Lead Poisoning and its Remediation through Chelation: A Review

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ABSTRACT *Lead has no known beneficial role in human biological function. Lead poisoning is a type of metal poisoning caused by lead in the body. Lead exposure is a main health concern causing intellectual disability, irritability, abdominal pain, constipation, headache, infertility and neurological problems, and at very high levels it can be deadly. The need of a more efficient means for the remediation of lead poisoning is obvious. Chelation therapy is the preferred remedial management for reducing the toxic effects of heavy metals. Different chelating agents like dimercaprol or British Anti Lewisite (BAL), meso-dimercaptosuccinicacid (DMSA), calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$) and D-penicillamine (DPA) are recommended for the treatment of lead poisoning. The sources of lead toxicity, the effects on human health, the remediation using selective chelating agents and consequences are highlighted in this review.*

Keywords: *chelating agents, human health, lead poisoning, remediation*

INTRODUCTION

Lead (Pb) is a bivalent bluish grey heavy metal (atomic number 82, atomic weight 207.2, density 11.34 g cm^{-3}) having no essential or beneficial role to human health [1]. Hippocrates (370 B.C.) was probably the first person to correlate lead with clinical symptoms, since when the harmful effects of lead in the body have been well recognized [2]. The low melting point and malleability of lead contributed to its early use in tools, moreover, due to bright colour and less costly of inorganic lead compounds facilitated to use as paints and pigments. Lead's use and exposure significantly enhanced with the discovery of tetra-ethyl lead (TEL) as an anti-knocking agent in 1924 [3]. The plentiful use of lead compounds as wine preservative and to make better taste was reported [4]. Lead carbonate was the most common white pigment in house paints before 1955. Besides this, lead chromate, lead(II, IV) oxide were also in use as paints and pigments. More than three fourths of global lead utilization is for the manufacture of lead-acid batteries for motor vehicles. Soil can become contaminated from smelter and mining activities, deteriorated paint etc. Lead contamination in water usually results from the leaching of lead from pipes, lead soldering and lead containing taps [5]. People can become exposed to lead through inhalation of lead particles generated by burning materials containing lead, stripping of leaded paint, using leaded gasoline, ingestion of lead contaminated dust etc [6]. Once lead goes into the body either through inhalation or through gastrointestinal tract, it is scattered to organs such as the brain, kidneys, liver, bones and other soft tissues of the body. Malnourished children are more at risk to lead because their bodies absorb more lead if other nutrients, such as calcium, are deficient. Lead can cause nervous system damage. Lead can also hamper the kidney, liver, reproductive system and brain functions. The toxic symptoms include anaemia, behavioural problems, vomiting, abdominal pain, loss of appetite, irritability and other related problems [7]. In most cases, exposure can be prevented or at least minimized and eliminated.

Chelation therapy is the recommended treatment of lead poisoning [8,9]. The term *chelation* comes from the Greek word *chele* or *khele*, it is used to explain the ability of some substances to grab atoms or ions to form complexes (coordination compounds). Chelation occurs when a chelating ligand or chelator (having more than one donor centres) binds to a metal ion forming a stable heterocyclic ring compound. The term 'chelate' was originally coined in 1920 by Sir Gilbert T. Morgan and H.D.K. Drew [10]. Ingested toxic metal ion like lead in the body with the suitable chelating agents forms a stable complex which removes through faeces and excreted mainly in urine without much hampering to other parts of the body. The four chelating agents like dimercaprol or British Anti Lewsite (BAL), meso-2,3-dimercaptosuccinic acid (DMSA), disodium calcium ethylenediaminetetraacetate ($CaNa_2EDTA$) and D-penicillamine (DPA); their chemical and biological principles, advantages and limitations in the treatment of lead intoxication are briefly delineated in this review article from the chemical point of view.

DISCUSSION

Lead is an extensive environmental toxin that is competent of causing many acute and chronic non-communicable diseases like neurological, intellectual imbalance, circulatory, haematological,

gastrointestinal, reproductive and immunological problems [11]. All lead compounds are poisonous, but the organic lead compounds must be metabolized in the liver into their active manifestations [12]. Lead compound is spread into three primary compartments: blood, soft tissue and mineralizing tissue. Lead combines to biological molecules and thereby interfering with their function by a number of mechanisms. Lead binds to sulfhydryl and amide groups of enzymes, altering their configuration and hampering their usual functions. Lead may also compete with essential cations for binding sites, inhibiting enzyme action, or changing the transport of essential cations such as calcium [13,14]. Ionic mechanism of action for lead mainly occurs due to its capability to substitute other bivalent cations like Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations like Na^{+} (though bivalent cations are more readily substituted), disturbing various crucial biological processes of the body [15]. Lead encourages oxidative stress representing an imbalance between the formation of free radicals and the biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. This phenomenon has been depicted as a major means of lead induced toxicity [16]. Under the influence of lead, beginning of oxidative stress happens on account of two different path ways running concurrently; first comes the generation of reactive oxygen species (ROS), like hydroperoxides ($HO_{2}^{\cdot}$), singlet oxygen and hydrogen peroxide (H_2O_2); and second, the antioxidant deposits become diminished [17-19].

Chelation treatment is to get rid of toxic metal ions from the exposed sites in the critical organs of the body via formation of complexes [1]. Chelate development needs that the chemical affinity of the complexing agent (here chelating ligand) for the unwanted toxic metal ion(s) [20]. When the effective stability constant of the complex formed from the particular chelating agent with the harmful metal ions is higher than that with the biological ligands, detoxification takes place [21]. In 1932 G.N. Lewis [22] defined a base as an electron pair donor (electron rich cloud) and an acid is an electron pair (electron cloud) acceptor. Lewis acids and bases can be classified as hard and soft ones. A hard metal ion is one that holds its valence electrons very strongly and has small size and high charge, whereas, a soft ion is relatively large and does not retain its valence electrons strongly. Here Pb^{2+} ion is a borderline acid due to its intermediate size and charge. According to Pearson [23] hard acids prefer to bind with hard bases and soft acids prefer to bind with soft bases, while borderline acid can combine with both hard and soft bases. That is why, Pb^{2+} ion can bind with both hard donor (N, O) centres as well as soft donor (S) sites. Chelating agents have more than one donor centres having lone pair of electrons (Lewis base) and metal ions have tendency to accept that lone pair of electrons (Lewis acid) forming a definite stable cyclic compound or chelate. Chelation therapy works by binding of certain chelating ligands to toxic metal ions in the blood and soft tissues and creating a relatively less toxic coordination compound that can be usually excreted in the bile and urine. Depending upon the extent of lead exposure such as the blood lead concentration particular chelating agent(s) is chosen. The two celebrated chelating ligands like dimercaprol or British Anti Lewsite (BAL) meso-2,3-dimercaptosuccinic acid (DMSA) containing both oxygen and sulphur donor sites; disodium calcium ethylenediaminetetraacetate ($CaNa_2EDTA$) having nitrogen and oxygen donor atoms; and D-penicillamine (DPA) having sulphur, oxygen and nitrogen donor atoms (Figure 1) are extensively used for detoxification of lead in the human body. Particular chelating agent(s) is selected depending upon the extent of lead exposure such as the blood lead concentration and exposed sites. Appropriate chelating agents(s) should be administered with proper clinical investigation and supervision by qualified medical practitioner in that field [5,7,18].

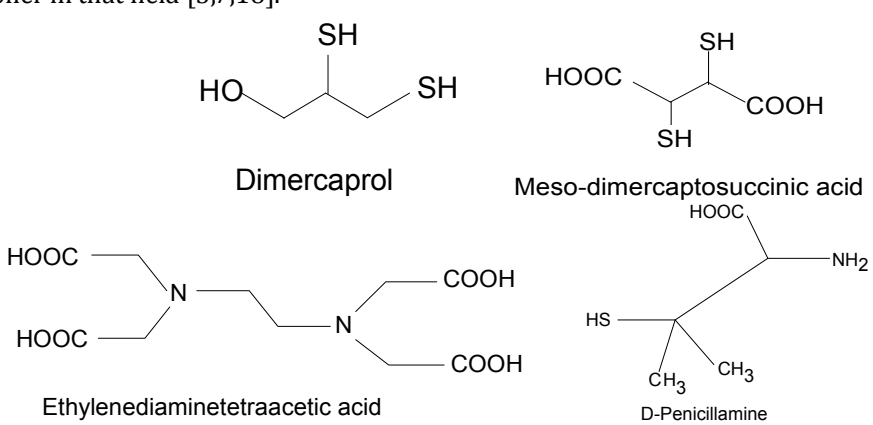

Figure 1: Structures of four lead chelators: Dimercaprol (BAL), meso-dimercaptosuccinic acid (DMSA), ethylenediaminetetraacetic acid (EDTA) and D-penicillamine (DPA).

Dimercaprol: Dimercaprol (British Anti Lewsite, or BAL) is a dithiol compound (2,3-dimercapto-1-propanol) which was used as a Pb chelator for several decades [24,25]. It forms 2:1 chelate with lead is then excreted in the bile and urine. This agent must be administered intramuscularly because of solubility characteristics [7]. The common adverse effects include hypertension, tachycardia (increased heart rates), vomiting and abdominal pain, headache, fever, anaemia: some of these effects may be also associated to the clinical conditions of the patients before therapy. Although this medication is very old and is attached with adverse effects, it is the drug choice for the severe lead poisoning [25-27].

Meso-dimercaptosuccinic acid: Meso-2,3-dimercaptosuccinicnic acid (succimer, DMSA) is a dithiol compound, a water soluble derivative of BAL and can be administered orally. The first choice of treatment in acute and chronic noticeable lead poisoning is now DMSA [5]. The cognitive, motor, behavioural, and neuropsycholological function was tested. DMSA chelated children achieved to some extent better on a developmental neuropsychological test [28,29]. It has a specific affinity for lead and less affinity for iron, zinc and calcium. A benefit to dimercaprol is that succimer does not have a toxic reaction when coadministered with iron [7,26]. Adverse effects in children include gastrointestinal problems, uneasiness, and hepatic problem, but lesser in extent in comparison to dimercaprol [26].

Edetate calcium disodium: Calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$) can be administered either intramuscularly or intravenously in lead poisoning treatment. EDTA is a poly dentate chelator with oxygen and nitrogen donor atoms. $CaNa_2EDTA$ not only binds lead, but also has an affinity for zinc. It has been found to increase lead concentration in the central nervous system and cause encephalopathy. $CaNa_2EDTA$ should not be used as the sole therapy; it is currently used only with dimercaprol in cases of severe encephalopathy. Other adverse effects include headache, fatigue, thirst, fever, vomiting, sneezing etc.[3,7,25]

D-Penicillamine: D-Penicillamine (DPA) is a β- β-dimethylcysteine sulfhydryl containing amino acid. Only the D-isomer is used because the L-isomer causes optic neuritis [30]. This chelating agent is not approved for lead poisoning according to the Food and Drug Administration of United States [7]. The D-isomer administered orally is well absorbed (40-70%) from the gastrointestinal tract. The chelated complex with lead is excreted mainly in urine. DPA removes lead from blood and soft tissues; it does not significantly remove lead from red blood cells [25]. Adverse effects include reversible leukopenia i.e. decrease in white blood cells, mild thrombocytopenia (low platelets count), allergic reaction and kidney diseases. Due to adverse effects, D-penicillamine should be used as third-line treatment for lead toxicity. Patients who do not tolerate $CaNa_2EDTA$ and succimer yet require further treatment may be candidates for D-penicillamine [3,5,26]

Table 1: Sources of Lead Poisoning

Types of Source	Examples	Reference
House related	Lead-based paints and pigments, some household tools, soldered things, children toys, leaching of lead from water pipes, lead containing brass taps	5, 31, 32
Industrial and leaded gasoline	Mining activities, industrial discharges from lead based industries, use of tetraethyllead in gasoline as antiknock compounds	33
Medicinal and cosmetics	Some herbal medicines and certain cosmetics, low-priced jewelleries	34, 35
Workplace	Metal welding, disassembly of spent ships, lead smelting, lead acid batteries, small garages working with old car batteries, house hold renovation	32, 33

Table 2: Effects of Lead Poisoning

Individual	Examples	Reference
Infants	High risks, affects brain, developmental problems	5, 36
Children	Abdominal pain, vomiting, constipation, change in appetite, anaemia, irritability, encephalopathy, intellectual and behavioural problems	7, 11, 37
Pregnant Women	High incidence of spontaneous abortion, neonatal deaths, decreased fertility rates, hypertension, renal failure, high blood pressure, gastrointestinal problems	37, 38

Adult Men	Decreased sperm counts, teratospermia, hypertension, renal failure, high blood pressure, gastrointestinal problems	37, 39

Table 3: Causes of Lead Poisoning

Types	Examples	Reference
Ionic mechanism	Substitution of essential cations like calcium, magnesium, iron and sodium ions by lead ions and inhibition of their biological roles	13, 14, 15
Oxidative stress	imbalance between the production of free radicals, generation of reactive oxygen species, depletion of antioxidant reserves	17-19
Others	Reaction with sulphur containing biomolecules and inhibit their activities	13

Table 4: Remediation of Lead Poisoning using Chelating Ligands

Chelating Ligand	Effectiveness	Side effects	Reference
BAL	Treatment of encephalopathy or severe symptoms of lead toxicity	Hypertension, increasing heart rates, kidney disease, painful treatment	3, 26
DMSA	Oral administration, less affinity for zinc, iron and calcium, better response, promising lead chelator, solely approved for paediatric use by FDA	Mild adverse effects include gastrointestinal complaints, feeling discomfort, decreased haemoglobin level, hypersensitivity	26,30,40, 41
$CaNa_2EDTA$	Effective to decrease blood lead level, less affinity for zinc	Hypocalcemia, cardiac instability, renal toxicity, fatigue	3,7,26
DPA	Administered orally or by intravenous route, not FDA-approved for lead poisoning, third-line treatment for lead toxicity after $CaNa_2EDTA$ and DMSA	Reversible leukopenia, mild thrombocytopenia, eosinophilia	26,30,41

CONCLUSION

Lead is a naturally occurring toxic metal found in the earth crust. There is no known level of lead exposure that is considered safe [6]. Lead poisoning is a chronic non-communicable disease, due to cumulative intake of lead [1]. Patients with high levels of lead often found to be iron-deficient. Using suitable chelating agent(s) to grab the toxic metal ion lead and removal of that coordination compound from the body is the preferred treatment. But the adverse effect(s) of this treatment is a very serious issue till today. So, further investigation and research are needed to get rid of from the toxic effects of the metals. DMSA is the promising chelator for led intoxification particularly for children. At the present time in some cases of severe lead toxicity combined chelation therapy are applied. The treatment of lead toxicity may be supplemented using selective antioxidant [41]. The management of lead intoxification should only be done by the well-qualified medical practioner in that field. It is a very good mark is that most of the countries in the world are able to ban the lead compounds in the gasoline and in the house paints [6]. But the use of lead in some inevitable cases cannot be stopped. Care should be taken for restricted use of low priced ornaments and children toys, unauthenticated herbal medicine and cosmetics. The key way to reducing the public burden lead poisoning is the removal of the cause of exposure, proper nutrition and education regarding lead poisoning [7].

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