the periodic table[1]. Cadmium's atomic number is 48. Cadmium, which has an atomic weight of 112.4, is bluish silver white and has soft, formable, bright and electropositive. The melting and boiling points are 320.9 and 765 degrees Celsius, respectively. The density is 8.65 grams per cm^3. For Cd, vapor pressure is 394^0C at 1 mmHg[2]. Cadmium, which has a share of about 0.01% on earth, is mostly found as cadmium sulfide (CdS). Pure Cd is not found in nature. It is found in some mineral shoots, mainly zinc, in nature. Cadmium emerges as a by-product while zinc ore is obtained. It is present in 0.5-2% of zinc sulphide minerals. Cadmium has 8 isotopes and the two most common isotopes are ^{112}Cd and ^{114}Cd. Cadmium; organic amine compounds, sulfur complexes, chloro complexes and chelates. Cadmium ions; forms soluble salts of carbonates, arsenates, phosphates and ferrocyanide compounds[3].

Methodology

For this study, the studies on the subject in the medical literature were screened through Google Scholar and Pubmed. Especially the articles published after 2000 were reviewed and presented in references. In this article, Cadmium's uses in industry, risk groups, acute and chronic health effects and the treatment of cadmium poisoning are examined and presented as subtitles.

Uses in industry

Cadmium is a heavy metal used in many industries due to its physical and chemical properties. It is especially used in cadmium-nickel cell structure, batteries, steel, iron, copper and zinc for protection against corrosion. It is used as a strengthening agent into alloys and plastic. The most widely used area is steel coating as it provides a surface which is resistant to oxidation and stable, protected from corrosion and has a metallic gloss. Besides, Cd is used to reduce friction. Coating is done by electrolysis or steam coating. Cadmium isotopes, a neutron absorber, are used in nuclear reactors as control bars, as well as in *Westan* standard batteries. Polyvinyl chloride can be used as a stabilizer for plastics, as well as in the manufacture of solder and some cast alloys[4-6].

Some Cd compounds are incorporated into the paints to provide yellow and red pigment. Cadmium is the leading material that gives yellow color in paint, soap, textile and paper sectors. Cadmium sulfide is used to obtain yellow color in dyes, as well as cadmium sulfide and selenite mixture gives yellow to red colors[7]. One of the substances used in medicine as antiseptic is Cadmium sulfate. Cadmium bromide and cadmium iodide are used in the formation of silver iodide in silver nitrate collodium plates. Cadmium chloride is used in cotton dyeing and galvanoplasty[3,8].

Cadmium is a significant consequence some human activities which are the fossil fuels use, metal ore combustion and waste

incineration etc. If wastewater contaminated water seeps into agricultural soil, Cd compounds are also absorbed by the plants. Cadmium is transferred to people who eat these plants as nutrients. As a result, Cd accumulates in various organs of the human body[9].

Cadmium is mainly supplied to the body in the form of dust and smoke through air, water, soil and food chains (such as rice, vegetables, seafood), and some inorganic compounds of Cd are taken through the skin[10]. Since Cd content is high in tobacco leaf and smoke, smoking increases Cd intake. Today, unfortunately, the most important role in Cd exposure is in tobacco use. Respiratory tract is more important in Cd absorption than digestive tract. Breathing of cigarette smoke is responsible for half of the Cd entering the body[11]. In non-smoking populations, Cd is most commonly taken by the diet (average 10-30µg daily). A significant amount of Cd is present in algae, offal and molluscs and crustaceans. However, they are not consumed much. Therefore, cereals, vegetables, starchy roots and tubers play a major role in the Cd intake through diet[12].

In bloodstream, it is transported by binding to protein and blood cells, come to the liver and is taken up by hepatocytes. It then stimulates the synthesis of metallothionine bound to Cd. As cadmium-metallothionine (Cd-MT), it filters through the glomeruli and then reabsorbed in the proximal tubules. The body remains mainly in the tubular cells, which increases the Cd load. Although Cd-MT has been reported to cause tubular damage in previous studies, ionic Cd is the most important factor causing tubular damage in recent studies[13]. Fanconi Syndrome is a proximal tubular reabsorption defect. If accumulation of Cd in high level realise in the kidneys, Fanconi Syndrome may occurs. This proximal tubular dysfunction causes to an increase in calcium and phosphate loss in the urine, contributing to the development of osteoporosis[14]. From the body with urine, feces, sweat, hair and milk, Cd excretion realise very slowly. Most of the Cd taken with food and water is excreted in the feces without absorption (approximately 5% is absorbed). Cadmium toxicity occurs acute and chronic[13,14].

If the exposure time is long, of Cd almost 3 in 4 stays in the liver and kidneys. The highest concentration in the body is found in the kidneys. Cadmium is a metallothionein protein that binds to organs and tissues in the accumulation. Metallothionein, which is very rich in cysteine which can bind other metals such as zinc, arsenic, tin and mercury, is important in terms of bioactivation and has small molecular weight. For Cd, 15-20 years half-life in the human body is known[15].

Daily Cd quantity up to 40mg/day may observed in the human body. The amount of Cd excreted from the body is 40mg/day. The European Food Safety Authority (EFSA) states that the tolerable amount of Cd that can be taken by the food chain is 2.5 µg/kg per week[16].

As temporary, maximum weekly Cd intake 7µg/kg was defined as tolerable dose by the Joint Food Experts Committee of the Food and Agriculture Organization / World Health Organization (FDA / WHO)[17].

In US, the time-weighted average threshold limit value for Cd is 0.005mg/m^3 [18]. The lethal dose$_{50}$ (LD_{50}) is 225mg/kg in rats[19].

Acute and Subacute Effects

Intake Cd via respiration causes irritation of the mucous membranes of the respiratory tracts. The signs of metal fume fever are cough, fever, sweating, dyspnea, chest pain and difficulty in swallowing, and may begin after half or a day than high level exposure to Cd vapor or fume. And after A few days, pulmonary edema may sometimes develop and even death. Cadmium taken orally for several weeks; it causes kidney, lung and circulatory system deficiencies, gastrointestinal system inflammation and liver damage. Early signs of Cd poisoning include kidney damage, proteinuria, calcium loss, and tubular lesion[20].

Chronic Effects

Chronic Cd intoxication affects the kidneys, lungs, circulatory and genital systems. The most important result of chronic exposure is Itai-itai disease. This disease was first seen in the Jinzu river basin of Toyama, Japan. The cause of the disease has been shown to be feeding with rice grown in rice fields irrigated with Cd and 29 mineral wastes, which are the by-products of zinc mining in the region. Long-term oral ingestion of Cd has been reported to cause *Itai-itai* disease[21]. Painful osteoporosis is remarkable in chronic Cd poisoning and the first symptom is usually femoral and low back pain. Over time, pain and bone fractures may spread to other parts of the body. Cadmium, which reduces serum parathyroid hormone levels, is thought to cause calcium release from bone tissue, thus causing osteomalacia or osteoporosis. Horiguchi et al.[22] reported that the main cause of bone demineralization in Cd poisoning may be the inadequacy of osteoblast and osteoclast function, as a result of renal dysfunction. In severe Cd poisoning, nephrotoxicity may occur due to the decrease in glomerular filtration rate as well as complications such as glucosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, polyuria and decreased buffering capacity[23]. The first sign of Cd-induced renal damage is disruption of functional integrity in proximal tubules, and proteinuria due to cellular damage. The most common proteins in urine are β2-microglobulin, retinol binding protein and α1-microglobulin[24].

Cadmium is thought to reduce sperm count, volume and density in men, increase immature sperm forms, decrease libido and serum testosterone levels. In women, it is reported that it inhibits ovarian function and development of oocytes and increases the rate of spontaneous abortion[25].

Some studies have shown that Cd facilitates the formation of atherosclerotic plaques, leads to hypertension, and increases peripheral arterial occlusion and cardiovascular mortality[26,27].

Cadmium is a neurotoxic substance and may cause polyneuropathy and neuropsychiatric symptoms[28]. Due to cellular damage and lipid peroxidation caused by Cd in the brain, some neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington may be occurred that accompanied by memory loss and behavioral changes[29,30].

Lampe et al.[31] reported that pulmonary inflammation and emphysema may develop, especially as a result of exposure to cadmium chloride. Godt et al.[32] reported that in some cases of Cd intoxication, hyperkeratosis and acanthosis may be seen with ulcerative changes in the skin. In a study by Rydzewski et al.[33], there was a significant relationship between Cd concentration in blood, urine and workplace air and odor disturbance. Cadmium is also known to have a mutagenic effect. It has been shown to alter the metabolism of both RNA and DNA. It has been reported to have effects on gene transcription and translation[34]. It has also been shown to be teratogenic in animal experiments[35].

The International Agency for Research on Cancer (IARC) classified Cd compounds as definite carcinogens (Group I)[36]. Cadmium causes prostate, kidney and lung cancers. It is reported that there was a relation Cd exposure and some cancers (hematopoietic system, liver, bladder, stomach, breast and pancreas cancers)[37].

Laboratory findings in cadmium poisoning

High urine and Cd concentrations are very important for the diagnosis of Cd toxicity. Cadmium levels are determined by using blood, urine, hair and nail samples in the diagnosis of Cd poisoning. Long-term Cd exposure effects kidneys, primarily. It is assumed that if urine Cd concentration is ≥0.5µg/g creatine, it is related with kidney damage, and if the concentration is ≥2.0 µg/g creatinine, the damage may be greater[38]. As a depend on developing tubular dysfunction, urinary excretion of low molecular weight proteins (ß2-microglobulin, α1 microglobulin, retinol binding protein), of some enzymes, such as N-acetyl-ß-glucosaminidase, besides of calcium are increase. The analysis of these proteins in urine analysis is a sign of exposure long duration[39].

Since blood and urine Cd levels are positively correlated with each other, both can be used to assess Cd body load[40]. Blood Cd level can be measured by electrothermal atomic absorption spectrophotometry or inductively coupled plasma mass spectrometry. The limit value for blood Cd concentration is 0.3µg/l.[41]

The mean amount of Cd in hair is reported to be 0.61±1.13µg per gram and 1.11±0.83µg per nail[42]. Saliva analysis can be an excellent method for long-term detection of heavy metal contamination. With a tolerable standard limit in the human body, the average Cd level in saliva is less than 0.55µg/l[43].

Cadmium concentration to lead to an increase in lipid peroxidation. Besides, and it causes changes in lipid metabolism[44]. The use of nanotechnology to diagnose and eliminate Cd poisoning can help to manage Cd poisoning and improve environmental safety[45].

Cadmium poisoning treatment

The treatment approach in Cd poisoning is based on the removal of Cd with chelating agents from the body. Since LD_{50} (lethal $dose_{50}$) for Cd is 5 grams in a 70kg male, if there is no vomiting in emergencies, gastric lavage should be performed immediately using a small nasogastric tube[46]. Some of the various chelating agents used in Cd poisoning are:

Ethylene Diamine Tetra Acetate (EDTA): Ethylenedi aminetetra acetic acid (EDTA) significantly increases the excretion of Cd from the body, especially urine. In the treatment, 500mg Ca^{++} EDTA is given with 50mg glutathione/kg within 24 hours and repeated infusion for 12 days. If Cd level in urine is more than 10µg/gr creatinine, it can cause irreversible renal damage[47].

D-Penicillamine: It has been reported to be ineffective when exposed to high levels of Cd exposure[48].

Dimercaprol (British anti-Lewisite, BAL): In the treatment of Cd poisoning, as in other heavy metal poisonings, BAL and its analogs (meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propane sulfonic acid) are used. In the case of acute Cd intoxication, it should be given as intra-muscular (IM) dose of 3-4mg/kg in the first 4 hours. It is given once every 4 hours for the first two days and twice a day for the next 10 days[49]. British anti-Lewisite treatment is not the preferred method for chronic Cd poisoning. Waters et al.[50] reported that BAL-cadmium complex is much more nephrotoxic than Cd alone.

Dithiocarbamates: It increases the urinary and biliary excretion of Cd and reduces the side effects and symptoms of poisoning. Animal studies have shown that dithiocarbamates reduce Cd toxicity. However, there are no studies on humans[46].

Dimercaptosuccinic Acid: New monoesters of Dimercaptosuccinic Acid - Combination therapy with chelating agents and other agents has been reported to be effective in heavy metal poisoning[51]. Optimum treatment can be achieved when a combination of Meso-2,3-dimercaptosuccinic acid (DMSA) and monoisoamyl DMSA (MiADMSA) is applied.[52] N-acetylstein NAC) and 2,3-Dimercapto-1-propanesulfonic acid (DMPS) are known to reduce Cd-induced hepatic and renal metallothionine levels. Babaknejad et al.[53] reported that vitamins A, C, E and selenium may reduce the toxic effects of Cd on certain organs and tissues such as liver, kidney, skeleton and blood.

Nanoparticle application in the treatment of cadmium poisoning: Cadmium can be adsorbed by Al_2O_3 nanoparticles. Generally, the Al_2O_3 nanoparticles are suitable for removing Zinc (Zn) and Cd from dissolution / absorbent systems.

Hemodialysis-plasmapheresis: Plasmapheresis (plasma exchange) should only be used in acute poisoning. Plasmapheresis treatment can be initiated 24-36 hours after the onset of clinical signs and symptoms in the absence of life-threatening toxicity and no alternative treatment. Hemoperfusion and hemodialysis are not useful in Cd poisoning. Hemodialysis may be useful in replacing renal function if severe kidney damage has occurred[54,55].

Massadeh et al.[56] suggested that consumption of garlic was protective of Cd toxicity. They also reported that they should be encouraged to eat garlic, a common ingredient in traditional Indian diets.

Conclusion

Cadmium is a carcinogenic substance which has a great harm to the environment and human health as a result of both environmental exposure and occupational exposure. Besides occupational exposure, air, water, soil and food chain can be taken into the body. One of the substances with high Cd content is cigarettes. In the protection, it is very important to avoid tobacco and its products, additionally water with high Cd content, and foods with high Cd content. It would be beneficial to conduct awareness-raising activities especially for those at risk with regard to the Cd's health hazards and ways of protection. Adequate and balanced nutrition is known to have a protective effect against Cd poisoning. In the protection of occupational exposures, both technical and medical measures should be implemented properly and adequately. Technical measures are in order of importance: welding (substitution, local ventilation, separation, shutdown, etc.), working environment (general ventilation, compliance with working environment measurements (MAC, threshold limit value etc.) and personal measures (personal protective equipment, personal dosimeter, workplace rotation etc.). The recruitment examinations, periodic examinations for early diagnosis and treatment, especially training and warning activities should be included in the selection of the appropriate person from the medical measures. In accordance with *the Regulation on Health and Safety Measures in Working with Chemical Substances (Turkey's a Regulation)*, to make appropriate arrangements and work organization in the workplace, to pay attention to the low number of employees, to keep the exposure dose and duration low, to pay attention to the order and cleanliness of workplace buildings and additions, training necessary for employees to comply with personal hygiene rules and the provision of environments are important measures to protect Cd from health hazards. In addition, the rules regarding Cd waste and residues in the workplace should be followed to the maximum level.

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