Review Article

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An Update on Lead Poisoning

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ABSTRACT

BACKGROUND AND OBJECTIVE: Lead poisoning have been reported from many parts of the world. They are one of global clinical problem that effect all body organs and many deaths every year. This review was done to survey toxicological aspects of lead compounds

METHODS: The data bank used in this study is web of science, Scopus, PubMed, PubMed central, SID. The keywords are Alzheimer's Disease, medical plants, acetylcholine, antioxidant.

FINDINGS: Metallic lead is used industrial, organic lead eg., tetraethyl and tetramethyl lead in gasoline additives to prevent engine knock, and inorganic lead salts combined with other elements. Majority of absorptive lead through the respiratory and gastrointestinal systems. Lead compounds can lead to clinical manifestation in neurologic system, hematopoietic, kidneys, cardiovascular, reproduction, bones. There are tests available to diagnose poisoning by measuring lead in blood, urine, hair and fingernails. Patients of lead toxicity need to decontamination (GI tract irrigation), supportive cares, use traditional and new chelating agents to combination therapy, also antioxidants, vitamins, and nanoparticle.

CONCLUSION: Based on the survey, it is recommended to detect contaminated areas and consider an educational plan for the exposed people to prevention of lead poisoning.

KEY WORDS: Lead Compounds, Dimercaprol, Dimercaptosuccinic Acid, Antioxidants.

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Introduction

In recent years, considering the community development and ease of access to drugs and toxins, the incidence of poisoning has markedly increased. Agents of organic origin, as well as chemical toxins, can have harmful effects on human body (1, 2). Abuse of certain drugs, use of environmental elements, industrial and agricultural products, and some food compounds can lead to deliberate or accidental poisoning (3, 4).

Heavy metals, which are naturally found in the Earth's crust, can pollute the air and soil. Metal poisoning, particularly poisoning by heavy metals, is one of the main ecological problems affecting the health of individuals (5-7).

Use of lead, as one of the most important metal contaminants, dates back to 6,000 years ago. The history of lead toxicity is nearly 2500 years old (8). Lead can travel through the soil into the plant tissues. In the past, lead pollution was related to mining activities and rendering processes. In fact, most paints and gasoline used in vehicles contained inorganic or organic lead compounds. Moreover, lead glazing in pottery intended for cooking (and water pipes) was among the uses of this element in the past (7, 8).

Lead poisoning has remained a significant problem especially for children in many parts of the world, despite the notable success in the production of non-lead gasoline and due to the significant lead exposure from other sources including lead-based industrial products (such as lead-containing paints), extensive lead exposure at traditional workshops of porcelain glaze, and lead-containing industrial waste (9).

Lead structure: Lead (Pb) is known by its atomic number 82 and atomic weight of 2.207. It is an odorless, glossy, pale blue element, with the melting point of 5.327 and boiling point of 1750 °C. This soft, flexible element, which is both divalent and tetravalent, has a weak electrical conductivity (10).

Toxicokinetics: The absorption of lead varies from one person to another, depending on the chemical form and type of exposure (11). Lead is mostly absorbed through the respiratory and digestive systems. Occupational exposure is a common cause of lead poisoning. Inorganic lead absorption through the skin is negligible, although organic lead compounds are easily absorbed through the skin, given the high fat solubility (12).

Distribution, storage, and disposal: Up to 99% of lead in the blood binds with hemoglobins in red blood cells, and only 1% is found in blood serum, which is absorbed by the tissue through dispersion. First, lead is distributed in liver and renal tissues and reaches the skeletal system and hair floccules during redistribution.

The elimination half-life of lead in blood is about 30 days. As previous research has indicated, the amount of lead stored in bone structure increases with age (from 70% in children to 95% in adults), with the elimination half-life of approximately 20 years.

Lead appears to be more mobile in trabecular bones than cortical bones; thus, in terms of lead elimination, shorter time is required in trabecular bones.

The lead in bone structure accounts for about 50% of blood lead. Therefore, it can be considered as an effective source of internal assessment (13). Ninety percent of ingested lead is eliminated via feces and urine; if inhaled, it is excreted through the kidneys. Lead can be also excreted through sweat and breast milk (11).

Toxicodynamics: The most severe effects of lead poisoning have been reported on the nervous system, and the highest vulnerability occurs during growth years. In fact, lead poisoning in children is more severe than adults (14). One key factor in lead poisoning is the quick succession of calcium by lead. In fact, lead can infiltrate through blood-brain barrier (BBB) since a large amount of it can substitute calcium ions (Ca^{2+}).

According to previous studies, lead can infiltrate into the brain (15). When BBB is exposed to high lead concentrations, plasma moves to the interstitial space, causing edema. Toxicity of central nervous system due to high lead concentration in blood can result in encephalopathy. Due to diffusion, lead contamination can cause cerebral edema, which mainly affects the cerebellum (16).

This type of brain injury leads to impairment in reading, calculation, and short-term memory, lack of understanding and vision, cognitive changes, behavioral disorders, and IQ deficit (14). Recent epidemiological studies suggest that lead can affect kidney function even at lowest levels in blood. As indicated by Ekong et al., 5 µg/dL of lead could harm the kidneys (17). Similarly, Muntener and colleagues in a trial on American adults with low blood lead levels demonstrated the presence of chronic kidney disease in these individuals (18). Oxidative damage to reproductive organs is another side-effect of lead poisoning, which results in decreased sperm motility, sperm count, and sperm-oocyte penetration rate (SOPR) in mice (19).

Menke et al. showed that the risk of death due to cardiovascular diseases and stroke increases by a blood lead concentration of 2 µg/dL (20). Animal studies have shown that the increased growth of vascular smooth

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cells results in the formation of atherosclerotic plaques. Besides, high lead concentration causes oxidative stress, with adverse effects on the cardiovascular system (21). In a study by Ding and colleagues, increased production of hydroxyl, lipid peroxidation, and oxidative stress in aortic endothelial cells were correlated with lead exposure in animals (22). In general, low lead concentration in humans can cause oxidative stress, which is due to the formation of free radicals.

Lead poisoning mechanism: Various studies have been conducted on the mechanism of lead poisoning, based on toxicity manifestations. Oxidative stress causes an imbalance between the production of free radicals and the ability of biological system for detoxification or damage repair. In most cases of lead poisoning, the process of oxidative stress begins simultaneously in two different paths: production of reactive oxygen species such as hydroperoxides and hydrogen peroxide and depletion of antioxidants (23).

The body's antioxidant defense system can cease the production of reactive oxygen species. Glutathione, which is a sulfhydryl-containing tripeptide and is more frequently found in mammalian tissues, plays the most important antioxidant role in cells. Antioxidants cause a reduction in the activity of free radicals (24).

Glutathione disulfide is the oxidated form of glutathione, which can have various reactions with oxygen similar to cysteine thiol group. Glutathiones, similar to restored cysteine thiol group, can react with oxygen species. After electron infusion, they can react with other glutathione molecules and form glutathione disulfide. Via glutathione reductase, glutathione can produce glutathione disulfide. Under normal conditions, 90% of the total content of glutathione is present as glutathione and about 10% as the oxidized form. However, under oxidative conditions, the concentration of glutathione disulfide is greater than that of glutathione (23).

Lead has the ability to share electrons and form electron pairs; these interactions occur between lead, composed of single-electron orbitals, and the sulfhydryl group. This ability is a result of glutathione synthesis from cysteine (through gamma-glutamyl transferase) due to glutathione consumption (23). Similarly, lead is inactivated by enzymes such as delta-aminolevulinic acid dehydratase (ALAD), glutathione peroxidase (GPx), and glutathione-S-transferase, which reduce glutathione level (21). Lipid peroxidation is one of the biomarkers of oxidative stress and is among the most important indices for the investigation of oxygen reactions in lipid membranes. Free radicals surround the electrons by the lipids in cell membranes and result in cell damage.

Apart from lipid peroxidation, lead causes the oxidation of hemoglobin, which directly leads to the hemolysis of red blood cells; this happens due to the presence of ALAD, which increases the concentration of substrate amino acids in blood and urine.

Increased amount of aminolevulinic acid facilitates the formation of hydrogen peroxides and superoxide radicals and results in the formation of hydroxyl radicals by impacting hemoglobin (25). The abovementioned mechanisms enhance cell vulnerability to oxidative stress, and lead poisoning might end in cellular death (23).

Clinical symptoms of lead poisoning: Lead has a wide range of destructive effects, which influence the nervous system, cardiovascular system, reproductive organs, red blood cells, and kidneys. Moreover, children seem to be more vulnerable to lead than adults (26). In recent decades, significant findings have been published about the effects of lead on the nervous system, especially in terms of cellular mechanisms. Moreover, brain is one of the most studied organs regarding lead poisoning.

The conducted studies have concentrated on cell death, excitation of neurotransmitters, release and change of mediator receptors, changes in mitochondrial function, second messenger mechanisms, and vascular endothelial cells. The symptoms may manifest immediately or with delay, causing memory loss, vision impairment, cognitive-behavioral disorders, nervous system dysfunctions, brain damage, and mental retardation (27).

Undoubtedly, lead poisoning affects children's nervous system, neural/behavioral system, and growth. As mentioned by Ibrahim et al., although no significant correlation has been found between poisoning symptoms and blood lead level, some lead concentrations can indicate the severity of symptoms. For instance, the lowest amounts of lead (1-50 µg/dL) can cause cognitive-behavioral changes; therefore, it is difficult to make a differential diagnosis in case of normal growth.

At medium lead levels (50-70 µg/dL), children might show decreased activity, grow uninterested in playing games, and experience less growth than their healthy counterparts. These signs have been classified as pre-encephalopathy symptoms, and the majority of cases occur within the age range of 1-5 years. Moreover,

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severe lead poisoning (higher than 70 µg/dL) may cause encephalopathy accompanied by coma, seizures, altered mental status, and symptoms of increased intracranial pressure (28).

When the amount of lead in blood is higher than 40 µg/dL, neurotoxic effects, which are related to occupational exposure in adults, are accompanied by behavioral disorders. Peripheral neuropathy sits among the classical symptoms of lead poisoning in adults. Moreover, nervous dysfunction occurs when blood lead level is below 40 µg/dL, which can be clearly revealed by the electrophysiological measurement of nerve conduction velocity (13).

Lead poisoning may occur in the somatic nervous system via two different ways: 1) severe autosomal dominant disorder, which is traditionally associated with lead poisoning at high doses and might secondarily cause porphyria symptoms, and 2) long-term manifestations with mild sensory impairment and automatic polyneuropathy, which are probably the direct effects of neurotoxicity with lead (29).

Anemia is one of the hematopoietic effects of lead. Ferrochelatase is one of sensitive enzymes to lead, which stimulates iron binding to porphyrin ring. In lead poisoning, it is quite common to see protein-binding irons in human duodenal mucosal secretion, which is due to the the competitive relation between lead and iron in binding. In general, lead can inhibit delta-aminolevulinic acid synthase, ALADs, and ferrochelatase.

Measurement of erythrocyte protoporphyrin or zinc protoporphyrin concentrations is used to determine the amount of lead in blood (30). It should be mentioned that lead affects the normal course of hemoglobin synthesis and has high affinity to red blood cells. Therefore, life of erythrocytes is shortened and synthesis is disrupted by lead poisoning (31).

Lead may cause morphological changes in erythrocyte by increasing blood cells with irregular structures, causing anemia (31). Anemia occurs only in severe cases of lead poisoning (such as iron deficiency, microcytic anemia, and hypochromic anemia) (13). Lead exposure results in the increased incidence of clinical cardiovascular disorders such as coronary artery diseases, peripheral artery disease, and other cardiovascular disorders including the increased incidence of ventricular hypertrophy and left ventricular masses, reduced fraction index, changes in heart rhythm (e.g., intraventricular conduction defect), increased QRS distance, and elevated blood pressure (32). Oxidative stress disrupts the performance of guided nitric oxides. Lead poisoning has been also associated with reduced cholinergic activity, elevated sympathetic activity (due to reduced vascular activity), increased beta-adrenergic receptor density, activation of renin, aldosterone, and angiotensin systems, elevated production of endothelin and thromboxane, reduced dilation of blood vessels, increased vasoconstrictive prostaglandins, increased cellular calcium (Ca2 +) (via inhibiting Na-K ATPase activity), induction of Na-Ca2 + exchange, reduced content of guanylate cycles in vascular tissues, and increased activity of protein kinase C (33, 34).

However, the most important manifestation of lead poisoning in the cardiovascular system is hypertension. In addition, endothelial damage and functional disorders lead to atherosclerosis, thrombus formation, and tissue damage. In chronic cases, increased incidence of atherosclerosis was also reported in experimental animal studies (35). In fact, in early atherosclerosis, lead contributes to intimal hyperplasia, which is the initiator of hypertension and other cardiovascular disorders (35, 36). Additionally, performed studies have shown that prolonged exposure to lead causes a slight increase in systolic and diastolic blood pressure (37).

Gastrointestinal symptoms of lead poisoning are non-specific and significant. Epigastric discomfort, nausea, vomiting, constipation, flatulence, loss of appetite (appetite disorders) and weight loss have been observed at medium lead levels in blood. At high concentrations, abdominal pain has been frequently reported (38, 39).

Lead poisoning might be misdiagnosed with intestinal obstruction, pseudo-obstruction, peptic ulcers, pancreatitis, appendicitis, mesenteric lymphadenitis, diabetic ketosis, and kidney stones. In fact, misdiagnosis may lead to unnecessary gastrointestinal assessments and abdominal surgery in patients. Clinical manifestations, accompanied by chronic or recurrent abdominal pain, are often diverse and crampy in nature; these manifestations are known as "lead colic" and are accompanied by gastrointestinal obstruction (39, 40). The importance of skeletal system in lead poisoning increases due to the high absorption of lead in this system. Over 90% of lead in the adult body is stored in bones. In fact, lead has a long half-life in bones and can be coordinated with metabolic and homeostatic mechanisms, associated with the function of parathyroid hormones, calcitonin, vitamin D, and other

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hormones influencing calcium metabolism. Lead substitutes calcium in bones and disrupts bone metabolism. It also affects osteoblasts, osteoclasts, and chondrocytes. Lead reduces the concentration of 1,25-dihydroxyvitamin D3 and inhibits osteocalcin. It also has modulatory effects on proteins associated with parathyroid hormone, TGF-β, activator protein 1, and nuclear factor-kappa B in chondrocytes (41, 42). In addition, lead has direct effects on osteoporosis and fracture healing (43). When children are exposed to severe lead poisoning, calcium deposits increase in areas of temporary calcification, leading to deficiencies in bone growth and inhibition of enamel and dentin mineralization (13, 42).

Lead has been classified as inorganic and organic. Inorganic lead compounds are mainly inhaled as particles or vapor (the size of particles is less than 1 micrometer). These particles can be transmitted through airways and be absorbed by blood immediately after reaching the alveoli. In mammals, lead affects different systems, and lungs are one of the major sites of lead accumulation in the body (44, 45).

Environmental pollution affects the morphology and physiology of respiratory system. Meanwhile, lead affects the pathogenesis of asthma, chronic obstructive pulmonary disease, and lung cancer (46). Investigations have suggested that the prevalence of respiratory disorders in industrial workers, who are in contact with lead compounds, is higher than that reported in non-industrial workers and farmers who deal with pesticides and other chemicals (47).

Moreover, a significant decrease was observed in pulmonary function test score (PFT), forced expiratory volume in one second/vital capacity ratio (FEV1/FVC), and maximum volume of pulmonary ventilation (MVV) in lead poisoning (44). Development of respiratory symptoms such as chest tightness, phlegm, and cough has been also reported. However, wheezing along with chronic obstructive pulmonary disease is less prevalent than asthma, and occurrence of wheezing, thick mucus, and shortness of breath indicate asthma (46). Another significant point is that lead acetate is potentially carcinogenic according to experimental animal studies (48).

Kidneys are the primary site of lead accumulation. Prolonged exposure to lead ends in occupational and environmental contamination under critical conditions. In more severe conditions, acute or chronic nephrotoxic effects have been observed; in fact, both acute and chronic nephropathies have been observed in humans (49, 50). In lead-induced nephropathy, many changes occur in terms of performance. These changes include reduced transfer of components, which require energy for transfer, and formation of a syndrome which is similar to Fanconi syndrome and is associated with aminoaciduria, glycosuria, and phosphate productivity. These changes followed errors in mitochondrial respiration, phosphorylation disorder, and delayed treatment.

Pathologic findings have indicated the presence of foreign bodies in the nuclei of primary renal tubular cells, which are formed by lead-protein complexes (42). It is assumed that the presence of foreign bodies in the nuclei of proximal tubes is among the pathognomonic symptoms of lead-induced nephropathy, which occurs only during the early years of lead exposure (51); however, chronic lead-induced nephropathy is a renal dysfunction with a high incidence rate.

Scientific studies have shown that lead at different levels influences reproductive organs or endocrine factors that control reproduction (52). Lead is involved in the abnormal formation of reproductive organs (impaired morphology and gonadal function in cases of infertility and decreased libido) and structural congenital anomalies (changes in structure and intrauterine fetal growth) (53).

Lead poisoning causes reduced fertility in men and women (52). Lead changes the histology and physiology of ovaries and uterus, affects follicular development in the ovary, and disrupts ovulation. Also, hypothalamic-pituitary-gonadal axis may be affected by lead; in this case, this element plays a key role in the control of different factors affecting reproduction (54).

Existence of lead in nature and exposure to it increase the risk of cancer; similar results have been reported regarding inorganic lead compounds (55). Additionally, workers who are exposed to lead, are mostly prone to lung, stomach, kidney, and brain cancers (55, 56).

Diagnosis of lead poisoning: To diagnose lead exposure, it is quite helpful to measure biological samples obtained from exposed subjects. In this context, direct measurement of lead in blood, biochemical parameters such as creatinine and blood urea nitrogen, and hematological tests of urine (or delta-aminolevulinic acid assays) are employed for the diagnosis of lead poisoning (57).

Blood: The most exclusive and effective way to determine lead level is to measure it in blood cells, since more than 95% of lead in the blood is concentrated in

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erythrocytes (58), reflecting recent and previous poisoning (42). The threshold level above which lead can be harmful is 10 µg/dL (59). Although blood lead level greater than 10 µg/dL should be considered high, clinical symptoms can be rarely seen below 60 µg/dL (60). However, it has been reported that even low levels of lead (10 µg/dL) in the blood can affect the physical and cognitive development of children (59). If blood lead level in a lead-exposed subject (such as factory workers) is over 60 µg/dL, he/she should be transferred to a lead-free work environment (61).

Urine: The initial aggregation of lead may occur in kidneys. After glomerular filtration, lead will enter nephron tubules and blood by reabsorption and spread throughout the body due to its physical nature (small particles) (62).

The half-life of lead in human blood is 25 days; thus, the measurement of blood lead level is a useful index, although the presence of lead in urine is a more useful indicator for the overall presence of lead in the body (63). With increased lead exposure, the activity of ALAD is decreased or inhibited, and the indirect activity of aminolevulinic acid synthetase (ALAS) (due to the regulation of negative lead-induced feedback) leads to increased aminolevulinic acids in different tissues and plasma; therefore, urinary delta-aminolevulinic acid (ALA-U) is eliminated from urine. Accordingly, the measurement of ALA-U for examining the effects of lead is recommended (64, 65).

Notably, the exact threshold concentration of lead in the blood must be above 35-40 µg/dL so that lead can be detected through aminolevulinic acids in urine (66). In order to determine the concentration of aminolevulinic acids, fluorometeric method along with liquid chromatography (with high functionality), is applied; this method is more sensitive and accurate than the calometric method (67, 68).

Hair and nails: In addition to liver and renal tissues and blood/urinary samples, nails, teeth and hair are also used for the analysis of lead (69). Hair and nails are discussed more than other diagnostic indicators for the assessment of metal concentrations, since they undergo fewer changes by the intake of food, air and water. Therefore, their status may remain stable for a long period (70). Sample collection of hair and nails is simple and non-invasive, and lead alterations in these samples are constant during storage (71). The total amount of lead in the human body (average weight of 70 kg) is almost 100-400 mg, which increases with age. Lead accumulates in bones, nails and hair three to five times more than other body tissues (72). This metal remains in the samples for long periods of time, thus reflecting lead concentration in other body tissues (73).

Other methods: Lead toxicity or plumbism affects various organs (74). Conventional radiography has shown the presence of lead bands particularly in bones, epiphysis, thick metaphyseal lines, and transverse bands or "lead bands", especially in hand and knee bones (75). In simple chest images, costal cartilage junction is highly evident (76). In addition, by the expansion of blood smear, basophilic erythrocytes (basophilic stippling), as well as microcytic, hemolytic, and hypochromic anemia are observed (74).

In case of lead poisoning, electroencephalography of brain shows a slight increase in delta wave activity. CT scan and MRI have shown different results, which might be related to the involvement of cerebellar white matter, basal ganglia, thalamus, or insula. Also, cerebral edema, demyelination of brain and cerebellar white matter, and lesions in brain vessels indicate vascular damage in the demyelinated peripheral nervous system (74, 77).

Lead exposure increases nephropathy and renal complications. Uric acid is a nephrotoxic agent and its low values, contrary to previous beliefs, will result in tubulointerstitial fibrosis, arthropathy of afferent artery, glomerular hypertrophy, glomerulosclerosis, glomerular sclerosis, and glomerular hypertension. Hence, examination of blood samples for urea nitrogen, serum creatinine, and uric acid, as well as urine analysis (i.e., analysis of N-acetyl-beta-D-glucosaminidase, retinol-binding protein, and creatinine) is required (78).

Treatment:

Removal of pollutants and supportive care of patients: The most important aspect of lead poisoning treatment is avoiding direct contact with lead. Lead poisoning, which is a major problem in adults due to occupational exposure, depends on the performance of public health system, as well as social and political systems (42).

Another issue is the lead in food products left in the gastrointestinal system. Activated charcoal has a relatively lower affinity than many other metals, and the inorganic lead absorption in the gastrointestinal system is discussed with uncertainty. Previous reports have shown that whole bowel irrigation can increase the rate of lead excretion. The intake of polyethylene glycol and electrolytes, which are administered orally or via nasogastric tubes (20 to 30 ml/kg of body weight per hour), could result in lead elimination (58). In terms of

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supportive care, three key objectives are pursued: 1) reduction or normalization of intracranial pressure; 2) maintaining adequate urine output for lead elimination; and 3) management of seizures with antiepileptic medications (58).

Elevated intracranial pressure indicates the progressive loss of consciousness, papilledema, cranial nerve dysfunction, abnormal response of pupils, and imapired nervous functioning. Elevated intracranial pressure is confirmed via cerebral images or direct measurement of intracranial pressure (58). If the patient has intraventricular catheter, by draining the cerebrospinal fluid, we can reduce intracranial pressure; also, the patients' bed should be tilted to 30 ° (79). The most common osmotic diuretic is mannitol, which should be injected intravenously (0.25-1.5 grams per kilogram of body weight) in 20% solution for 20 to 30 minutes (80).

Short-term hyperventilation will reduce brain internal pressure by inducing hypercapnia and vasoconstriction (79). If seizure occurs, the patient is placed in a lateral position so that the head is above 30 degrees to minimize aspiration. Oxygen will be provided through the nasal canal by cannula. Use of intravenous lorazepam (1.0 mg per kg of body weight) for 2 to 3 minutes is recommended(maximum of 8 mg). Subsequently, diazepam (2.0 mg per kg) can be also used intravenously at a dose of 5 mg per minute.

If the patient's seizure lasts longer than 5 minutes or generalized tonic-clonic seizures occur more than twice an hour, other measures should be taken. In these cases, fosphenytoin (20 mg per kg of body weight, not more than 150 milligrams per minute) is prescribed. In case of hypersensitivity to drugs, phenobarbital can be used (81).

Another point is that lead is mainly excreted through the kidneys. Lead elimination is considered adequate in case the urinary output is 1 to 2 ml per kg per hour. The volume of fluid intake must be carefully managed so that increased volume and worsening cerebral edema can be avoided. In some cases, use of loop diuretics is effective for the treatment of cerebral edema, secondary to prescribing mannitol (58).

Chelating agents: Chelating agents are organic or inorganic compounds used for heavy metal poisoning. Chelating agents are molecules which can bind with metals. Effective chelating agents lower free metal concentration, and the formed complex can be easily eliminated through urine, resulting in reduced levels of toxicity (82, 83).

Traditional chelating agents: EDTA is an amino acid compound with high affinity to lead, aluminum, zinc, iron and cadmium (fig 1). Calcium-EDTA (Ca-EDTA) and sodium-EDTA (Na-EDTA) are two compounds that are administered intravenously, since their gastrointestinal absorption is poor and lead can be eliminated fast via intravenous injection (84). These compounds bear the same effects at a dosage of 3 g for chelating lead. Ca-EDTA has been also recommended by the American Food and Drug Administration (FDA) for the treatment of serious cases of lead poisoning (85). The highest lead excretion in urine (24-hour urine sample) has been reported after receiving 30 mg per kg of body weight of CA-EDTA, i.e., greater than 2 g of Ca-EDTA via intravenous infusion (86).

Penicillamine is a white, crystalline, water-soluble derivative of penicillin. Its D-isomer is dominant (fig 2), since it has lower affinity to L-isomer (87). It is prescribed at a dose of 0.5-1.5 g, 3-4 times a day for a span of 5 days (consumed at least one hour before a meal). In adults, prescription of penicillamine once a day for 2-3 months is well tolerated. During prolonged therapy, the dosage should not exceed 40 mg per kg of body weight per day (88).

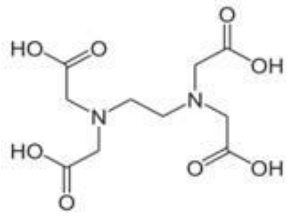

Figure 1. EDTA

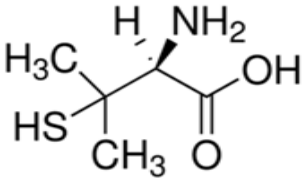

Figure 2. D-penicillamine (DPA)

Dimercaprol or British Anti-Lewisite (BAL) is a chelating agent, known for the treatment of heavy metal poisoning. BAL revolutionized the treatment of heavy metal poisoning and has been medically prescribed for more than 60 years. During World War II, BAL minimized the risk of injury or death and today, it is one of the most effective drugs for the treatment of heavy metal poisoning (89). Figure 3 indicates the chemical formula of BAL and its analogs (DMSA and DMPS).

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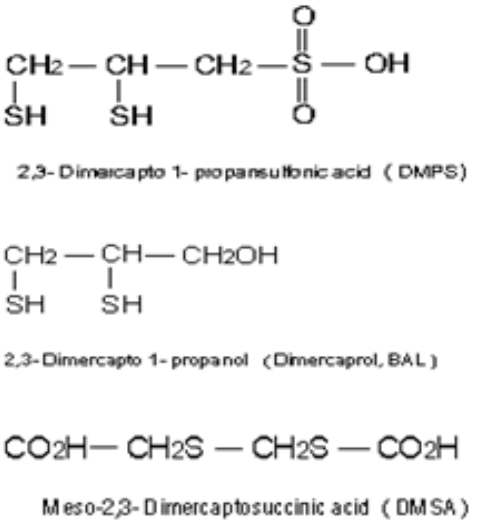

Figure 3. The chemical formulae of DMPS, BAL, and DMSA

The American Children Academy recommended the intravenous administration of Ca- disodium EDTA and dimercaprol for lead levels above 70 micrograms per deciliter (90). Some believe that Ca-disodium EDTA should bre used after the administration of dimercaprol. On the other hand, some believe that the simultaneous use of these two agents may facilitate the decline of lead concentration in blood (91). BAL is administered intramuscularly at a dose of 25 mg per kg per day in six divided doses (4.16 mg per kg per injection) for two to five days (92).

New chelating agents: Succimer 2,3-dimercaptosuccinic acid (succimer, DMSA) has been used since 1950 as an antidote to lead poisoning in Russia, Japan and China (93). DMSA is a water-soluble analog of dimercaprol, which increases urinary elimination of lead and decreases blood lead concentration. It is believed that this agent is effective for the excretion of lead from soft tissues, although it has not been efficient for chelating lead in bones (87, 94). In America, DMSA is only used in form of oral medications, while the intravenous administration has been successfully used in other areas. This drug binds with amino acid cysteine in the body and probably forms a disulfide solution in kidneys by ratios of 1:1 and 1:2; these complexes are suspected to be activating the chelating process. Half-life elimination of DMSA is approximately 2-4 hours (87). This medication is administered at a dosage of 30 mg/kg/day for 5 days and then 20 mg/kg/day for 14 to 21 days. The lower dosage of DMSA binds with lead again when chelating is stopped (95). Thiol ion 2, 3-dimercapto-1-propanesulfonic acid (Unithiol, DMPS) is a dimercapto chelating agent and a water-soluble analog of dimercaprol. DMPS has been available since 1985 in Russia and other countries in former Soviet Union; also, it has been administrated in Germany since 1976. Elimination half-life of DMPS (the original medication and its derative products) is approximately 20 hours (87) and its combinations are administrated orally, intravenously, rectally, or locally; after intravenous injection, it is exclusively eliminated from the kidneys (96). Aquatic products of DMPS (50 mg/ml in sterile water) can be prescribed with a dose of 3-5 mg/kg every 4 hours via slow intravenous infusion over 20 minutes. Fast intravenous infusion may cause vascular relaxation and hypotension. If after a few days of treatment, cardiovascular and gastrointestinal conditions are stabilized, oral treatment can be continued with a dose of 4-8 mg/kg every 6-8 hours (87). Side-effects of treatment with DMSA or DMPS include gastrointestinal upset, skin reactions, mild neutropenia, and elevated liver enzymes. DMPS appears to be better tolerated than DMSA by stomach. In some patients, especially patients with allergic asthma, DMPS may cause hypersensitivity (97).

Recently, many studies have shown that DMSA esters may be effective as antidotes for heavy metal poisoning. These compounds are in form of mono- and di-esters of DMSA, leading to increased tissue excretion of chelating agents (82). Among new chelators, we can mention monoisoamyl 2,3-dimercaptosuccinic acid (MiADMSA), which is an alkyl monoester of DMSA and a water-soluble, yet lipophilic chelating agent (fig4). Ester may be used as a chelating agent in reducing lead, mercury, and cadmium (98). MiADMSA can penetrate into cells and be widely distributed. It is capable of removing heavy metals from the inside and outside of cells (99).

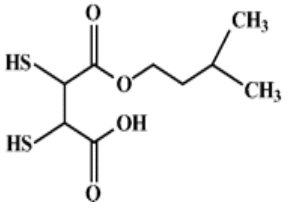

Figure 4. The chemical formula of MiADMSA

MiADMSA can reduce oxidative stress in two ways. First, it can attract heavy metals from body organs and then, it can summon reactive oxygen species

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through sulfhydryl groups (99). MiADMSA has lipophilic properties, and its molecular mass facilitates the removal of heavy metals and provides better therapeutic effects (98). Other new DMSA analogs include MmDMSA and MchDMSA. MmDMSA has a straight chain and branched methyl groups, whereas MchDMSA has a carbon ring chain (fig 5). Both agents possess lipophilic properties and have the ability to penetrate into the cells; they are among chelating agents which are administered orally (100).

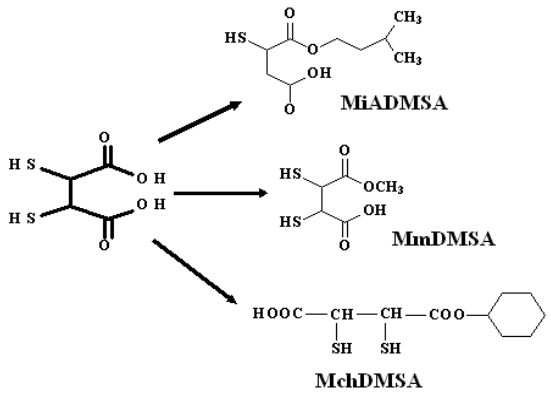

Figure 5. New monoesters of DMSA

Combination therapy: Today, one of the main controversies in the treatment of heavy metal poisoning is using combination therapy. Use of DMSA along with MiADMSA is more effective than the sole application of DMSA. In this case, not only fat oxidation can be controlled but also low catalase activity might be monitored. Therefore, by reducing the dosage of chelatin agent, the adverse effects may reduce (82, 101). In a study by Flora et al., it was indicated that the combination of DMSA and MiADMSA can have significant positive effects on loweirng lead concentrations in the blood. Also, from the clinical perspective, it provides a better chance of recovery for the brain, compared to single-drug treatments. In another study carreid out by Flora, it was revealed that DMSA and CaNa2EDTA combination against severe lead toxicity could modify biochemical parameters and result in more definitive lead elimination; also, no redistribution of lead occured in any body organ (103). Pande and colleagues found that acetylcysteine can be adminstrated as a therapeutic agent when combined with DMSA/MiADMSA in lead poisoning treatment (104). In addition, the effective role of lipoic acid against lead poisoning for chelating in blood and soft tissues has been reported (105). The role of antioxidants in reducing oxidative effects has been also determined (106-109). Today, the clinical significance of medicinal plants with high antioxidant effects such as Centella asiatica and plants containing thiol has been confirmed. These compounds act like chelating agents. Thus, oxidative stress imposed by the use of lead compounds can be controlled (110). Reports indicate that some vitamins such as vitamin B, C, and E and food compounds like amino acid methionine (methionine), due to having groups with chelating features, can have beneficial effects on reducing lead poisoning (82, 111).

Use of nanoparticles in the treatment of lead poisoning: Use of nanotechnology for health and medical treatment has been emphasized in biological studies. In fact, nanotechnology has revolutionized medical sciences and drug manufacture (112). The main benefits of using nanoparticles in comparison with traditional agents is the increased contact with the produced material. This means that it has a great potential for the development of chemical reactions and physical interactions (113). This technology is widely used in tissue, cell, and gene structure and medical instruments. Moreover, it has been evaluated particularly in relation to biomedical research, diagnosis, and treatment (112, 114). Nanoparticles have been used for the diagnosis and detection of different forms of poisoning such as lead poisoning. In the past decade, colorimetric tests have been proposed for the detection of Pb2 + in non-polar solvents. In other words, the colorimetric sensor composed of gold nanoparticles is widely used for the discovery and detection of DNA, proteins, and metal ions. The accumulation of gold nanoparticles is often accompanied by color changes. In general, colorimetric sensors function based on the concentraion and polymerization of gold nanoparticles (115). Evaluation of the uptake of heavy metals by carbon nano tubes is also an effective procedure.

Oxidation of nanoxide tubes can result in the absorption of cations (117). Recillas and colleagues demonstrated that the use of nanoparticles such as Fe3O4, TiO2, and CeO2 increases lead elimination from water. They also demonstrated that Fe3O4 and TiO2 nanoparticles have no toxic properties and can be used as lead absorbants (113). Also, Saberi in a comparative study on bimetallic Ni/Fe nanoparticles and zero-valent iron showed that they both are effective in the removal of Pb2+ (118). Finally, it should be noted that long-term use of nanoparticles in medicine needs further evaluation in terms of clinical and community health for resolving concerns regarding the use of nanoparticles. Another application of nanotechnology is

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the reduction of water contaminants such as bacteria, pesticides, insecticides and heavy metals (lead, mercury, cadmium, zinc, etc.). Nano catalysts and nano filters can absorb toxins and pollutants. In fact, nanotechnology may increase purity (116).

Plasma exchange, peritoneal dialysis, hemodialysis and plasma phoresis: Plasma exchange takes place within 24 to 36 hours after poisoning detection. When the patient's life is at risk, plasma exchange is used only in emergency cases. If toxic plasma concentration is high and there is no credible alternative, the rapid elimination of toxin can stop the progression of poisoning. This method can be also used in cases with severe symptoms of poisoning in which we cannot wait for the patient's response to drug treatment (119). In cases of lead poisoning accompanied by renal failure, before performing peritoneal dialysis, 500 mg of Ca-EDTA is administered intravenously in final stages. The amount of lead uptake in the material obtained by dialysis is equal to 4.5, resulting in the elimination of 8.16 mg of lead in 20 hours. In patients with chronic renal failure, intravenous administered dosage of Ca-EDTA (1 g) will elevate from 0.016 to 1.932 mg per day after four days of lead elimination.

Furthermore, the intravenous adminsitration of 1 g Ca-EDTA one hour before hemofiltration will lead to the increased elimination of lead in patients with end-stage renal failure. It is also well-known that succimer cannot help with the removal of lead by hemodialysis (58). Hemodialysis is the best method for water-soluble and dialysable materials. However, compounds, which form strong bonds with plasma proteins, cannot be removed by hemodialysis. In such cases, plasma phoresis, which has the ability to remove heavy metals bound to plasma proteins, would be the most effective procedure (120).

Discussion

Lead poisoning results in dysfunctions of the nervous, cardiovascular, gastrointestinal, respiratory, urinary, and reproductive systems. Moreover, hematologic effects and immune system deficiencies may be caused by lead poisoning. Lead can be transmitted via contact with lead-containing paint, gasoline, soil, and plants and some electrical appliances such as electric batteries and electrical cord covers. Lead exposure may occur in the uterus, or after birth, or even during adulthood and old age, resulting in numerous changes and clinical symptoms in various body organs.

Therefore, lead elimination should be one of the main tasks of healthcare organizations. Healthcare policy makers and private organizations are required to remove contaminated materials and suggest a solution for providing lead-free water, air, and food. Continuous screening of water, food, soil and air and the control of suspected cases of lead poisoning via laboratory studies and observing clinical manifestations can help reduce toxicity. In this regard, supportive and conservative treatments, combination therapy (using chelating agents), and use of antioxidants, vitamins, and nanoparticles may be helpful. Finally, training and continuous monitoring of the population, especially from young age, is the most important measure for the prevention of lead poisoning and the associated adverse effects.

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